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Short- and Long-Term Efficacy and Safety Evaluation of Multiwavelength Photobiomodulation in Nonexudative Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis

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Abstract

Multiwavelength photobiomodulation (PBM) is a novel non-invasive intervention that targets mitochondrial dysfunction in nonexudative (dry) age-related macular degeneration (AMD). This systematic review and meta-analysis aimed to evaluate the short- and long-term efficacy and safety of PBM in patients with dry AMD. A systematic search of major databases (PubMed, Embase, CENTRAL, Scopus, Web of Science) and trial registries was conducted until August 2026. Randomized controlled trials (RCTs) comparing multiwavelength PBM (e.g., 590/660/850 nm) to sham or no treatment were included. Continuous and dichotomous outcomes were pooled using random-effects models with the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment. The risk of bias (Cochrane Risk of Bias 2 (RoB 2)) and certainty of evidence (Grading of Recommendations Assessment, Development, and Evaluation (GRADE)) were systematically evaluated.

Ten reports from nine unique studies (four RCTs, one non-randomized comparative study, and four uncontrolled studies) were included. A meta-analysis of four RCTs (365 eyes) revealed a fragile, short-term (< 12 months) improvement in best-corrected visual acuity (BCVA) (mean difference (MD): +1.44 ETDRS letters; 95% confidence interval (CI): 0.12 to 2.76), which lost significance after adjustment for the correlation between the two eyes of the same patient (MD: 1.37; 95% CI: −0.03 to 2.77 at an assumed intraclass correlation of 0.5) and in leave-one-out analyses. However, in a post-hoc analysis, PBM increased the likelihood of a clinically meaningful ⩾ 5-letter BCVA gain (risk ratio (RR): 2.77; 95% CI: 2.08-3.68; p = 0.0015), which was unchanged after excluding one trial's full-protocol subgroup (RR: 2.84; 95% CI: 1.86-4.32). Reductions in macular drusen volume (standardized mean difference (SMD): -0.18; p = 0.081) and contrast sensitivity were not statistically significant. One large trial reported a significant reduction in incident geographic atrophy at 24 months (RR: 0.29).

PBM demonstrated a favorable safety profile, with no increased risk of ocular adverse events or progression to neovascular AMD. The overall certainty of the evidence was graded as low to very low due to the high risk of bias, small sample sizes, and imprecision. Multiwavelength PBM significantly increased the proportion of patients who achieved categorical visual gains and maintained a favorable safety profile. However, the continuous visual and anatomical benefits are modest and fragile. High-quality, independently funded RCTs with standardized sham controls and long-term follow-ups are warranted to definitively establish the role of PBM in AMD management.

Categories: Ophthalmology
Keywords: age-related macular degeneration, drusen, geographic atrophy, low-level light therapy, meta-analysis, multiwavelength, photobiomodulation, systematic review

Introduction And Background

Age-related macular degeneration (AMD) is the leading cause of irreversible visual impairment and legal blindness among older adults globally, affecting approximately 200 million individuals, with a prevalence projected to approach 288 to 300 million by 2040 [1,2]. The disease is classified into exudative (wet) and nonexudative (dry) phenotypes. Nonexudative AMD accounts for 85-90% of all cases and is characterized by progressive deterioration of the macula, driven by the accumulation of extracellular drusen and intracellular lipofuscin between the retinal pigment epithelium (RPE) and Bruch's membrane [3]. While significant pharmacological advancements, such as anti-vascular endothelial growth factor (VEGF) therapies, have revolutionized the management of wet AMD, therapeutic options for early and intermediate dry AMD remain limited [4]. The current standard of care is restricted to lifestyle modifications and high-dose antioxidant supplementation (e.g., the AREDS2 formula), which modestly reduces the risk of progression to advanced stages, such as geographic atrophy (GA) [5]. There is a critical unmet clinical need for early disease-modifying interventions capable of preserving retinal tissue prior to the onset of irreversible cellular apoptosis.

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The pathogenesis of nonexudative AMD is complex and multifactorial, with mitochondrial dysfunction, chronic oxidative stress, and complement-mediated inflammation recognized as central drivers of RPE and photoreceptor degeneration [6,7]. The RPE is a metabolic tissue; with advancing age, a decline in mitochondrial oxidative phosphorylation leads to excessive generation of reactive oxygen species (ROS) and a deficit in cellular bioenergetics [8]. This oxidative imbalance triggers structural damage, lipid peroxidation, and upregulation of pro-inflammatory cytokines, culminating in the apoptotic death of the RPE-photoreceptor complex [6,9]. Targeting this underlying mitochondrial dysfunction at an early stage represents a logical and attractive therapeutic strategy.

Photobiomodulation (PBM), also referred to as low-level light therapy, has emerged as a promising non-invasive biophysical intervention for retinal degenerative diseases [10]. PBM utilizes specific wavelengths of light in the visible red to near-infrared (NIR) spectrum (600-1000 nm) to induce photochemical rather than photothermal effects within target tissues [11]. At the molecular level, photons are absorbed by endogenous mitochondrial chromophores, principally cytochrome c oxidase (CCO) in the electron transport chain [12]. Photoactivation facilitates electron transfer, enhances adenosine triphosphate (ATP) synthesis, and modulates the release of ROS and nitric oxide (NO) [13]. These primary bioenergetic shifts trigger secondary intracellular cascades that activate redox-sensitive transcription factors (e.g., NF-κB, CREB), leading to the downregulation of pro-inflammatory mediators and upregulation of antioxidant enzymes, angiogenic regulators, and neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) [12,14].

Multiwavelength PBM, which employs a combination of yellow (590 nm), red (660 nm), and NIR (850 nm) light, has been designed to simultaneously target different cellular layers of the retina and choroid [15]. Recent prospective clinical trials, the TORPA and LIGHTSITE series (I, II, and III), have evaluated multiwavelength PBM in patients with dry AMD, demonstrating encouraging results [15,16]. Several of these studies reported statistically significant improvements in best-corrected visual acuity (BCVA), contrast sensitivity, and electroretinography (ERG) parameters, alongside anatomical stabilization, such as reduced drusen volume and delayed progression of GA [15,17].

While some randomized controlled trials (RCTs) indicate functional recovery, other studies and preliminary meta-analyses have reported transient effects that wane after six months, high methodological heterogeneity, and a failure to meet minimally clinically important differences in anatomical outcomes [18,19]. Furthermore, evidence regarding the durability of therapeutic benefits over extended follow-up periods, the necessity of repeated treatment cycles, and the long-term safety profile of cumulative light exposure remains inconclusive [18].

To address these critical gaps, this systematic review and meta-analysis aimed to quantitatively synthesize the evidence from clinical studies evaluating the efficacy of multiwavelength PBM in patients with nonexudative AMD. Specifically, this study evaluated the short-term (< 12 months) and long-term (≥ 12 months) efficacy of PBM in terms of visual function, retinal anatomical alterations, and disease progression, while assessing treatment-related adverse events. By stratifying outcomes by follow-up duration, this analysis aims to clarify the therapeutic viability, durability, and safety of PBM, thereby informing future clinical practice and research guidelines.

Review

Methods

Protocol Registration and Guidelines

This systematic review and meta-analysis was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [20] and the Cochrane Handbook for Systematic Reviews of Interventions [21]. The a priori study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration Number: CRD420261454161).

Search Strategy

A systematic literature search was performed across major electronic databases, including PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science, from inception to August 2026. The search syntax was constructed using a combination of Medical Subject Headings (MeSH), Emtree terms, and free-text keywords incorporating Boolean operators (AND, OR, NOT) and truncations. The core search concepts included ("Age-Related Macular Degeneration" OR "Dry AMD" OR "Geographic Atrophy") AND ("Photobiomodulation" OR "Low-Level Light Therapy" OR "Multiwavelength Light Therapy"). The proportion of eyes gaining ≥ 5 ETDRS letters was not named in the PROSPERO record; it was added after registration as the dichotomous form of the BCVA outcome. To ensure literature saturation, gray literature and ongoing trials were screened via ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). Additionally, backward and forward citation chasing ("snowballing") of the included studies and relevant systematic reviews was performed. No temporal or linguistic restrictions were imposed.

