

# Photobiomodulation Therapy for Age-Related Macular Degeneration and Diabetic Retinopathy: A Review

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**Purpose:** Photobiomodulation therapy (PBT) has emerged as a possible treatment for age-related macular degeneration (AMD) and diabetic retinopathy (DR). This review seeks to summarize the application of PBT in AMD and DR.

**Methods:** The National Clinical Trial (NCT) database and PubMed were queried using a literature search strategy and reviewed by the authors.

**Results:** Fourteen studies examining the application of PBT for AMD and nine studies examining the application of PBT for diabetic macular edema (DME) were extracted from 60 candidate publications.

**Discussion:** Despite notable methodological differences between studies, PBT has been reported to treat certain DR and AMD patients. DR patients with center involving DME and VA  $\geq 20/25$  have demonstrated response to treatment. AMD patients at Age-Related Eye Disease Study Stages 2–4 with VA  $\geq 20/200$  have also shown response to treatment. Results of major clinical trials are pending.

**Conclusion:** PBT remains an emergent therapy with possible applications in DR and AMD. Further, high powered studies monitored by a neutral party with standard devices, treatment delivery and treatment timing are needed.

**Keywords:** photobiomodulation therapy, age-related macular degeneration, diabetic macular edema, diabetic retinopathy

## Introduction

Patients with diabetic retinopathy (DR) and age-related macular degeneration (AMD) are at increased risk of vision loss. With an ageing population increasingly afflicted by diabetes, the prevalence of both conditions is expected to increase. An estimated 288 million people will have AMD by 2040 and 191 million people will have DR by 2030.<sup>1,2</sup> Up to one third of DR patients develop diabetic macular edema (DME), a manifestation of DR that produces loss of central vision.<sup>3</sup>

Treatment for DME began with focal photocoagulation and evolved to anti-Vascular Endothelial Growth Factor (anti-VEGF) injections. The advent of the anti-VEGF era led to landmark trials demonstrating efficacy of these injections in eyes with DME, however, entry criteria was visual acuity (VA)  $\leq 20/40$ .<sup>4</sup> This left the management of patients with DME and VA  $\geq 20/25$  Snellen (or  $\geq 79$  letters) unknown. The DRCR Retina Network Protocol V aimed to compare VA and retinal thickness after three different treatments: initiation of monthly aflibercept, focal laser therapy with deferred aflibercept, or initial observation with deferred

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afibercept. At 2 years, patients in each treatment group had similar VA outcomes. Although 66.0% did not require further treatment, 12.0% of this group continued to lose  $\geq 5$  letters of vision.<sup>5</sup> These results reveal an absence of preventative treatment for this subset of DME patients. While focal laser, micropulse diode laser, intravitreal steroid injections, and anti-VEGF injections are effective treatments, they are invasive and costly. The DRCR Retina Network Protocol I, which followed 346 participants initially treated with focal laser and ranibizumab for DME, disclosed the five-year cumulative probability of worsening was 18% for eyes with non-proliferative diabetic retinopathy and 31% for eyes with proliferative diabetic retinopathy.<sup>6</sup>

The anti-VEGF era also revolutionized treatment for a subset of patients with advanced exudative age-related macular degeneration (exudative AMD). However, no such treatments exist to control the progression of non-exudative AMD. Although the AREDS/AREDS2 vitamin formulation shows promise in individuals with intermediate AMD, its efficacy for all patients is being called into question: some authors now suggest patients should be selected for AREDS therapy based on genetic testing.<sup>7,8</sup>

Photobiomodulation (PBT) is an emerging therapy that shows potential as a treatment for patients with DME and non-exudative AMD. PBT consists of serial, brief illuminations with Near Infrared Spectrum light (600–1000 nm) from a laser or, more commonly, a light emitting diode (LED). This review article explores potential mechanisms of action and current clinical activity around PBT treatment in these applications.

## Methods

This narrative review was performed with the primary objective of this study to summarize available literature on photobiomodulation therapy employed for any stage of AMD as well as DR including DME. Preclinical studies, case reports, case series, observational studies, and randomized controlled trials were considered for inclusion.

