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Low-Level Nighttime Light Therapy for Age-Related Macular Degeneration: A Randomized Clinical Trial

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Purpose. To investigate the safety, acceptability, and effectiveness of light therapy on the progression of AMD over 12 months.

Methods. This was a phase I/IIa, prospective, proof-of-concept, single-center, unmasked randomized controlled trial. Sixty participants (55 to 88 years) with early AMD in the study eye and neovascular AMD (nAMD) in the fellow eye were recruited from a hospital nAMD clinic. Eligible participants were randomized (ratio 1:1) to receive light therapy or to an untreated control group. Light therapy was delivered via a light-emitting mask (peak 505 nm, 23 scotopic Td), which was worn each night for 12 months. Co-primary outcome measures were disease progression (onset of nAMD or increased drusen volume beyond test-retest limits) and change in time constant of cone dark adaptation. Other main outcomes included adverse events, compliance, and subjective sleep quality data.

Results. Disease progression over 12 months was seen in 38.1% (18.1%–61.6% confidence interval [CI]) of intervention participants and 48.3% (29.4%–67.5% CI) of controls (Mantel-Haenszel test, common odds ratio = 0.763, $P = 0.495$). A significantly larger delay in cone adaptation was observed in the intervention group (1.66 ± 0.61 minutes) than in the control group (0.66 ± 0.49 minutes) over the follow-up period. No reported adverse events were deemed to be associated with the intervention.

Conclusions. Although acceptable to the patients, light therapy did not have a substantial effect on the progression of early AMD over 12 months. Further investigation is necessary to discover the permanency and cause of the adverse effect of light therapy on dark adaptation.

Keywords: age-related macular degeneration, light therapy, randomized controlled trial

There is a critical need to evaluate potential therapeutic interventions aimed at treating AMD in its early stage before the onset of advanced AMD. The pathogenesis of AMD is not fully understood; however, there is evidence to implicate hypoxia as a factor.[1,2] Animal studies using microelectrodes to measure the in vivo oxygen profile of the macaque retina show that, in a healthy retina, the oxygen tension at the proximal side of dark-adapted photoreceptor inner segments is close to zero.[3,4] This finding has been attributed to maintenance of the "dark current" in the retina's approximately 92 million rods.[5] Pathology-induced anatomic changes, such as disruption of choroidal circulation,[6–8] poor ocular perfusion,[7,8] and changes to Bruch's membrane,[9–11] further exacerbate the situation, placing the retina on a "physiological knife edge." The finding of hypoxia-inducible factor in the outer retina of those with AMD, and the upregulation of VEGF, further support the role of hypoxia in AMD pathogenesis,[12–15] whilst the functional loss seen in patients with AMD[16–21] mirrors that reported in healthy individuals under conditions of simulated hypoxia.[22–26]

If outer retinal hypoxia does have a role in the pathogenesis of AMD, treatments that mitigate this may slow or halt disease progression. One approach would be to prevent full dark adaptation, thereby reducing the oxygen demand.[27] In practice, this could be achieved on a nightly basis by the provision of light therapy. Pilot studies have shown no adverse effects associated with this approach over the course of 12 months in people with diabetes.[27,28] Furthermore, when assessing the effect of light therapy on diabetic macular edema, a reduction in retinal thickness after 3 months[28] and an improvement in functional measures after 6 months[29] were observed. In the present (ALight) trial, we aimed to determine whether low-level nighttime light therapy would provide a similar therapeutic benefit to those with early AMD.

The primary aim was to collect preliminary phase I/IIa proof-of-concept trial data from people with early AMD in one eye and neovascular AMD (nAMD) in the fellow eye, to establish the safety and acceptability of the intervention and assess the treatment effect of light therapy on disease progression in the eye with early AMD.

Methods

Study Design

The methods for the ALight trial are described in detail elsewhere.[30] Briefly, this was a phase I/IIa prospective proof-of-concept, single-center, parallel-group, randomized clinical trial conducted at Bristol Eye Hospital, Bristol, UK. Participants were allocated to the intervention or the untreated control arm of the trial in a 1:1 ratio. Participants randomized to light

4531

Figure 1. Principal components of the OLED sleep mask. The *left panel* shows the light-emitting "pod" of peak output 505 nm. The *right panel* shows the cushioned fabric mask that houses the pod.

therapy wore a Noctura 500 organic light-emitting diode (OLED) mask (PolyPhotonix Medical, Ltd., Sedgefield, UK; see Fig. 1) every night for 12 months.