Eligibility Criteria

Study eligibility was determined using the PICOS (Population, Intervention, Comparator, Outcomes, and Study Design) framework. The population included adults (≥ 50 years) with a confirmed diagnosis of nonexudative (dry) AMD, including intermediate AMD and GA. The intervention was multiwavelength PBM (e.g., combinations of 590, 660, and 850 nm wavelengths), delivered via any clinically approved device,

regardless of treatment duration or frequency, and the comparator was Sham PBM, placebo, observation, standard ophthalmic care, or no treatment.

The primary outcomes included changes in BCVA, retinal anatomical alterations assessed by optical coherence tomography (OCT) (e.g., drusen volume and central subfield thickness), and treatment-related adverse events, whereas the secondary outcomes encompassed contrast sensitivity, microperimetry, low-luminance visual acuity, vision-related quality of life (e.g., NEI VFQ-25), and progression to exudative AMD or geographic atrophy. The eye was the unit of analysis, as in all included trials; because the patient was the unit of randomization, the correlation between fellow eyes was addressed as described under Statistical Analysis and Data Synthesis. Outcomes were stratified as short-term (< 12 months) and long-term (⩾ 12 months), and where a study reported more than one visit, the longest available follow-up was considered.

RCTs served as the primary evidence. Prospective, non-randomized controlled clinical studies, prospective single-arm cohorts, and case series were also included for qualitative synthesis only and were excluded from all pooled estimates where methodologically appropriate. Animal studies, in vitro models, case reports, retrospective designs, and studies evaluating single-wavelength PBM or other laser therapies (e.g., photocoagulation) were excluded. Conference abstracts were eligible for narrative synthesis only if they reported sufficient numerical outcome data.

Study Selection and Data Extraction

The retrieved records were imported into reference management software, and duplicates were removed. Two independent investigators screened the titles and abstracts, followed by a full-text review of potentially eligible articles. The inter-rater reliability for study inclusion was quantified using Cohen's kappa coefficient (k). Data extraction was performed independently by two reviewers using a standardized matrix. The extracted variables included study characteristics (author, year, country, design), participant demographics (sample size, age, baseline AMD stage), intervention protocols (wavelengths, fluence, irradiance, session frequency), and prespecified primary and secondary outcomes.

Multiple reports of the same trial were linked and analyzed as a single study, with one time point contributed per outcome to prevent double counting. For each trial, we also extracted the unit of randomization, the numbers of patients and eyes per arm, and whether the trial's analysis accounted for the correlation between fellow eyes. Outcome data were extracted as eye-level arm summaries, because individual patient data were not available. Where a standard deviation (SD) was not reported, it was derived from the reported standard error, confidence interval (CI), or p-value using the methods described in the Cochrane Handbook [21]. Discrepancies at any stage were resolved by a third reviewer.

Quality Assessment and Certainty of Evidence

The methodological quality and risk of bias (RoB) of the included RCTs were independently appraised by two reviewers using the revised Cochrane Risk of Bias 2 (RoB 2) tool, which evaluates bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result [22]. For non-randomized comparative studies, the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was utilized [23]. Uncontrolled studies were appraised against the same domains; those judged to have critical overall risk of bias were excluded from all pooled estimates and from the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment and contributed to narrative synthesis only.

The overall certainty of the evidence for each critical outcome was graded using the GRADE framework, which categorizes evidence quality as high, moderate, low, or very low based on the risk of bias, inconsistency, indirectness, imprecision, and publication bias [24]. Imprecision was judged against a prespecified optimal information size of 400 eyes for continuous outcomes and 300 events for dichotomous outcomes.

Statistical Analysis and Data Synthesis

All meta-analytical computations were performed using the meta, metafor, and robvis packages in R software (version 4.6.1; R Foundation for Statistical Computing, Vienna, Austria) [25,26]. For continuous outcomes (e.g., BCVA, drusen volume, and contrast sensitivity), treatment effects were pooled as mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs, depending on the uniformity of the measurement scales used across the studies. Dichotomous outcomes (e.g., adverse events and progression to wet AMD) were synthesized by calculating risk ratios (RRs) with 95% CIs.

Given the anticipated clinical and methodological heterogeneity of light therapy protocols and AMD populations, a random-effects (RE) model was employed for all pooled analyses [27]. The restricted maximum likelihood (REML) estimator was used to calculate the between-study variance (τ^2). Because the number of included studies was small ($k < 10$), the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment was applied to yield more robust and conservative CIs, mitigating the risk of false-positive results typical of standard RE models in small meta-analyses [28].

Statistical heterogeneity was quantified using the I^2 statistic and evaluated via Cochran's Q test (significance defined as $p < 0.10$), and 95% prediction intervals (PIs) were computed for every outcome with $k \geqslant 2$. Heterogeneity was interpreted as low, moderate, substantial, or considerable, corresponding to I^2 values of < 25%, 25-50%, 50-75%, and > 75%, respectively [29]. To explore potential sources of

heterogeneity, predefined subgroup analyses were conducted based on follow-up duration (short-term (< 12 months) vs. long-term (⩾ 12 months)); subgroup analysis was undertaken only where at least two studies contributed to each stratum, a criterion met for follow-up duration.

Furthermore, leave-one-out sensitivity analyses were performed by iteratively removing one study at a time to ascertain the robustness of the pooled estimates and to determine whether any single study disproportionately influenced the overall effect size. For the responder outcome, post-hoc sensitivity analyses excluded LIGHTSITE II, whose data came from a full-protocol subgroup, and then also LIGHTSITE I, whose responder stratification was defined post-hoc. Prespecified sensitivity analyses compared alternative meta-analytic models (random effects without the HKSJ adjustment, DerSimonian-Laird, and fixed effect) and restricted the synthesis to studies not at high risk of bias. Because all trials randomized patients but included both eyes of some patients, eyes within an arm are not independent. In the absence of individual patient data, we inflated each trial's within-study variance by a design effect, $1 + (m - 1) \times ICC$, where m is the mean number of eyes per patient, and ICC is the inter-eye correlation, assumed to be 0.2, 0.5, or 0.8 [21]. This adjustment was added after protocol registration. Baujat and Draper plots were used for influence diagnostics.

Regarding publication bias and small-study effects, the Cochrane Handbook states that funnel plots and statistical tests for funnel plot asymmetry (e.g., Egger's regression test) lack sufficient statistical power to distinguish chance from real asymmetry when the number of pooled studies is < 10. Because our review included fewer than 10 studies, quantitative assessments and visual inspections for publication bias were not conducted [30].

Results

Literature Search and Study Selection

The systematic literature search yielded 1,078 records from electronic databases and clinical registries. After removing 181 duplicate records, 897 unique titles and abstracts were screened, leading to the exclusion of 879 irrelevant records. Eighteen full-text reports were sought for retrieval, of which 16 were retrieved and assessed for their eligibility. Six reports were excluded for failing to meet the inclusion criteria (three had insufficient data, one included the wrong population, one assessed the wrong intervention, and one utilized an ineligible study design). Ten reports representing nine unique studies were included in the systematic review, with four RCTs providing quantitative data suitable for meta-analysis (Figure *1*).