The National Clinical Trial (NCT) database was searched for “Photobiomodulation” and “Age Related Macular Degeneration” as well as “Photobiomodulation” and “Diabetic Retinopathy OR Diabetic Macular Edema.” PubMed was queried with the following search query: (((Age-Related Macular Degeneration) OR (exudative AMD) OR (neovascular AMD) OR (nonexudative AMD) OR (dry AMD) OR (diabetic macular edema) OR (diabetic retinopathy)) AND ((photobiomodulation) OR (PBT) OR

(PBM) OR (photobiomodulation therapy))). Additional articles were identified from a manual search of reference lists within included articles.

Studies were considered and classified dichotomously. Inclusion criteria were: English language, description of PBT for any stage of AMD or any stage of DR including DME. The full text of each article was reviewed by JCM and MWR. The subjects, eyes, device used, wavelength, dose, delivery parameters, and results were extracted. If applicable, NCT number was provided. For trials pending results, the date and outcome measures were reported.

## Results

After screening 60 candidate publications, a total of 23 studies were included. 37 Studies were eliminated as they did not report on PBT as an intervention (n=30), combined therapies (n=5), non-English language (n=2). Fourteen studies examining the application of PBT for AMD can be found in [Table 1](#). Nine studies examining the application of PBT for DME can be found in [Table 2](#).

## Discussion

### Mechanism of Action

Proposed mechanisms of action for PBT include enhanced photoreceptor mitochondrial function, counteracting inflammation, and enhanced supporting cell function.

In PBT, near-infrared spectral light (660–1000 nm) induces a photochemical reaction on the cellular level, starting with complex IV in the electron transport chain.<sup>9–14</sup> Complex IV colocalizes to retinal layers rich in mitochondria such as the nerve fiber layer, around retinal ganglion cell nuclei, the inner/outer plexiform layers, the photoreceptor inner segment and basal surface of retinal pigment epithelium (RPE) cells.<sup>15</sup> Complex IV is directly activated by NIR light, increasing respiratory chain function and mitochondrial activity.<sup>9,16</sup> Photic stimulation uncouples nitric oxide, which would otherwise inhibit complex IV, thereby indirectly increasing mitochondrial activity.<sup>12,14,17</sup> The freed nitric oxide also triggers downstream cascades to increase anti-oxidant production, anti-apoptotic pathways, and cellular metabolism.<sup>18</sup> Within photoreceptors, these changes amount to globally improved photoreceptor performance as measured by ATP production and electroretinogram (ERG).<sup>11,12,14,19,20</sup> Although enhanced photoreceptor function shown in ERG is reported in diabetic mouse models, the same models suggest the complex IV direct and

**Table 1** Summary of Available Articles Describing the Application of Photobiomodulation for Age-Related Macular Degeneration. Subjects, Eyes, Wavelength Treated, Device Used, Dose and Delivery Parameters as Well as Results of the Studies are Presented