The trial adhered to the tenets of the Declaration of Helsinki and was approved by the NHS National Research Ethics Committee (13/NW/0609) and the Medicines and Healthcare Products Regulatory Agency. An independent trial steering committee provided oversight of the trial, and acted as a data and safety monitoring committee.

Participants

Full eligibility criteria are available in the study protocol.[30] In brief, participants were between 55 and 88 years with early AMD in the study eye and nAMD in the fellow eye. An Early Treatment of Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA) of 0.3 logMAR or better was required for the study eye and the participant had to be within a month of their third ranibizumab injection in the fellow eye. To improve a lower than projected recruitment rate, an amendment was made to the eligibility criteria 6 months after trial inception to include those who were outside their 3-month ranibizumab loading phase at the time of baseline assessment. Participants were excluded if they had an ocular condition other than macular disease, were taking medication known to affect visual function, had a systemic condition that would compromise participation in a 12-month study, had insufficient English language comprehension to complete the questionnaires, had a cognitive impairment, wore an oxygen mask at night, or were unwilling to adhere to the allocated treatment for the duration of the trial. In addition, a participant's inclusion in the study was suspended if the subject wished to discontinue, exhibited an unexpected change in clinical status, or if a serious adverse event arose (for example, conversion to nAMD in the study eye).

Study Protocol

The study flow diagram in Figure 2 outlines the appointment schedule. Screening assessment involved a standardized examination procedure, including documenting ocular and medical history and current medication, assessment of logMAR BCVA using the ETDRS test chart, and a clinical eye examination. An abridged version of the Mini-Mental State Examination was used to screen for cognitive impairment.[31] Self-reported visual function was also measured using the Veterans Affairs Low Vision Visual Function Questionnaire (VFQ-48),[32] and health-related quality of life with the EuroQol-5D Instrument (EQ-5D).[33]

Procedures conducted at baseline included optical coherence tomography (OCT) imaging (five 6×6-mm macular cube scans; Zeiss Cirrus SD-OCT 4000 [Carl Zeiss Meditec, Inc., Dublin, CA, USA]) to derive drusen volume measurements (within a 5-mm-diameter circle), color fundus photography (30°-diameter images centered on the fovea; Topcon 3D-OCT 2000 [Topcon Medical Systems, Inc., Oakland, NJ, USA]), BCVA measurement (ETDRS number of letters read), chromatic threshold measurement (Color Assessment and Diagnosis Test [CAD],[18] version 2.2.4. [City Occupational Ltd., London, UK]), 14-Hz flicker threshold measurement, dark adaptation assessment (2°-radius solid yellow circular stimulus), and a self-reported sleep quality questionnaire (Pittsburgh Sleep Quality Index [PSQI]).[34] The experimental procedures used for functional tests have been published elsewhere.[17,35] Following baseline data collection and randomization, drusen volume and PSQI data were collected for both study groups on a monthly basis for 12 months. The final visit was the same as the baseline visit with the addition of the VFQ-48 and EQ-5D.

Fundus images were graded according to the Age-Related Eye Disease Study (AREDS) Simplified Severity Scale[36] by two independent graders. Randomization was performed immediately following baseline data collection as described in the study protocol.[30] Briefly, computer-generated random permuted blocks (block size randomly varied among 2, 4, and 6) stratified for AMD severity grade were used to randomize the participants. Each stratum was distributed in three separate piles of sealed, numbered envelopes by the chief investigator. The envelopes belonging to each AMD stratum were used in numerical order by the trial investigator to allocate participants to a study group.

The trial investigator and participants were not masked to the randomization group during this study. It was not possible to mask the trial investigator, as his duties involved not only collecting outcome data, but also providing the intervention light masks as well as instruction on usage, and guidance regarding any issues with the masks throughout the trial. Treating ophthalmologists reviewing participants for ranibizumab injections were masked to the treatment arm to prevent bias in retreatment decisions for the fellow eye.