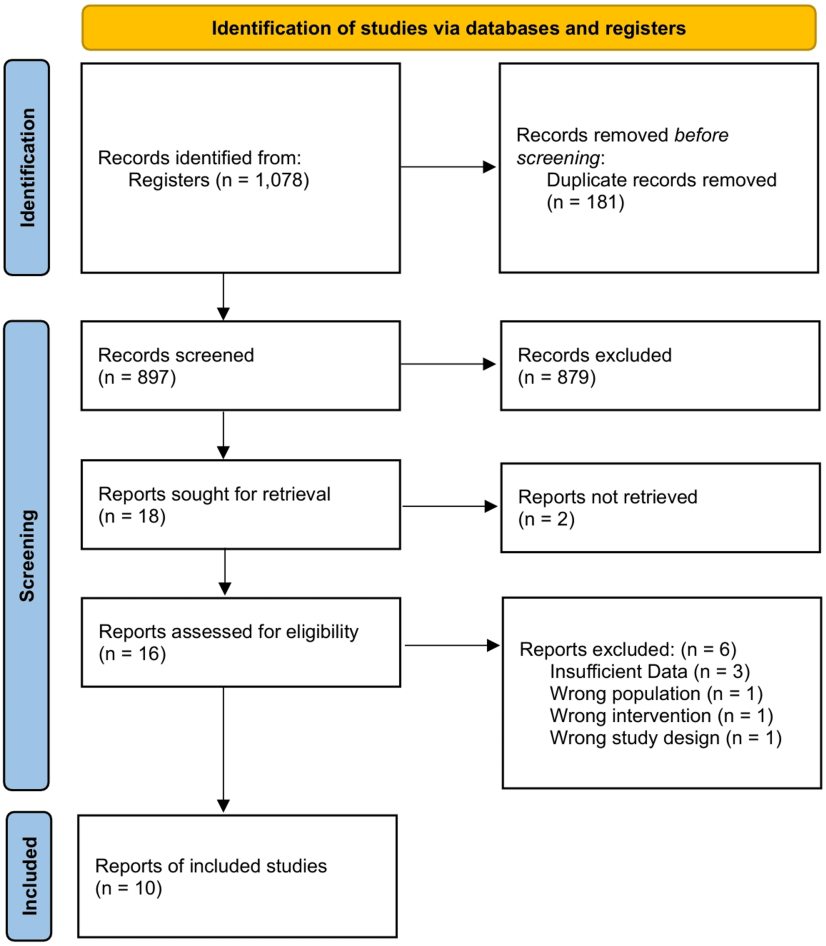


FIGURE 1: PRISMA 2020 flow diagram for study identification, screening, and inclusion

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Study Characteristics

Table *1* demonstrates the characteristics of the included studies and their respective interventions. The 10 included reports covered four double-masked, sham-controlled RCTs [15-17,31,32], one prospective non-randomized comparative study evaluating treated versus untreated fellow eyes [33], and four uncontrolled single-arm studies or open-label extensions [34-37]. The analyzed population predominantly consisted of females (mean ~60-80%), with mean ages ranging from 68.6 to 78.5 years. Baseline disease severity spanned the AREDS categories 1-4. The LumiThera Valeda system (590/660/850 nm) was the primary intervention in most studies, whereas the EYE-LIGHT trial [32] utilized a 590/630 nm device. Sham controls involved an identical device procedure delivering a reduced fluence (e.g., ~100-fold reduction) or omitting the near-infrared wavelengths. All four RCTs randomized patients and assigned both eyes of bilaterally enrolled patients to the same arm. Both eyes were enrolled when eligible in LIGHTSITE I (30 patients, 46 eyes) and LIGHTSITE II (44 patients, 53 eyes), in 48 of 100 patients in LIGHTSITE III (148 eyes), and in all 76 patients in EYE-LIGHT (152 eyes). LIGHTSITE I to III analyzed eyes with mixed-effects models nesting eyes within patients; EYE-LIGHT reported eye-level analyses without this adjustment. A 12-month report of EYE-LIGHT [38], published within the search period and identified during peer review, was linked to this trial. In 78 patients (138 eyes), it reported a between-group BCVA difference of 3.75 letters (95% CI: 1.16 to 6.34), a reduction in drusen volume, and macular neovascularization in four sham-treated eyes versus none with PBM. Pooled analyses use the interim four-month data.

Study	Design	Country	Patients (n)	Eyes (n)	Eyes PBM/sham	Age, mean (SD), years	Female (%)	AMD stage	Baseline BCVA (letters)	Follow-up (months)	Device	Wavelengths (nm)	Irradiance	Session (s)	Treatment protocol	Comparator	F
Markowitz et al., 2020 (LIGHTSITE I) [16]	Double-masked RCT, sham-controlled, parallel, single-center	Canada	30	46	24/22	76 (8.3)	60	AREDS 2-4 (67% cat 4; 74% GA)	Sham 71.9; PBM 73.8 letters	12	LumiThera Valeda	590/660/850	590nm 5 mW/cm^2; 660nm 65 mW/cm^2; 850nm 8 mW/cm^2	250	3x/week x 3-4 wk; 2 series (BL, M6)	Sham PBM (approx. 100x fluence reduction)	L N
Burton et al., 2023 (LIGHTSITE II) [17]	Double-masked RCT, sham-controlled, parallel, multicenter	UK/Italy/Spain/France/Germany	44	53	34/19	74.1 (8)	61.4	AREDS 1-4 (66% cat 3)	Sham 70.5; PBM 70.1 letters	9	LumiThera Valeda	590/660/850	590nm 5; 660nm 65; 850nm 8 mW/cm^2	250	3x/week x 3-4 wk; 3 series (BL, M4, M8)	Sham PBM	L
Boyer et al., 2024/Jaffe et al., 2026 (LIGHTSITE III) [15,31]	Double-masked RCT, sham-controlled, parallel, multicenter	USA/Germany	100	148	93/55	75.4 (7.1)	68	AREDS 2-3; 72% intermediate; 8% GA	Sham 70.1; PBM 70.7 letters	24	LumiThera Valeda	590/660/850	590nm 5; 660nm 65; 850nm 8 mW/cm^2	250	3x/week x 3-5 wk; 4 series to M13, 6 series to M24 (q4mo)	Active sham (590nm reduced, 660nm reduced, 850nm omitted)	L
Borrelli et al., 2024/Iovino et al., 2026 (EYE-LIGHT) [32,38]	Double-masked RCT, sham-controlled, multicenter (interim)	Italy/Turkey/France/UK	76	152	76/76	68.6 (10.2)	76.3	AREDS 1-4 (approx. 46% cat 3)	Sham 68.3; PBM 62.6 letters	4	EYE-LIGHT	590/630	Continuous + pulsed modes (NR)	—	2x/week x 4 wk; 1 cycle	Sham PBM	E G
Nassisi et al., 2024 (PBM4AMD) [33]	Prospective non-randomized; treated eye vs. untreated fellow eye	Italy	38	38	38/18	78.5 (6.76)	63.2	Early/intermediate AMD	77.8 letters (treated eyes)	6	LumiThera Valeda	590/660/850	590nm 5; 660nm 65; 850nm 8 mW/cm^2	250	3x/week x 3 wk; 1 series	Untreated fellow eye (observation)	In in (i
Merry et al., 2016 (TORPA II) [34]	Prospective single-arm case series	Canada	24	42	42/0	78 (7.83)	62.5	AREDS 2-4 (31% GA)	86.3 letters	3	Multiwavelength LED (Photospectra)	590/670/790	NR	—	3x/week x 3 wk (9 sessions)	None	P H S
Benlahbib et al., 2023 [35]	Prospective single-center pilot, single-arm	France	20	20	20/0	— (—)	—	Large soft drusen/drusenoid PED	NR	6	LumiThera Valeda	590/660/850	590nm 5; 660nm 65; 850nm 8 mW/cm^2	250	2x/week x 5 wk	None	N d
Küçükerdönmez and Tedford, 2025 [36]	Real-world single-arm cohort	Turkey	27	41	41/0	— (—)	81.5	Early-stage dry AMD	76.5 letters	16	LumiThera Valeda	590/660/850	590nm 5; 660nm 65; 850nm 8 mW/cm^2	250	3x/week x 3-5 wk, q4mo (1-4 series)	None	L
Do et al., 2025 (LIGHTSITE IIIB) [37]	Open-label prospective extension (abstract)	USA	36	63	—/—	— (—)	—	Early/intermediate dry AMD	65-75 letters	5	LumiThera Valeda	590/660/850	590nm 5; 660nm 65; 850nm 8 mW/cm^2	250	4 series q4mo over 13 months	None (historical arms)	L

TABLE 1: Characteristics of the included studies

"In meta-analysis" indicates whether the study contributed to any pooled estimate. The EYE-LIGHT device delivers 590/630 nm and therefore differs from the LumiThera Valeda multiwavelength protocol (590/660/850 nm); this was retained as within-scope photobiomodulation and recorded as an applicability note rather than a GRADE indirectness downgrade

AMD: age-related macular degeneration; AREDS: Age-Related Eye Disease Study severity category; BCVA: best-corrected visual acuity (ETDRS letters); GA: geographic atrophy; NR: not reported; PBM: photobiomodulation; RCT: randomized controlled trial; BL: baseline; M: month; NA: not applicable; NR: not reported; PBM: photobiomodulation; q4mo: every four months; Tx: treatment; wk: week; SD: standard deviation; PED: pigment epithelial detachment; LED: light-emitting diode

Risk of Bias and Quality Assessment

The risk of bias for the four RCTs was appraised using the RoB 2 tool (Figures *2*-*3*). Three of the four RCTs were judged to be at an overall high risk of bias [16,17,32], while LIGHTSITE III [15,31] was rated as having some concerns. The primary drivers of bias across the evidence base were missing outcome data (Domain 3) and the selection of reported results (Domain 5). When weighted by the number of randomized eyes, 63% of the pooled evidence originated from trials with a high risk of bias.