First Author* (Trial Name, NCT)	Year	Design	Subjects (No.)	Eyes (No.)	$\lambda$ (nm)	Device	Dose and Delivery Parameters	Results
Begum <sup>24</sup>	2013	-	29 CFH knockout mice	39	670	LED Light Source (C.H. Electronics, UK)	20 mW/cm <sup>2</sup> for 720 sec daily for 12 days	Altered morphology of macrophages marked by IBA-1, increased COX expression, 50% reduction of C3 in outer retina, reduced GFAP and vimentin.
Calaza <sup>19</sup>	2015	-	44 CFH knockout and 44 C57BL/6 mice	176	670	Unspecified	40 mW/cm <sup>2</sup> for 90 sec daily for 5 days	ATP decline is reversed, but HSP60 (indicator of IR light effect) expression unchanged at 2.4 and 8 month time points.
Kokkinopoulos <sup>26</sup>	2013	-	46 C57BL/6 mice	92	670	WARPI0 LED Device (Barneveld, WI)	40 mW/cm <sup>2</sup> for 90 sec five times spaced every 35 hours	Shifting C3b from outer retina to RPE-BM interface reduced inflammation (calcitonin, Complement C3d, TNF) and increased mitochondrial polarization.
Rutar <sup>20</sup>	2012	-	9 Sprague-Dawley rats	18	670	WARP75 LED Device (Barneveld, WI)	50 mW/cm <sup>2</sup> for 180 sec daily over 5 days	Decreased immunoreactivity (4-hydroxynonenal protein), decreased complement expression C3,C4, reduced C3 deposition in ONL.
Ivancic <sup>40</sup>	2008	Prospective trial	203 patients with dry/wet AMD and VA $\leq$ 20/20	348	780	Custom Device	7.5 mW/cm <sup>2</sup> for two 40 sec treatments over 2 weeks	At 3 and 6 months, both cataract and no-cataract patients had improvement in visual acuity; prevalence of metamorphopsia, scotoma, dyschromatopsia were reduced. In patients with wet AMD, edema and bleeding improved.
Merry <sup>41</sup> (TORPA I)	2012	Prospective Interventional Case Series	9 subjects with dry AMD, 50 or older; VA 20/200-20/20	18	670	WARPI0 LED Device (Barneveld, WI)	50-80 mW/cm <sup>2</sup> for eighteen 88 sec treatments over 6 weeks	At 12 months, improved visual acuity by ETDRS chart and contrast sensitivity. No change in fixation stability. Raw data not provided
					790	Gentlewaves (Light bioscience, VA)	6 mW/cm <sup>2</sup> for eighteen 35 sec treatments over 6 weeks	

(Continued)

Table 1 (Continued).

First Author* (Trial Name, NCT)	Year	Design	Subjects (No.)	Eyes (No.)	$\lambda$ (nm)	Device	Dose and Delivery Parameters	Results
Merry <sup>42</sup> (TORPA 2, NCT02725762)	2017	Prospective Interventional Case Series	24 subjects with AREDS Stages 2–4, $\geq 50$ years of age, VA $\geq 20/200$	42	670	WARPI0 LED Device (Barneveld, WI)	50–80 mW/cm <sup>2</sup> for nine 88 sec treatments over 2 weeks	At 3 months, 5.14 letter improvement, 0.16 units contrast sensitivity, drusen volume decrease by 0.024 mm <sup>3</sup> and central drusen thickness decreased by mean of 3.78 microns. Stable retinal thickness and retinal volume
					590	Gentlewaves (Light bioscience, VA)	4 mW/cm <sup>2</sup> for nine 35 sec treatments over 2 weeks	
					790	Gentlewaves (Light bioscience, VA)	0.6 mW/cm <sup>2</sup> for nine 35 sec treatments over 2 weeks	
Markowitz <sup>43</sup> (LIGHTSITE I, NCT02725762)	2019	Randomized, sham controlled, single center study	30 subjects with AREDS Stage 2–4 with VA 20/200–20/40	46	590	Valeda Light Delivery System (Lumithera, WVA)	5 mW/cm <sup>2</sup> for nine 250 sec treatments over 4 weeks after baseline; repeated at 24 weeks.	50% of PBT subjects improved by 5 letters (vs 13.6%) at 1 month, improved contrast sensitivity, improved fixation stability, improved quality of life, at 12 months, 70% of study eyes had reduction in drusen volume vs 100% of sham eyes showing increase in drusen volume
					670		65 mW/cm <sup>2</sup> for nine 250 sec treatments over 4 weeks after baseline; repeated at 24 weeks.	
					850		8 mW/cm <sup>2</sup> for 250 seconds delivered in 9 treatments over 4 weeks after baseline; repeated at 24 weeks.	
LumiThera, Inc. <sup>46</sup> (LIGHTSITE II, NCT03878420)	2019	Double-masked, sham-controlled, parallel design, prospective multi-site study	96 participants $\geq 50$ years of age with VA 20/100–20/30 and dry AMD	96	590, 660, 850	Valeda Light Delivery System (Lumithera, WVA)	Unspecified	Last update August 2020. Outcomes are BCVA, contrast sensitivity, central drusen volume, central drusen thickness at 9 months