Intervention

Participants randomized to the intervention arm were given a Noctura 500 OLED mask for nightly usage. When activated via a touch sensor, the light sources emitted a dim green light (peak output 505 nm). When adjusted for the average eye lid transmission (assumed as 1%),[37–39] and pupil diameter (approximately 4 mm in the age group 60–85 years),[40] this equated to a retinal illuminance of approximately 23 scotopic
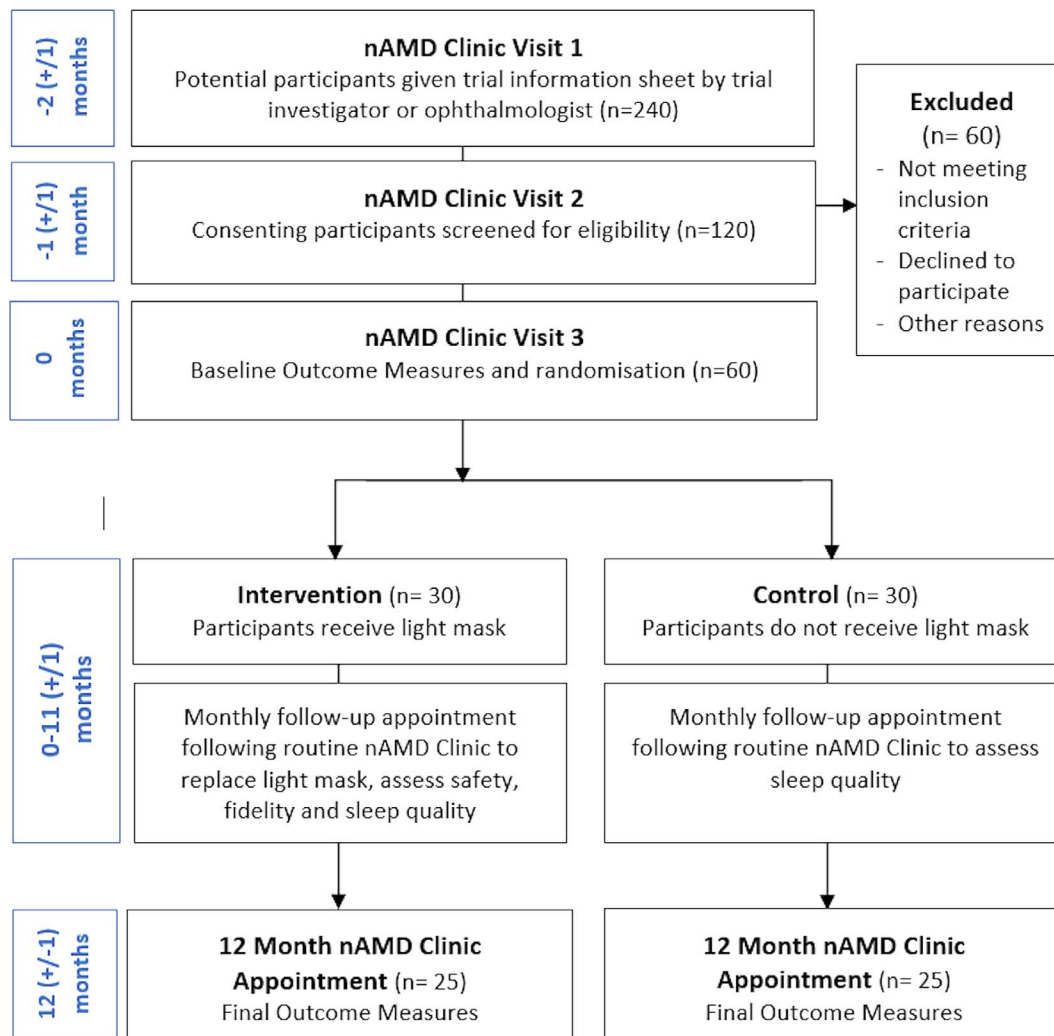
FIGURE 2. Study flow diagram showing participant timeline. It was anticipated that sixty participants would be recruited, who had nAMD and were scheduled for three ranibizumab injections over a 3-month period within the nAMD clinic (nAMD clinic visit 1–3). Participants recruited after the amendment of the protocol did not have to be within the 3-month loading phase to enroll in the trial. Bracketed number of trial information sheets distributed, participants excluded following screening, and participants at the 12-month nAMD clinic appointment show projected figures before trial inception. Adapted from McKeague C, Margrain TH, Bailey C, Binns AM. Low-level night-time light therapy for age-related macular degeneration (ALight): study protocol for a randomized controlled trial. *Trials.* 2014;15:246.