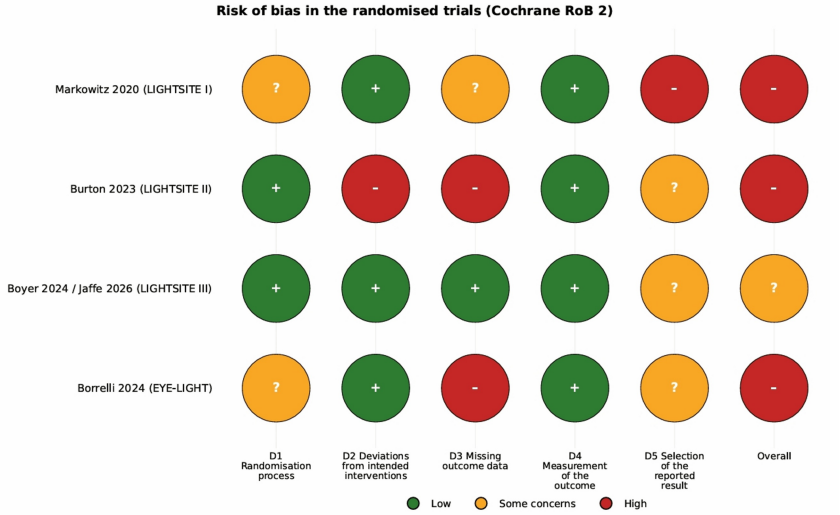


FIGURE 2: RoB 2 traffic-light plot for the four randomized trials

Each row is a trial, and each column is a RoB 2 domain, with the final column showing the overall judgement. Green (+) denotes low risk of bias, yellow (?) denotes some concerns, and red (−) denotes high risk of bias. Three of the four trials [16,17,32] are at overall high risk of bias, and one [15,31] is at some concerns; no trial is at overall low risk of bias

RoB 2: Cochrane Risk of Bias 2

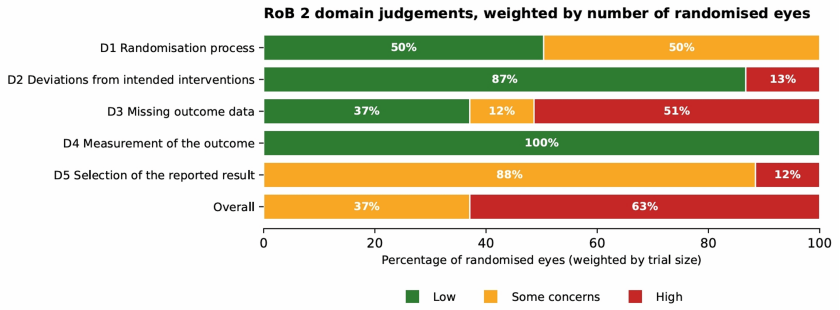


FIGURE 3: RoB 2 weighted summary plot

Domain-level judgements are weighted by the number of randomized eyes in each trial. The weakest domains are D3 (missing outcome data; 51% of randomized eyes in trials judged high risk) and D5 (selection of the reported result; 88% at some concerns or worse). Measurement of the outcome (D4) is at low risk across 100% of randomized eyes, reflecting consistent use of masked assessors and independent reading centers. Overall, 63% of randomized eyes are contributed by trials at high risk of bias

RoB 2: Cochrane Risk of Bias 2

For the non-randomized comparative study [33], the ROBINS-I tool indicated a serious overall risk of bias, driven by baseline confounding and unmasked outcome measurement (Figure *4*). The four uncontrolled, single-arm studies were graded as having a critical risk of bias due to the absence of a concurrent comparator to account for the natural progression of AMD; consequently, these were restricted to narrative synthesis and excluded from all pooled estimates.

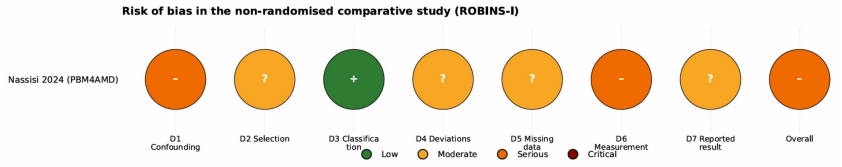


FIGURE 4: ROBINS-I traffic-light plot for the non-randomized comparative study

Colors denote low (green), moderate (yellow), serious (orange), and critical (red) risk of bias. Serious risk arises from confounding (D1) and from measurement of the outcome (D6), the latter because neither participants nor assessors were masked [33]

ROBINS-I: Risk of Bias in Non-randomized Studies of Interventions

Efficacy Outcomes

Best-corrected visual acuity (BCVA): The effect of PBM on BCVA was stratified according to the follow-up duration. At short-term follow-up (< 12 months), the pooled meta-analysis of four RCTs (215 PBM-treated vs. 150 sham-treated eyes) demonstrated a statistically significant improvement in BCVA favoring PBM, with an MD of +1.44 ETDRS letters (95% CI: 0.12 to 2.76; p = 0.040). No statistical heterogeneity was detected (I^2 = 0%, τ^2 = 0) (Figure 5).

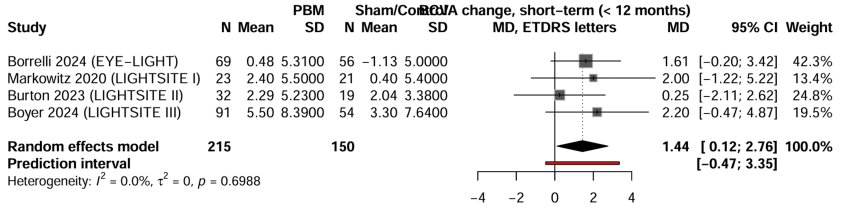


FIGURE 5: Forest plot: change in BCVA at short-term follow-up (< 12 months)

Random-effects meta-analysis of four randomized trials [15-17,32] contributing 215 photobiomodulation-treated and 150 sham-treated eyes. The pooled mean difference favors photobiomodulation by 1.44 ETDRS letters (95% CI: 0.12 to 2.76; p = 0.040), with no statistical heterogeneity (I^2 = 0.0%, τ^2 = 0, p = 0.699). The prediction interval (−0.47 to 3.35) includes no effect, and the pooled estimate lies well below the conventional five-letter minimum clinically important difference. Squares are study estimates sized by weight; horizontal lines are 95% CIs; the diamond is the pooled estimate, and the bar beneath it is the prediction interval

BCVA: best-corrected visual acuity; PBM: photobiomodulation; SD: standard deviation; MD: mean difference; CI: confidence interval

At long-term follow-up (≥ 12 months), pooling data from two RCTs (114 PBM vs. 74 sham eyes) yielded a non-significant MD of +1.59 ETDRS letters (95% CI: -13.28 to 16.46; p = 0.404) (Figure 6).