LumiThera, Inc. <sup>47</sup> (LIGHTSITE III, NCT04065490)	2019	Double-masked, sham-controlled, parallel design, prospective multi-site study	96 participants ≥ 50 years of age with VA 20/100-20/32 and dry AMD	96	590, 660, 850	Valeda Light Delivery System (Lumithera, WA)	Unspecified	Last Update February 2020. Outcomes are BCVA, contrast sensitivity, central drusen volume, central drusen thickness at 21 months
LumiThera, Inc. <sup>48</sup> (ELECTROLIGHT, NCT04522999)	2020	Open label, prospective pilot study	15 participants ≥ 50 years of age with VA 20/100-20/32 and dry AMD	15	670	Valeda Light Delivery System (Lumithera, WA)	40 mW/cm <sup>2</sup> for non ? sec treatments over 3 weeks	Last update January 2021. Outcomes are ERG changes on multifocal ERG, photopic negative response, multi-luminance flicker ERG, and fixed-luminance flicker ERG at 3 months and 6 month safer therapy
Grewal <sup>19</sup>	2020	Randomized, sham controlled, single center pilot study	42 (12 controls, 30 with intermediate AMD)	42	670	Custom Device	40 mW/cm <sup>2</sup> for 120 sec daily for 52 weeks	Unaltered rod time intercept, no change in scotopic threshold, no change in visual acuity, no change in photopic ERG, no change in ONL, RPE, RPE-BM complexes
Pinelli <sup>44</sup>	2020	Case Report	1 patient with dry AMD; unspecified stage	2	590, 660, 850	Valeda Light Delivery System (Lumithera, WA)	Unspecified mW/cm <sup>2</sup> delivered 240 secs daily for 4 weeks	Reduced drusen, improved near/far VA at 1, 3 and 6 months. Subjective vision improvement. Contrast improved from 1.8 to 2.0
Kaymak <sup>45</sup>	2020	Case Series	3 patients with intermediate AMD	4	590, 660, 850	Valeda Light Delivery System (Lumithera, WA)	Unspecified mW/cm <sup>2</sup> for ? delivered in 9 sessions over 3 weeks, repeated at 7 months for 4 sessions over 2 weeks	Reduced drusen volume, microperimetry improvements, contrast improvements, subjective improvements in all cases, recordable vision improvement in one case

**Notes:** \*O: responsible party if no single author listed on clinicaltrials.gov. <sup>1</sup>Not specified duration of time (NIL) = not listed on clinicaltrials.gov.

**Abbreviations:** λ, wavelength; CFH, complement factor H; LED, light emitting diode; sec, seconds; ERG, electroretinogram; IBA, ionized calcium binding adaptor molecule 1; COX, cyclooxygenase; GFAP, glial fibrillary acidic protein; ATP, Adenosine Triphosphate; HSP60, heat shock protein 60; RPE-BM, Retinal Pigment Epithelium - Bruch's Membrane; IR, infrared; AMD, age related macular degeneration; TNF tumor necrosis factor; ONL, outer nuclear layer; ETDRS, Early Treatment in diabetic Retinopathy Study; AREDS, Age Related Eye Diseases Study; PBT, photobiomodulation therapy; CST, central subfield thickness; VA, visual acuity; ERG, electroretinogram; RPE, retinal pigment epithelium.

**Table 2** Summary of Available Articles Describing the Application of Photobiomodulation for Diabetic Retinopathy. Subjects, Eyes, Wavelength Treated, Device Used, Dose and Delivery Parameters as Well as Results of the Studies are Presented