Trolands. This was estimated to reduce the rod-circulating current by 40%, thus diminishing the eye's oxygen requirements.[29] The masks were programmed at the time of issue to function for a maximum of 8 hours within a predetermined time window (20:00 to 10:00). Once activated, the mask would remain lit for the 8-hour treatment period. Compliance data, based on capacitive sensing, were recorded automatically, stored on a chip within the mask, and extracted from the mask monthly. To ensure consistent luminance throughout the trial the light source was replaced every 3 months.

Outcome Measures

The study included two co-primary outcome measures, reflecting structural and functional status: (1) the proportion of people showing disease progression in the eye with early AMD over 12 months based on the onset of advanced AMD or an increase in drusen volume beyond test-retest 95% confidence intervals (95% CIs),[41] and (2) the change in cone τ (time taken for cone photoreceptors to recover their sensitivity to approximately 63% of the pre-bleach value after being exposed

to a bright adapting light). Outcome measures used to assess the safety and acceptability of the intervention included 12-month objective mask compliance data, change in self-reported sleep disturbance (PSQI), and adverse events related to the intervention. Secondary outcome measures included the 12-month change in drusen volume. chromatic threshold, BCVA ETDRS number of letters read, flicker threshold, self-reported visual function (VFQ-48), and health-related quality of life (EQ-5D), and the ranibizumab retreatment rate in the fellow eye (assessed through review of medical records at the end of 12 months).

Analysis

An available-case analysis was performed using IBM SPSS Statistics (SPSS for Windows, Version 20.0; SPSS Inc., IBM Corp., Chicago, IL, USA). No interim analysis was performed. As this was an exploratory study, we aimed to recruit 60 participants that, allowing for 15% dropout throughout the year,[29] was expected to leave a final cohort of 51. Details of the sample size calculation can be found in the trial protocol.[30] In

TABLE 1. Baseline Descriptive Statistics for Participants

Participant Characteristic	Intervention		Control	
	Full Cohort	Completed Study Cohort	Full Cohort	Completed Study Cohort
Number of participants	30 (60% female)	21 (43% female)	30 (53% female)	29 (48% female)
Mean age (±SD)	78.30 (±6.56)	78.43 (±7.03)	77.17 (±6.95)	77.00 (±7.02)
AREDS grade 2, *n*	9	6	9	9
AREDS grade 3, *n*	13	9	9	8
AREDS grade 4, *n*	8	6	12	12
Mean BCVA study eye, ETDRS letters read (±SD)	50.63 (±6.49)	50.76 (±6.54)	51.10 (±6.24)	51.07 (±6.35)
Mean BCVA fellow eye, ETDRS letters read (±SD)	35.53 (±15.44)	34.95 (±14.74)	33.90 (±16.10)	34.03 (±16.36)
Number currently taking ocular supplements (% of cohort)	11 (36)	7 (33)	6 (20)	7 (24)
Ocular supplement history, mean years taken (±SD)	0.93 (±1.29)	0.76 (±1.38)	0.32 (±0.63)	0.33 (±0.63)
Smoking history, mean pack years (±SD)	13.89 (±20.07)	12.43 (±20.21)	12.42 (±18.50)	12.68 (±18.77)

Characteristics are shown for the entire cohort (full cohort) and those who completed the 1-year study duration or withdrew as a result of nAMD onset in the study eye (completed study cohort). Twenty-one intervention and 29 control participants either completed the trial or withdrew as a result of nAMD onset in the study eye, and are included in the magnitude of effect analysis (see Fig. 3). Those who completed the full study period (20 intervention, 27 control) are included in the secondary outcome analysis.

accordance with the consensus relating to randomized controlled trials, differences in baseline characteristics between groups were not assessed.[42,43] Descriptive statistics were used to summarize participant demographics, as well as the proportion of individuals showing disease progression in each group (±95% CIs using "exact" calculation) and the magnitude of changes in secondary outcome measures. The primary outcome measure (proportion demonstrating disease progression at 12 months) was assessed using a stratified Mantel-Haenszel test. Analysis of covariance (ANCOVA) compared the 12-month change in cone τ, BCVA, and the ranibizumab retreatment rate between the study groups. Age, sex, ocular supplement intake, history of smoking, and baseline data relating to each outcome measure were covariates. A Kruskal-Wallis test was used to compare the 12-month change in drusen volume, flicker threshold, and red-green (RG) and yellow-blue (YB) chromatic threshold data, which remained nonparametric even after log transformation. PSQI, VFQ-48, and EQ-5D questionnaires were scored using established scoring systems.[34,44–46] In accordance with present consensus regarding Likert scale analysis,[47–50] 12-month changes in questionnaire data between study groups were analyzed with parametric (ANCOVA; PSQI) and nonparametric (Kruskal-Wallis; VFQ-48 and EQ-5D) tests as appropriate.