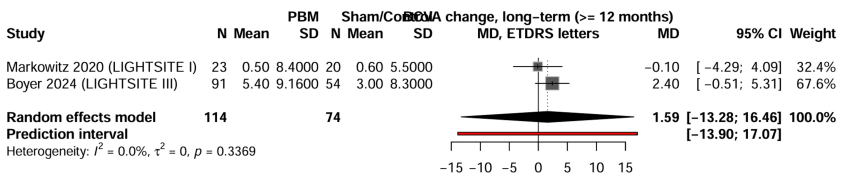


FIGURE 6: Forest plot: change in BCVA at long-term follow-up (≥ 12 months)

Random-effects meta-analysis of two randomized trials [15,16] contributing 114 photobiomodulation-treated and 74 sham-treated eyes. The pooled mean difference is 1.59 ETDRS letters (95% CI: −13.28 to 16.46; p = 0.404). The very wide interval reflects the Hartung–Knapp correction applied to only two studies rather than genuine between-study disagreement (I^2 = 0.0%, p = 0.337); the uncorrected random-effects interval is −0.80 to 3.98. LIGHTSITE I shows complete waning of the treatment effect by month 12, whereas LIGHTSITE III shows a sustained gain

BCVA: best-corrected visual acuity; PBM: photobiomodulation; SD: standard deviation; MD: mean difference; CI: confidence interval

Subgroup analysis comparing short- and long-term effects revealed no significant difference in the

magnitude of the treatment effect between time points ($\chi^2 = 0.01$, p = 0.904) (Figure 7).

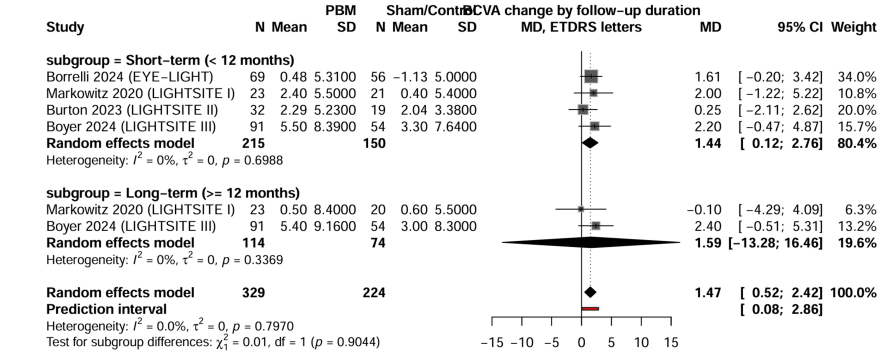


FIGURE 7: Forest plot with subgroup analysis: change in BCVA by follow-up duration (short-term < 12 months versus long-term ≥ 12 months)

The test for subgroup differences is not significant (χ^2_1 = 0.01, df = 1, p = 0.904), providing no evidence that the magnitude of the visual-acuity effect differs between short-term and long-term follow-up. Overall heterogeneity is absent (I^2 = 0.0%, τ^2 = 0, p = 0.797). Because LIGHTSITE I [16] and LIGHTSITE III [15,31] contribute to both subgroups, the subgroup comparison is not independent and is presented as exploratory

BCVA: best-corrected visual acuity; PBM: photobiomodulation; SD: standard deviation; MD: mean difference; CI: confidence interval

A categorical responder analysis examining the proportion of eyes gaining ⩾ 5 ETDRS letters revealed a statistically significant benefit favoring PBM. Across four RCTs (201 eyes treated with PBM vs. 144 sham eyes), PBM treatment was associated with a nearly three-fold increase in the likelihood of achieving a ⩾ 5-letter gain (RR, 2.77; 95% CI: 2.08 to 3.68; p = 0.0015), with no observed heterogeneity (I^2 = 0%) (Figure 8). Excluding the LIGHTSITE II full-protocol subgroup gave an RR of 2.84 (95% CI: 1.86 to 4.32; p = 0.0087). Also, excluding LIGHTSITE I, whose responder data came from a post-hoc stratification at month one, gave an RR of 2.72 (95% CI: 0.78 to 9.43; p = 0.062), with the wide interval reflecting the HKSJ correction applied to two studies.

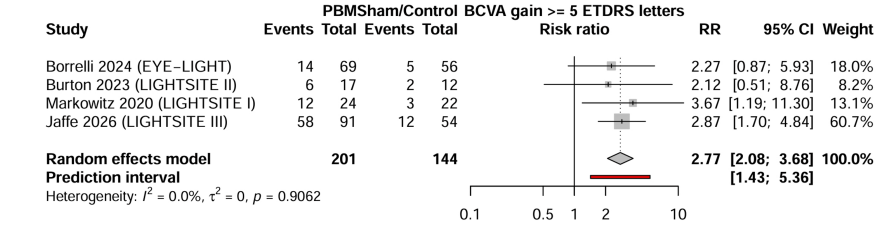


FIGURE 8: Forest plot: proportion of eyes gaining ≥ 5 ETDRS letters

Random-effects meta-analysis of four randomized trials [16,17,31,32] contributing 201 photobiomodulation-treated and 144 sham-treated eyes. The pooled risk ratio is 2.77 (95% CI: 2.08 to 3.68; p = 0.0015) with no heterogeneity (I^2 = 0.0%, τ^2 = 0, p = 0.906) and all four point estimates favoring photobiomodulation. LIGHTSITE III contributes 60.7% of the weight at its 24-month time point; restricting the analysis to that trial alone gives log-RR 1.054 (0.531 to 1.576), leaving the direction and significance unchanged

PBM: photobiomodulation; BCVA: best-corrected visual acuity; RR: risk ratio; CI: confidence interval

Macular drusen volume: Changes in macular drusen volume were pooled as SMDs due to variations in OCT platforms and measurement scales across the three RCTs (189 PBM vs. 141 sham eyes). The pooled SMD was -0.18 (95% CI: -0.42 to 0.06; p = 0.081) (Figure 9). While directionally favoring PBM (indicating a greater reduction in drusen volume), this finding was not statistically significant.

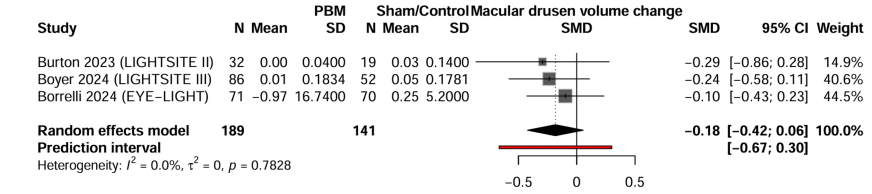


FIGURE 9: Forest plot: change in macular drusen volume

Random-effects meta-analysis of three randomized trials [15,17,32] contributing 189 photobiomodulation-treated and 141 sham-treated eyes, pooled as a standardized mean difference because drusen volume was measured on non-comparable optical coherence tomography platforms and scales (arm-level standard deviations range from 0.04 to 16.74 mm³). The pooled SMD is −0.18 (95% CI: −0.42 to 0.06; p = 0.081), directionally favoring photobiomodulation but compatible with no effect. A negative SMD indicates a greater reduction in drusen volume with photobiomodulation

PBM: photobiomodulation; SD: standard deviation; SMD: standardized mean difference; CI: confidence interval

Contrast sensitivity: A meta-analysis of contrast sensitivity from two RCTs (123 PBM vs. 73 sham eyes) showed no significant difference between the intervention and sham groups (MD: -0.06 log units; 95% CI: -0.72 to 0.59; p = 0.435). This outcome exhibited substantial heterogeneity (I^2 = 65.7%, p = 0.088), likely attributable to the use of different testing charts and distances between trials (Figure *10*).

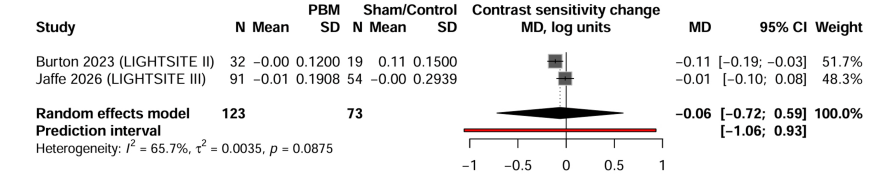


FIGURE 10: Forest plot: change in contrast sensitivity

Random-effects meta-analysis of two randomized trials [17,31] contributing 123 photobiomodulation-treated and 73 sham-treated eyes. The pooled mean difference is −0.06 log units (95% CI: −0.72 to 0.59; p = 0.435) with substantial heterogeneity (I^2 = 65.7%, τ^2 = 0.0035, p = 0.088). The two trials used different charts and tested distances (Mars versus FACT), which is the most likely source of the divergence; the pooled estimate should therefore be regarded as uninformative rather than as evidence of harm

PBM: photobiomodulation; SD: standard deviation; MD: mean difference; CI: confidence interval

Safety Outcomes and Disease Progression

Ocular adverse events: The relative risk of experiencing any ocular adverse event (AE) did not differ significantly between the PBM and sham interventions (RR: 0.87; 95% CI: 0.39 to 1.97; p = 0.627). However, substantial heterogeneity was observed (I^2 = 55.4%), driven by discordant effect directions between studies (e.g., AEs were more frequent in the sham arm of the EYE-LIGHT trial but more frequent in the PBM arm of LIGHTSITE I) (Figure *11*). Narrative safety synthesis confirmed no definitive signs of phototoxicity attributable to multiwavelength PBM in any of the included studies.