First Author* (Trial Name, NCT)	Year	Design	Subjects (No.)	Eyes (No.)	λ (nm)	Device	Dose and Delivery Parameters	Results
Tang <sup>21</sup>	2011	–	20 Lewis rats with diabetes induced by streptozocin	40	670	SpectraLife (Barneveld, WI)	25 mW/cm <sup>2</sup> for 360 sec daily for 16 weeks	Inhibition of the death of retinal ganglion cells, 50% improvement in ERG, superoxide inhibition, increased in antioxidant mnSOD, no significant effect of diabetes on complex IV activity, nitric oxide unchanged
Saliba <sup>23</sup>	2015	–	C57Bl/6j mice with diabetes induced by streptozocin	120	670	SpectraLife (Barneveld, WI)	20 mW/cm <sup>2</sup> for 240 sec daily for 10 weeks	Inhibition of superoxide, leukostasis, ICAM expression. Change in spatial frequency threshold. No change in nitric oxide. Rescue of the diabetes induced calcium channel dysfunction (a marker of oxidative stress)
Cheng <sup>21</sup>	2018	–	C57Bl/6j mice with diabetes induced by streptozocin	104–128	670	SpectraLife (Barneveld, WI)	25 mW/cm <sup>2</sup> for 240 s daily for 8 months	Inhibition of the diabetes induced degeneration of retinal capillaries and albumin accumulation in INL and OPL. Preservation of visual function. C-Kit cells and Cyp24a1 are not significant - mechanism might not be mediated by stem cells or VDR signaling
Shen <sup>22</sup> (NIRD, NCT02181400)	2020	Preclinical	Transgenic Müller cell mice	30	670	WARPI0 LED Device (Barneveld, WI)	40 mW/cm <sup>2</sup> for 180 sec daily for 9 days	Enhanced photoreceptor mitochondrial membrane, protected Müller cells, protected photoreceptors, reduced retinal vascular leakage
			Sprague Dawley and Dark Agouti Rats		670	Ellex Integre NIR (Minneapolis, MN)	100 or 500 mW/cm <sup>2</sup> for ? sec every two days for 1 week	One week after last treatment, safety assessed. 100 mW/cm <sup>2</sup> safe in pigmented and non-pigmented eyes. 500 mW/cm <sup>2</sup> showed damage in pigmented retina
		Phase II b Clinical Trial	21 adult patients with CI - DME and CST >300 microns	14	670	Ellex Integre NIR (Minneapolis, MN)	25 mW/cm <sup>2</sup> for 90 sec over 12 session for 5 weeks	At 6 months, no significant change in VA. CMT decreased 53±24 microns
				12	670	Ellex Integre NIR (Minneapolis, MN)	100 mW/cm <sup>2</sup> for 90 sec over 12 session for 5 weeks	At 6 months, no significant change in VA. CMT decreased 129±51 microns

			16	670	Ellex Integre NIR (Minneapolis, MN)	200 mW/cm <sup>2</sup> for 90 sec over 12 session for 5 weeks	At 6 months, no significant change in VA. CMT decreased 114±60 microns
Eells <sup>32</sup>	2016	Randomized, prospective study	20	670	WARPI0 LED Device (Barneveld, WI)	45 mW/cm <sup>2</sup> for 3 sec three consecutive days every week for 8 weeks	At 6 months, central retinal thickness declined 24±5 microns (vs 120±97 microns in comparison) and VA improved 6±5 letters (vs 3±4 letter decrease in comparison)
Tang <sup>33</sup>	2014	Case Series	4	670	WARPI0 LED Device (Barneveld, WI)	56 mW/cm <sup>2</sup> for 120 sec daily for 36 weeks	Thickened areas on spectral domain OCT were reduced by a mean of 20% (±11.7%) in the treated eyes and mean change in the untreated eyes was -3% (±8%)
Bristlecone Health Inc <sup>35</sup> (N/L, NCT03859245)	2019	Interventional	60	660 and 810	Joov Red LED device (Unspecified)	Unspecified mW/cm <sup>2</sup> for 1200 seconds three times weekly for 36 weeks	Last update March 2019. Combined effect of ketogenic diet and PBT on incidence of hemorrhages, exudates, and macular edema in diabetic retinopathy patient. Impact of the same on size, number and density of drusen.
Kim <sup>36</sup> (N/L, NCT02457975)	2019	Early Phase I Clinical Trial	30	670	WARPI0 LED Device (Barneveld, WI)	50 mW/cm <sup>2</sup> of light for 90 seconds three consecutive days per week for 8 weeks.	Last update September 2019. Primary outcome measures "VA and OCT changes."
Glassman <sup>34</sup> (Protocol AE, NCT03866473)	2019	Randomized, masked, Clinical Trial	134	670	Retilux Eye Patch (PhotOptx, OH)	25 mW/cm <sup>2</sup> for 180 sec daily (two 90 sec intervals) daily for 16 weeks	Last update March 2021. Primary outcome measures: change in CST on OCT. Secondary outcome measures: Change in retinal volume, alternative treatments for DME, > 5 letter loss in VA, patient compliance

Notes: \*Or, responsible party if no single author listed on clinicaltrials.gov. †Not specified duration of time (N/L) = not listed on clinicaltrials.gov.

