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LETTER

Letter to the Editor Regarding "Safety, Tolerability, and Short-Term Efficacy of Low-Level Light Therapy for Dry Age-Related Macular Degeneration"

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Dear Editor,

We read with interest the article titled "Safety, Tolerability, and Short-Term Efficacy of Low-Level Light Therapy for Dry Age-Related Macular Degeneration" by authors Borrelli et al. [1]. We are excited to see photobiomodulation (PBM) as a treatment for ocular diseases like age-related macular degeneration (AMD). The field of PBM has gathered much interest over the past few years with recent excitement seen in the ophthalmology arena. PBM is complicated as different treatment and performance parameters can be modified for wavelength, waveform specifications, and treatment protocols, which can have differential effects on anatomical and clinical outcomes. Therefore, experts in the PBM field have raised a call to action to better ensure standardized reporting on the devices and the subsequent knowledge gained in PBM research. The current study utilizes the EYE-LIGHT® device (Espansione Group, Funo, Italy) which employs two wavelengths; 590 nm (yellow) and 630 nm (red). While the wavelengths and treatment protocol are provided, other key device parameters for the treatment modality are not included and must be disclosed. Notably, the power and energy density of the wavelengths—key parameters necessary to evaluate any PBM treatment—are not provided. In addition, the study included a sham mode which was assumed at < 30% of the standard output and stated to have no biological effect on target tissues. The sham mode should exhibit a uniform reduction and data should be provided demonstrating that this reduction indeed has no biological effect. Other studies that have employed low dose PBM and sham-controlled designs have published clinical benefit in these modes [2, 3]. Further information is necessary for researchers and clinicians to evaluate the methodology of the treatment modes in the study.

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The primary outcome is stated as the evaluation of the safety, tolerability, and compliance outcomes of patients. It is unclear why efficacy of the treatment is not a primary endpoint as no published data exists for this device as promoted for treatment of dry AMD. In terms of efficacy for this device to impact vision, the reported results do not appear compelling. An average change in best-corrected visual acuity (BCVA) at the predetermined timepoint of 4 months shows < 1 letter change (0.48 letters) in the PBM-treated group and approximately a 1-letter loss in the sham group ($p > 0.05$). This was statistically insignificant and is clinically not meaningful. The delta between treatment groups (< 2 letters) is stated as being significant ($p = 0.026$) but the < 2 letter change raises concerns regarding what is clinically meaningful in this population of earlier to intermediate stage patients with mild visual acuity deficits. Additionally, the authors state that a significantly higher percentage of patients in the PBM group gained five or more letters (one-line improvement or better) compared to the sham group (20.3% vs. 8.9%, respectively; $p = 0.043$), however; the average change in the PBM group is only 0.48 letters. This signals that a large proportion of PBM-treated eyes also lost vision. This data should be discussed and presented for transparency.

The study also analyzed anatomical outcomes including drusen volume and states that mean drusen volume increased significantly from baseline to month 4 in the sham group ($p = 0.048$), while a nonsignificant reduction was found in the PBM group ($p = 0.10$). The absolute values provided for drusen volume as baseline and month 4 timepoints are not possible as measured via optical coherence tomography (OCT) in either sham or PBM groups (baseline values: PBM, 36.18 mm^3; sham, 23.21 mm^3). Whether it is a miscalculation or something that was not conventionally reported, values of drusen volume from several papers are at odds with what is reported in this publication. For reference, a prospective observational study in early/intermediate AMD (Age-Related Eye Disease Study [AREDS] categories 2 and 3) designed to evaluate drusen volume development over time reports a mean drusen volume of 0.17 mm^3 via gradings from 24,000 individual B-scans [4]. In addition, the LIGHTSITE I, II, and III studies, which also evaluated the effects of PBM in patients with dry AMD, report drusen volume baseline values between 0.58 and 0.941 mm^3 in PBM treatment groups [2, 5, 6]. The reported numbers for drusen volume values in the current study are over 25 times higher than other studies which have analyzed similar patient populations for drusen volume and warrant investigation into the data. This is also similar for the reported values for drusen thickness measurements. Along these lines, it is stated that 76 subjects and 152 eyes were evaluated in this interim (4-month) analysis. The results presented in Table 2 by Borrelli et al. [1] show only a total of 125 eyes evaluated for BCVA, 113 eyes evaluated for central subfield thickness (CST), and 141 eyes evaluated for mean drusen volume (MDV). The authors state that all patients (100%) of both the sham and PBM groups were fully compliant and only 3 patients were withdrawn from the study, so it is unclear why so many eyes (up to 39 eyes) are removed from outcome analyses at the 4-month timepoint.

With enthusiasm mounting for the utility of PBM in dry AMD, it is critical that investigators demonstrate transparency and accuracy in reporting of trial findings and device specifications. Over enthusiastic statements on the impact of new devices in this field detract from science-founded conclusions that should drive the acceptance of these novel technologies into the clinic.

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Declarations

Conflict of Interest. Albert J. Augustin and Michael Koss have nothing to disclose.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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