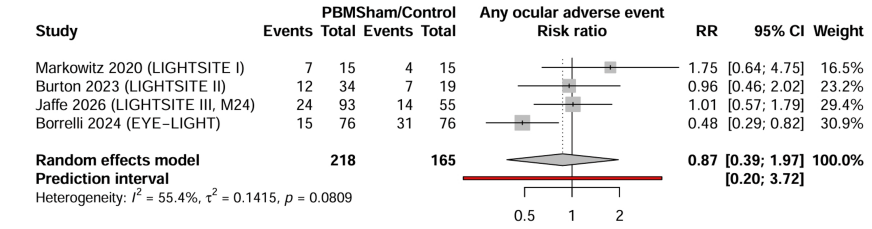


FIGURE 11: Forest plot: any ocular adverse event

Random-effects meta-analysis of four randomized trials [16,17,31,32] contributing 218 photobiomodulation-treated and 165 sham-treated eyes. The pooled risk ratio is 0.87 (95% CI: 0.39 to 1.97; p = 0.627) with substantial heterogeneity (I² = 55.4%, τ² = 0.1415, p = 0.081). Effect directions are discordant: adverse events were more frequent in the sham arm of EYE-LIGHT (RR: 0.48, 0.29 to 0.82) and more frequent in the photobiomodulation arm of LIGHTSITE I (RR: 1.75, 0.64 to 4.75). Adverse-event definitions and denominators (eyes versus subjects) are not harmonized across trials

PBM: photobiomodulation; RR: risk ratio; CI: confidence interval

Conversion to neovascular AMD and incident geographic atrophy: There was no significant difference in the risk of progression to neovascular (wet) AMD between the PBM and sham groups across the four RCTs (RR: 1.11; 95% CI: 0.16 to 7.41; p = 0.878), with low heterogeneity (I^2 = 2.5%) (Figure *12*).

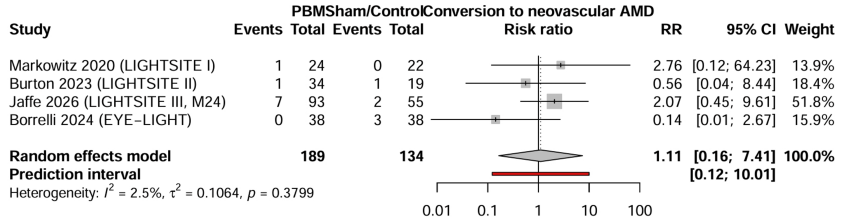


FIGURE 12: Forest plot: conversion to neovascular age-related macular degeneration

Random-effects meta-analysis of four randomized trials [16,17,31,32] contributing 189 photobiomodulation-treated and 134 sham-treated eyes, with only 15 events in total. The pooled risk ratio is 1.11 (95% CI: 0.16 to 7.41; p = 0.878; I² = 2.5%). The interval is compatible with both appreciable benefit and appreciable harm. The numerical imbalance in LIGHTSITE III (7/93 versus 2/55) is confounded by an approximately three-fold higher prevalence of high-risk fellow eyes in the photobiomodulation arm at baseline

PBM: photobiomodulation; AMD: age-related macular degeneration; RR: risk ratio; CI: confidence interval

Incident geographic atrophy was reported comparatively in only one large trial [31], which demonstrated a statistically significant reduction in the risk of developing new geographic atrophy among PBM-treated eyes at 24 months (RR: 0.29; 95% CI: 0.11 to 0.72; p = 0.0076) (Table *2*).

Outcome	Studies (k)	Units analyzed (eyes)	Design	Starting certainty	Effect measure	Effect (95% CI)	P	I² (%)	tau²	95% prediction interval
BCVA change, short-term (< 12 months)	4	365	Randomized trials	High	MD	1.44 (0.12 to 2.76)	0.0403	0	0	1.44 (-0.47 to 3.35)
BCVA change, long-term (≥ 12 months)	2	188	Randomized trials	High	MD	1.59 (-13.28 to 16.46)	0.404	0	0	1.59 (-13.90 to 17.07)
Proportion gaining ≥ 5 ETDRS letters	4	345	Randomized trials	High	RR	2.77 (2.08 to 3.68)	0.0015	0	0	2.77 (1.43 to 5.36)
Macular drusen volume change	3	330	Randomized trials	High	SMD	-0.18 (-0.42 to 0.06)	0.0813	0	0	-0.18 (-0.67 to 0.30)
Contrast sensitivity change	2	196	Randomized trials	High	MD	-0.063 (-0.717 to 0.591)	0.4347	65.7	0.0035	-0.06 (-1.06 to 0.93)
Any ocular adverse event	4	383	Randomized trials	High	RR	0.87 (0.39 to 1.97)	0.6268	55.4	0.1415	0.87 (0.20 to 3.72)
Conversion to neovascular AMD	4	323	Randomized trials	High	RR	1.11 (0.16 to 7.41)	0.8775	2.5	0.1063	1.11 (0.12 to 10.01)
Incident geographic atrophy	1	137	Randomized trials	High	RR	0.29 (0.11 to 0.72)	0.0076	—	0	—

TABLE 2: Full GRADE evidence profile: quantitative summary

Effect estimates are presented on the reporting scale (risk ratios back-transformed from the log scale). Units analyzed are eyes. A prediction interval is not estimable for the single-study geographic-atrophy outcome

GRADE: Grading of Recommendations Assessment, Development, and Evaluation; CI: confidence interval; BCVA: best-corrected visual acuity; MD: mean difference; RR: risk ratio; SMD: standardized mean difference; AMD: age-related macular degeneration

Sensitivity Analyses and Certainty of Evidence (GRADE)

The robustness of the primary findings was rigorously tested. Leave-one-out influence analyses revealed that the statistical significance of the short-term BCVA improvement was fragile; omission of any single trial (except LIGHTSITE II) caused the pooled estimate to lose nominal significance (p > 0.05).

In contrast, the ≥ 5-letter responder effect remained statistically significant in every leave-one-out iteration.

Baujat and Drapery plots confirmed these observations, showing wide prediction intervals encompassing the null effect for continuous visual acuity changes (Figures *13*-*14*).

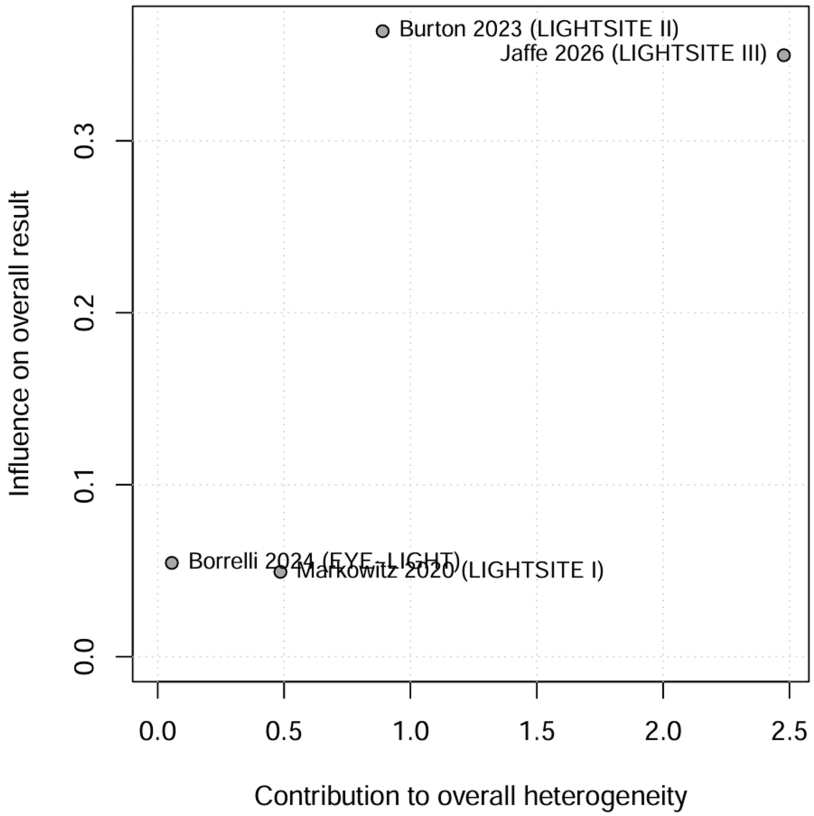


FIGURE 13: Baujat plot: contribution to heterogeneity versus influence on the pooled result for BCVA change at longest follow-up