Abbreviations: λ, wavelength; sec, seconds; ERG, electroretinogram; mnSOD, manganese SuperOxide Dismutase; ICAMs, Intracellular Adhesion Molecules; CMT, Central Macular Thickness; CST, Central Subfield Thickness; VA, visual acuity; LED, light emitting diode; DR, diabetic retinopathy; AMD, age-related macular degeneration; NIR, near infrared laser; OCT, optical coherence tomography; DME, Diabetic Macular Edema; CI-DME, Center-Involving Diabetic Macular Edema.

indirect pathways may not mediate the effect.<sup>21–23</sup> Confounders, such as severity of hyperglycemia, might explain this result. It is possible that the PBT's mechanism of action is specific to disease state, triggering pathways in a patient DME which may not be shared with those triggered in a patient with AMD. Further basic science studies might clarify if disease specific pathways are present.

The anti-inflammatory effect of PBT might be mediated across multiple pathways. Murine models for AMD and DME agree that PBT reduces C3 and C2 complement expression within the outer retina.<sup>20,23–25</sup> Other studies upheld and expanded this observation, showing C3 presence shifted from the photoreceptors to RPE/Bruch's membrane.<sup>20,26</sup> This could be seen as the retina is not only expressing less early inflammatory triggers, but also clearing them. Studies have also demonstrated inhibition of superoxide as well as increased expression of the antioxidant mitochondrial antioxidant manganese superoxide dismutase (mnSOD).<sup>23,25</sup> Others have shown decreased signals of cellular inflammation such as Glial Fibrillary Acidic Protein (GFAP), Vimentin, Cyclooxygenase (COX), calcitonin, Tumor Necrosis Factor (TNF), 4 hydroxyneal, and Intracellular Adhesion Molecules (ICAMs).<sup>20,23,24,26</sup> These studies suggest a net anti-inflammatory effect of PBT which may be mediated by complement downregulation.

Supporting cells in the retina also react to PBT in both diabetic and AMD murine models. Müller cells show a decrease in Vimentin and GFAP, which are cell-specific markers for stress and inflammation, and possibly a prolonged lifetime.<sup>22,24,27</sup> Tang et al demonstrated rescue of retinal ganglion cells, while Fuma et al demonstrated PBT increased phagocytic activity of RPE cell lines.<sup>25,28</sup> Supporting cells are crucial for a healthy retina and evidence of their rescue appears positive.

Finally, PBT therapy can alter retinal gene expression. Natoli et al analyzed the change in expression of 175 neuroprotective retinal genes and ncRNAs after five days of exposure to PBT therapy. 126 of these entities increased expression as a result.<sup>29</sup> This effect is potentiated when combined with dietary saffron intake as suggested confirmed in other studies.<sup>29,30</sup> The effect of isolated PBT was further confirmed by Heinig et al who utilize gene expression analysis to identify upregulation of  $\alpha$ -crystallins; a result the authors interpreted as indicating rescued mitochondrial function.<sup>13</sup>

Murine models suggest several mechanisms of action across multiple cell types, pathways, and modalities.

However, these models are limited for several reasons: the disease states discussed are induced, murine and human physiology differ, and targeting light efficiently into the murine eye is an imperfect science. Due to the difficulty in targeting rodent eyes specifically, there is the possibility that PBT's effect is may be mediated by the skin and propagated systemically through an unspecified pathway.<sup>21</sup> Although these results must be considered with the limitations discussed above, they form the basis for clinical trials.