RESULTS

Participant Characteristics

Thirty intervention and 30 control participants were recruited from July 2014 to November 2015. Each participant was reviewed monthly over a year (average time on study ± SD, 372.00 ± 18.59 days). All participants exhibited early AMD (soft drusen and/or focal pigmentary changes) in one eye and nAMD in their fellow eye (confirmed by fluorescein angiography). During the course of the trial, no participant exhibited lenticular opacification greater than grade 1 according to any parameter on the Lens Opacity Classification System.[51] Descriptive statistics of each study group are shown in Table 1.

Primary Outcome Measures

Characteristics relating to the change in drusen volume of those who completed the study are shown in Table 2. One intervention participant and two controls progressed to nAMD during the course of the study. When combined with those

who showed significant drusen growth, 38.1% (*n* = 8, 8.1%–61.6% CI) of the intervention and 48.3% (*n* = 14, 29.4%–67.5% CI) of the control group showed disease progression over the course of the trial. Although the risk of disease progression was reduced in the intervention group, this did not reach statistical significance (Mantel-Haenszel test, Common Odds Ratio = 0.763, *P* = 0.495). Considering disease progression on the basis of change in dark adaptation, slower cone τ values relate to a greater deficit in dark adaptation. When measured after 12 months, the mean cone τ of the mask-wearers and controls was slower than initially recorded (by 1.59 and 0.70 minutes, respectively) suggesting a worsening over the study duration. Over 12 months, the delay in cone τ was significantly greater (*P* = 0.018) in the intervention group (1.66 ± 0.61 minutes) than in the control group (0.66 ± 0.49 minutes) when adjusted for covariates (see Fig. 4).

Safety of the Intervention

During the course of the study, 33 adverse events (AEs) were recorded. Eight ocular AEs were recorded (four control, four intervention), of which two occurred as a direct result of ranibizumab administration. Nineteen AEs were related to general health issues and six (five control, one intervention) were related to falls (all of which occurred during daylight hours). Nine serious AEs (SAEs) were reported. Three related to the onset of nAMD in the study eye and five were attributed to changes in general health. No AE or SAE was deemed to be associated with the intervention. It should be noted, however, that the treatment group exhibited a significantly greater delay in cone dark adaptation over the year than the control group (see primary outcome measure analysis).

Acceptability of the Intervention and Compliance to Mask Wear

Figure 3 details the number of participants who left the trial, with reasons. The mean (±SD) number of days of mask wear before withdrawal was 61 (±43). Details of reported intervention discomfort issues are outlined in Table 3. All discomfort issues relating to the temples, nasal bridge, and eyelash irritation tended to be reported for the duration of the trial. Facial overheating was primarily seasonal, and issues with fabric housing odor of newly issued masks resolved within 1 week. At first exposure, the light level was well tolerated by more than 90% of the cohort. For those who completed the

TABLE 2. Drusen Volume Characteristics of Each Study Group

Change in Drusen	Intervention		Control	
	n (%)	Mean (±SD)	n (%)	Mean (±SD)
Growth	8 (40.0)	0.012 (±0.006)	16 (59.2)	0.018 (±0.030)
Significant growth	7 (35.0)	0.013 (±0.005)	12 (44.4)	0.027 (±0.035)
Shrinkage	5 (25.0)	0.036 (±0.047)	5 (18.5)	0.018 (±0.024)
Significant shrinkage	5 (25.0)	0.036 (±0.047)	4 (14.8)	0.022 (±0.025)
No change	7 (35.0)	0.000 (±0.000)	6 (22.2)	0.000 (±0.000)

Percentages given relate to total number in each cohort that completed the entire study duration (intervention, 20; control, 27). "Growth/shrinkage" defines participants for whom an increase/decrease in drusen volume was reported over 12 months. "Significant growth/shrinkage" defines those for whom the increase/decrease in drusen volume was outside 95% test-retest CIs as derived from Gregori et al.[41] "No change" defines those who had the same drusen volume at baseline and final study visits.

entire study, the average compliance based on the objectively measured hours of mask wear per night and self-reported mean number of hours sleep per night (7.19 ± 0.89) was 78% ($\pm 23\%$ CI). No significant difference ($P > 0.05$) in mean hours of mask use per month was found over the study duration. When assessing self-reported sleep disturbance over the study duration, no significant difference in change of PSQI global score was found between groups ($P = 0.19$).