The horizontal axis is each trial's contribution to overall heterogeneity (squared Pearson residual), and the vertical axis is its influence on the pooled estimate. Studies in the upper-right quadrant are simultaneously the most heterogeneous and the most influential. Burton 2023 [17] and Jaffe 2026 [31] occupy that quadrant, while Borrelli 2024 [32] and Markowitz 2020 [16] sit close to the origin. This is consistent with the leave-one-out analysis, in which omitting Jaffe 2026 lowers the pooled estimate from 1.39 to 0.98 letters and omitting Burton 2023 raises it to 1.86 letters

BCVA: best-corrected visual acuity

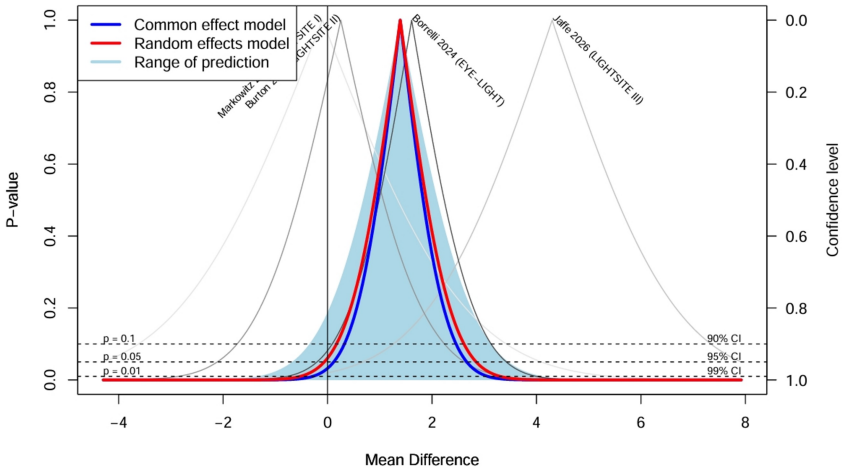


FIGURE 14: Drapery plot: p-value function for BCVA change at longest follow-up

Each curve maps candidate values of the mean difference to their p- values, so that a horizontal slice at any confidence level reads off the corresponding interval; the horizontal reference lines mark p = 0.10, 0.05, and 0.01. The plot shows the common-effect and random-effects curves together with the range of prediction, making explicit that a wide band of effect sizes spanning zero, including values below the five-letter minimum clinically important difference, remains compatible with the data

BCVA: best-corrected visual acuity

Adjusting for intra-patient correlations (clustering of two eyes within the same patient) at varying Intraclass Correlation Coefficients (ICCs) further attenuated the short-term BCVA results to non-significance at assumed ICCs of 0.5 (MD: 1.37; 95% CI: −0.03 to 2.77; p = 0.053) and 0.8 (MD: 1.34; 95% CI: −0.09 to 2.76; p = 0.059), whereas the categorical responder outcome remained robust regardless of the assumed ICC (Table *3*).

Outcome	Assumed ICC	Mean design effect	Adjusted estimate	95% CI	P	Statistically significant
BCVA change, short-term (< 12 months)	0	1	1.4402	0.1194 to 2.761	0.0403	Yes
BCVA change, short-term (< 12 months)	0.2	1.124	1.4097	0.0518 to 2.7675	0.0456	Yes
BCVA change, short-term (< 12 months)	0.5	1.311	1.3703	-0.0278 to 2.7684	0.0525	No
BCVA change, short-term (< 12 months)	0.8	1.498	1.3372	-0.0894 to 2.7638	0.0585	No
BCVA change, long-term (≥ 12 months)	0	1	1.5894	-13.2798 to 16.4586	0.4040	No
BCVA change, long-term (≥ 12 months)	0.2	1.128	1.5682	-13.3993 to 16.5357	0.4101	No
BCVA change, long-term (≥ 12 months)	0.5	1.321	1.5438	-13.5302 to 16.6178	0.4171	No
BCVA change, long-term (>= 12 months)	0.8	1.513	1.5254	-13.6244 to 16.6751	0.4224	No
Proportion gaining ≥ 5 ETDRS letters	0	1	1.0189	0.7341 to 1.3036	0.0015	Yes
Proportion gaining ≥ 5 ETDRS letters	0.2	1.124	1.0195	0.7313 to 1.3076	0.0015	Yes
Proportion gaining >= 5 ETDRS letters	0.5	1.311	1.0195	0.7269 to 1.3121	0.0016	Yes
Proportion gaining >= 5 ETDRS letters	0.8	1.498	1.019	0.7227 to 1.3154	0.0016	Yes
Contrast sensitivity change	0	1	-0.063	-0.7173 to 0.5907	0.4347	No
Contrast sensitivity change	0.2	1.095	-0.064	-0.7177 to 0.5889	0.4289	No
Contrast sensitivity change	0.5	1.239	-0.066	-0.7179 to 0.5856	0.4201	No
Contrast sensitivity change	0.8	1.382	-0.068	-0.7173 to 0.5816	0.4112	No

TABLE 3: Unit-of-analysis sensitivity: effect of adjusting for the correlation between two eyes of the same patient

ICC: intraclass correlation coefficient; CI: confidence interval; BCVA: best-corrected visual acuity

The certainty of the evidence for all outcomes was evaluated using the GRADE framework (Table 4). The certainty of evidence for the proportion of eyes gaining ≥ 5 ETDRS letters and incident geographic atrophy was rated as low. The evidence for all other critical outcomes, including short- and long-term BCVA change, macular drusen volume change, contrast sensitivity, and adverse events, was rated as very low, driven by serious downgrades for risk of bias, inconsistency across testing modalities, and severe imprecision due to small sample sizes that failed to meet optimal information size thresholds.

Outcome	Studies (k)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty	Rationale
BCVA change, short-term (< 12 months)	4	RCTs	Serious (-1)	Serious (-1)	Not serious	Serious (-1)	Publication bias undetected (k < 10, not assessable)	Very low	Downgraded for risk of bias (3 of 4 trials High overall on RoB 2), inconsistency, and imprecision (CI crosses the 5-letter MCID and, with HKSJ, the null)
BCVA change, long-term (≥ 12 months)	2	RCTs	Serious (-1)	Serious (-1)	Not serious	Very serious (-2)	Publication bias undetected (k < 10, not assessable)	Very low	Only 2 trials with divergent results (LIGHTSITE I showed complete waning at M12; LIGHTSITE III showed a sustained gain); very wide HKSJ interval with k = 2
Proportion gaining ≥ 5 ETDRS letters	4	RCTs	Serious (-1)	Not serious	Not serious	Serious (-1)	Publication bias undetected (k < 10, not assessable)	Low	Consistent direction across all 4 trials, but events are few and one trial contributes a post-hoc full-protocol subgroup
Macular drusen volume change	3	RCTs	Serious (-1)	Not serious	Serious (-1)	Serious (-1)	Publication bias undetected (k < 10, not assessable)	Very low	Drusen volume is a surrogate endpoint of uncertain patient-importance; measurement scales are not comparable across devices; one SD imputed
Contrast sensitivity change	2	RCTs	Serious (-1)	Serious (-1)	Not serious	Very serious (-2)	Publication bias undetected (k < 10, not assessable)	Very low	Only 2 trials, different charts (Mars vs FACT) and distances; both point estimates near null with very wide intervals
Any ocular adverse event	4	RCTs	Serious (-1)	Serious (-1)	Not serious	Serious (-1)	Publication bias undetected (k < 10, not assessable)	Very low	Direction of effect is inconsistent (adverse events were more frequent in the sham arm of the EYE-LIGHT trial); definitions and denominators (eyes vs subjects) differ
Conversion to neovascular AMD	4	RCTs	Serious (-1)	Not serious	Not serious	Very serious (-2)	Publication bias undetected (k < 10, not assessable)	Very low	Very few events; the LIGHTSITE III imbalance is confounded by a 3-fold higher prevalence of high-risk fellow eyes in the PBM arm
Incident geographic atrophy	1	RCTs	Not serious	Not applicable (k = 1)	Not serious	Serious (-1)	Publication bias undetected (k < 10, not assessable)	Low	Single trial, but a large and consistent effect at both M13 and M24 with a plausible dose-response over time; not downgraded for inconsistency