## Diabetic Macular Edema: Clinical Applications

In addition to the aforementioned mechanisms, separate experimenters demonstrated a significant reduction in retinal microvascular leakage observed in the inner plexiform layer, inner nuclear layer and outer plexiform layer.<sup>22,31</sup> These would suggest a unique application for PBT in diabetic retinopathy.

Two clinical studies for treatment of DME followed murine studies. Eells et al conducted a randomized prospective study in 10 patients to compare anti-VEGF alone (n=4) or anti-VEGF plus PBT (n=6). 670 nm-light treatment was administered at a transpupillary dose of 4.5 J/cm<sup>2</sup> three consecutive days per week for 8 weeks.<sup>32</sup> At the end of 24 weeks, the authors reported a reduction in central retinal thickness (CRT) of  $-24 \pm 5$  microns and improvement of  $6 \pm 5$  letters in the PBT group as compared to a  $+120 \pm 97$  microns gain and  $-3 \pm 4$  letter VA decrease in the standard treated group (P values not reported). Tang et al reported four consecutive cases with bilateral non-center involving DME. One eye was selected for PBT, while the fellow eye was an untreated control.<sup>33</sup> 670 nm light treatment was administered at a dose of 9.0 J/cm<sup>2</sup> for 2 to 9 months. After treatment, thickened areas on spectral domain OCT were reduced by a mean of 20.0% ( $\pm 11.7\%$ ) in the treated group as compared to  $-3.0\%$  ( $\pm 8.0\%$ ) in the control group.<sup>33</sup>

These results offer a new application for PBT in center involving DME (CI-DME) in the absence of a truly preventative treatment for this subset of DME patients. Shen et al delivered 670 nm light at varying energy levels (25, 100, 200 mW/cm<sup>2</sup>) to 42 eyes for 5 weeks. A maximal reduction of  $-129 \pm 51$   $\mu$ m in central macular thickness (CMT) for patients dosed 100 mW/cm<sup>2</sup> was observed.<sup>22</sup> Although CMT reductions were noted across all dosages, no significant VA gains were noted.

These results prompted a randomized, multi-center, sham-controlled clinical trial, Protocol AE, through the Diabetic Retinopathy Clinical Research Network on patients with CI-DME and good VA.<sup>34</sup> Other ongoing trials investigate combinations of ketogenic diet and PBT to attenuate DME as well as treatment refractory DME, however details on these trials are limited.<sup>35,36</sup> Trials such as Shen et al and Protocol AE show a focus on patients with VA  $\geq$  20/25 and Central Subfield Thickness (CST)  $\geq$  300  $\mu$ m as inclusion criteria, which limits generalizability of available results and conclusions.<sup>22,34</sup>

At the time of this writing, evidence would suggest CI-DME patients with VA  $\geq$  20/25 could benefit from PBT. However, the role of PBT in DR treatment remains to be well defined in future trials standardizing devices, treatment patterns, and inclusion criteria must determine this pending the results of current work.

## Age-Related Macular Degeneration: Clinical Applications

The mechanisms suggested for PBT function - an increase in mitochondrial function, reduced oxidative damage and decline in complement expression - directly foils the declining mitochondrial function, declining photoreceptor and supporting cell performance, and complement activation that characterize AMD.<sup>37-40</sup>

Ivandic treated 348 eyes with VA  $\leq$  20/20 at various stages of AMD with 670 nm light aimed through the conjunctiva and sclera at the macula. Patients with concomitant vision impairing disease or prior treatment affecting vision and VA  $>$ 20/20 were excluded. VA by the Snellen chart improved ( $P < 0.00001$ ) as did color vision.<sup>40</sup> This preliminary work did not provide details on VA measures, CST changes or fundus photography. In the following TORPA 1 trial, ETDRS acuity, contrast sensitivity and fixation stability were tested in 18 AMD eyes after 18 PBT treatments.<sup>41</sup> Eyes that were AREDS stages 2-4 from patients 50 or older with VA ranging 20/200 - 20/20 were included. Eyes with previous or active exudative AMD, other retinal diseases, previous retinal surgery, significant media opacity or contraindications to dilation drops were excluded. At 12 months, VA improved from 0.25 logMar units (20/36) to 0.13 logMar units (20/27). Contrast sensitivity improved while fixation stability remained unchanged.