TABLE 4: GRADE certainty-of-evidence summary

All evidence starts at high certainty because every contributing study is a randomized trial. “−1” and “−2” indicate the number of levels downgraded in each domain. Publication bias could not be assessed because fewer than 10 studies contributed to every outcome; funnel-plot asymmetry and Egger's test are uninformative at this k

GRADE: Grading of Recommendations Assessment, Development, and Evaluation; BCVA: best-corrected visual acuity; RCT: randomized controlled trial; RoB 2: Cochrane Risk of Bias 2; CI: confidence interval; MCID: minimally clinically important difference; HKSJ: Hartung-Knapp-Sidik-Jonkman; SD: standard deviation; AMD: age-related macular degeneration; PBM: photobiomodulation

Discussion

This systematic review and meta-analysis synthesized clinical evidence regarding the efficacy and safety of multiwavelength PBM for nonexudative AMD. Our quantitative analysis of four RCTs highlights the nuanced therapeutic profile. While pooled continuous measures of BCVA demonstrated a statistically significant short-term benefit (+1.44 ETDRS letters), our rigorous sensitivity analyses, including adjustments for intra-patient correlation (ICC ⩾ 0.5) and leave-one-out iterations, revealed that this continuous outcome was highly fragile and driven by specific trials. The post-hoc categorical responder analysis gave the most consistent finding of this study: PBM-treated eyes were nearly three times more likely to achieve a clinically meaningful visual gain of five ETDRS letters (RR: 2.77; 95% CI: 2.08-3.68) compared to sham-treated eyes.

Reductions in macular drusen volume trended in favor of PBM but did not reach statistical significance. Evidence from the largest included trial with the longest follow-up (LIGHTSITE III) demonstrated a significant 71% relative risk reduction in the development of incident geographic atrophy at 24 months [31]. Furthermore, PBM exhibited a highly favorable safety profile, and a meta-analysis confirmed no increased risk of overall ocular adverse events or conversion to neovascular (wet) AMD. However, applying the GRADE framework, the overall certainty of the evidence was judged to be low to very low, constrained by the high risk of bias in three of the four RCTs, manufacturer funding across all trials, and imprecision inherent to the small cumulative sample sizes.

The observed categorical visual improvements and potential delay in geographic atrophy progression align

with the established preclinical mechanisms of PBM. As RPE undergoes age-related mitochondrial decline, the cellular capacity to clear oxidative debris diminishes, accelerating apoptosis [6,8]. PBM, particularly within the 590-850 nm spectrum, penetrates the retinal tissue to selectively photoactivate cytochrome c oxidase [12]. This cascade elevates ATP production, normalizes the NADH/FAD redox ratio, and mitigates the pathological accumulation of ROS [13,14]. The categorical functional benefits observed in our analysis may reflect the rescue of dormant, hypometabolic photoreceptors situated on the perimeter of advancing drusen or nascent atrophy rather than the regeneration of already apoptotic cells. This rescue mechanism underscores the importance of early intervention in intermediate dry AMD, particularly when RPE cells retain sufficient mitochondrial integrity to respond to photobiomodulation.

Our findings provide methodological advancements over those of previously published meta-analyses. Earlier reviews by Henein and Steel [18] and Chen et al. [19] highlighted the transient nature of PBM's benefits and reported non-significant effects on continuous BCVA and anatomical outcomes in patients with diabetes. While our primary continuous BCVA estimates confirm this modest effect, our categorical five-letter responder analysis provides a more clinically relevant metric that has previously been underreported. In degenerative diseases like AMD, where the natural history dictates a progressive loss of approximately 2.5 letters per year [39], preventing decline or achieving a five-letter gain is a profound clinical success.

Furthermore, prior meta-analyses often utilized standard DerSimonian-Laird random-effects models, which are known to produce falsely narrow confidence intervals and inflated Type I error rates when the number of included studies is small ($k < 10$) [28]. By employing HKSJ variance correction, our meta-analysis provides highly conservative, statistically robust intervals. In addition, we approximated the effect of the unit-of-analysis problem, where binocular data from a single patient are treated as statistically independent. By deflating effective sample sizes using various ICCs, we demonstrated that the continuous BCVA benefit is highly sensitive to intra-eye clustering, whereas the five-letter responder benefit remains statistically robust, regardless of the assumed ICC.

The primary strength of this study was its methodological and statistical rigor. We adhered to the Cochrane guidelines, employed the HKSJ adjustment for small meta-analyses, and mapped the boundaries of statistical fragility using Baujat plots, drapery plots, and leave-one-out sensitivity models. Finally, the integration of a rigorous GRADE assessment provides clear directives for guideline developers.

This review has several notable limitations. First, the available evidence base is small, relying on only four RCTs for quantitative synthesis. Second, the methodological quality of the included RCTs raises significant concerns. Three of the four trials were graded as having a high risk of bias, due to high attrition rates, differential missing data, and the post-hoc selection of reported results or responder subgroups [16,17,32]. Third, 100% of all pooled RCT evidence originated from industry-sponsored trials, which elevated the risk of funding bias. Fourth, there was substantial heterogeneity in the design of the sham comparators across studies; while some trials utilized an inactive light source [32], others utilized a 100-fold reduced fluence of active wavelengths [16,17], which may still induce sub-therapeutic biological effects (hormesis) and confound the true magnitude of the treatment effect. Fifth, the patient was the unit of randomization and the eye the unit of analysis; without individual patient data, clustering could only be approximated by a design effect at assumed ICCs. Sixth, EYE-LIGHT contributed its interim four-month data to the pooled analyses; its 12-month report [39] is summarized narratively and points in the same direction.

For clinicians, multiwavelength PBM represents a safe, non-invasive adjunctive therapy that may offer meaningful categorical visual improvements and potentially alter the trajectory of geographic atrophy in carefully selected patients with early-to-intermediate dry AMD. However, patients must be counseled appropriately regarding the modest overall mean improvements and the necessity of repeated ongoing treatment cycles to maintain bioenergetic benefits.

For researchers, PBM literature demands a pivot toward methodological rigor. Future RCTs must prioritize independent, non-industry funding to establish unbiased efficacy profiles; large, multicenter designs adequately powered to assess long-term (24 months) anatomical endpoints, such as GA progression; the use of true, biologically inert sham controls to avoid confounding by sub-threshold light exposure; and adherence to intention-to-treat (ITT) principles with robust strategies to manage missing data.

Conclusions

Multiwavelength PBM is a biologically plausible, safe, and potentially effective intervention for nonexudative AMD. In a post-hoc analysis, it increased the probability of achieving clinically meaningful visual gains (≥ 5 ETDRS letters) and shows promise in reducing the incidence of GA. However, the continuous visual and anatomical benefits remain modest and are statistically fragile. Given the low to very low certainty of evidence driven by high risks of bias and small sample sizes, multiwavelength PBM should be viewed as a promising but still emerging modality. Rigorous, large-scale, independently funded clinical trials are imperative to conclusively establish long-term efficacy and solidify its role in standard ophthalmic care.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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