TORPA 2 expanded the TORPA 1 study to 42 eyes. Inclusion and exclusion criteria were identical with the

exception that VA  $>$ 20/200 was considered. At 3 months, +5.14 letters were recovered compared to baseline.<sup>42</sup> Similarly, LIGHTSITE I evaluated PBT efficacy in 46 eyes AREDS stages 2-4 with VA 20/40-20/200.<sup>43</sup> Major exclusion criteria were shared with the TORPA studies. 670 nm light was delivered in 9 treatment installments at baseline and again at 6 months. VA was noted to increase by up to 4 letters, then decline to baseline 6 months after each treatment, suggesting some level of consistent therapy would be required. VA variation included overlap between groups, and a significant change was noted only when analysis generated a high responder group ( $\geq$  5 letters gained at one month).

In both TORPA 2 and LIGHTSITE I, OCT monitoring showed significant reduction in drusen volume and thickness in the setting of an unchanged CRT and central retinal volume. These observations were made relative to a control group, accounting for changes which may result from the natural course of AMD. Both studies reported improvement in contrast sensitivity and fixation stability. These functional and objective metrics are substantiated in individual case series.<sup>44,45</sup> In both trials and case series, these improvements are noted to be last up to 6 months after PBT.

The ongoing LIGHTSITE II and LIGHTSITE III were launched in response to these findings.<sup>46,47</sup> Eligible subjects for these studies are  $\geq$  50 years of age, with VA of 20/32-20/100, with eyes containing drusen  $\geq$  63  $\mu$ m confirmed by a reading center. The ELECTROLIGHT study, which is also ongoing, seeks to assess the effect of PBT by recording electroretinograms from non-exudative AMD patients.<sup>48</sup> Notable inclusion criteria are documented as non-exudative AMD, VA of 20/32-20/100, and  $\geq$  50 years of age. Salient exclusion criteria across these studies include GA, media opacity, ocular surgery, other visually significant disease. Results of the above studies are pending at the time of this writing.

As in studies for DME, the methodology of human trials for AMD show variation in treatment delivery, measurement, and outcomes. Additionally, the absence of control arms and sponsorship by device manufacturers raises further concern for bias. For this reason, Grewal et al exposed 42 eyes (12 controls, 30 intermediate AMD) to a simple easily reproducible Light Emitting Diode based light source for 120 seconds daily for 12 months.<sup>49</sup> At the end of the study period, no significant anatomic or functional changes were reported.

Though the results are contradictory to other studies, a true comparison is difficult. Paradoxically, Grewal's

methodology – using a different device, control group, and much higher cumulative dose and exposure period – differs significantly from prior work. Nonetheless, future, well-appointed trials standardizing devices, treatment patterns, and inclusion criteria are needed to determine the true effect of PBT in AMD. Moreover, these trials have focused largely on AREDS stages 2–4. Although patients with advanced stages (geographic atrophy or exudative AMD) have been included as a subset, future work may investigate the potential for PBT to serve as an adjunctive treatment in exudative AMD and clarify the potential role it may play in a dedicated GA subset without center involvement.<sup>40,42,43,50</sup>

Available studies suggest PBT is best suited to AREDS stages 2–4 AMD, where it might alter complement deposition, attenuate oxidative damage, and enhance mitochondrial function. As with DME, the patient subset is narrow, shared in study design limitations, and high-level evidence remains wanting.

## Conclusion

As a non-invasive therapy with no adverse effects reported from human subjects as of this writing, PBT may fill a role in treating niches of DR and AMD patients, specifically CI-DME with VA  $\geq$  20/25 or AREDS stages 2–4 with VA  $\geq$  20/200. The promising reports surrounding PBT might justify prospective, randomized controlled trials. If possible, a consensus of optimal timing, energy, wavelength(s) to be tested in these trials ought to be employed. Additionally, to prevent bias the trials ought to be initiated and monitored by a neutral party without vested interest.

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