Secondary Outcome Measures

There was no significant difference in median change in functional or self-reported secondary outcome measures between study groups (see Figs. 4, 5; Supplementary Table S1). Twenty-one participants (10 intervention, 11 control) were recruited within their initial ranibizumab loading phase. Ranibizumab use was ceased in favor of aflibercept for seven participants (four intervention, three control) during the course of the study. No significant difference ($P = 0.30$) was found between the mean ($\pm SD$) number of anti-VEGF injections received over 12 months by the intervention (5.28 ± 2.54) and control (4.38 ± 2.91) groups (Fig. 4; Supplementary Table S2).

Protocol Violations

For six participants (four control, two intervention), final visits were conducted outside the proposed timescale of 12 months (± 4 weeks). The intervention participants within this group were 6 and 7 days over the 12-month (± 4-week) schedule and continued to wear the mask through this additional period. Due to a malfunction of the Zeiss Cirrus SD-OCT 4000 for a 9-week period, drusen volume data were not collected over two consecutive monthly follow-up visits for 24 participants. During this period end-of-study appointments for five participants (four intervention, one control) were still conducted in accordance with the protocol. Following the end-of-study visit, mask wear was ceased and missing data were collected as soon as possible thereafter. The mean delay in drusen volume measurement was 7.20 (± 2.89) weeks post final study visit.

DISCUSSION

The findings of this study suggest that low-level nighttime light therapy, although acceptable to the patients, does not have a large effect on drusen progression or progression to nAMD in patients with early AMD over 12 months. Although a greater proportion of controls than mask-wearers showed disease progression over the trial, this difference failed to reach significance. It must, however, be noted that this was an exploratory study, and as such was not powered to detect small

differences between study groups. Post hoc sample size calculations suggest that a sample size of 381 per group would be required to detect an effect of the magnitude seen in this trial (80% power, $P = 0.05$) at 12 months.

In the present study, the only outcome measure to show a significantly different change over 12 months between the study groups was dark adaptation. There is an emerging body of evidence to suggest that dark adaptation is a sensitive biomarker of AMD,[16,17,21,52–60] although there are limited longitudinal data to show the sensitivity of the test to disease progression,[56,61] particularly when used over a 1-year as opposed to a 2-year period.[62] Cone adaptation was selected rather than rod adaptation as an outcome measure in this study primarily for pragmatic reasons. Assessment of rod adaptation for a longitudinal study can be time-consuming and fatiguing for the participant, whereas cone adaptation may be evaluated more rapidly. For example, in a study investigating the dark adaptation characteristics of individuals with intermediate AMD, where time taken to reach a criterion threshold on the second component of rod recovery was measured, nearly a third of individuals required longer than 30 minutes, with recovery times ranging from 8.8 to 124.4 minutes.[62] There is substantial evidence to suggest that, despite the proposed alternative mechanism for photopigment regeneration available to cones through the Müller cell pathway,[63,64] cone adaptation is also adversely affected by AMD disease progression.[17,21,52,53,58,59,65]

The significant increase in cone τ seen in the intervention group when compared with the controls suggests that cone adaptation was selectively impaired in the treatment group. However, there are no published data regarding the long-term effect of reducing the rod-circulating current on the dynamics of cone adaptation. Hence, although the delayed dark adaptation metric may herald the development of early AMD, it is also possible that it is a consequence of disrupting retinal physiology. It would be useful to evaluate this effect before any future phase 3 trials of efficacy are initiated into this treatment to further evaluate the safety of the intervention. For example, a short-term study evaluating the time course and longevity of any effect of the intervention on rod and cone dark adaptation rates both in people with and without pathology would be valuable.

The proposed aim of this treatment to moderate retinal physiology might be considered to be analogous to other putative interventions that have aimed to reduce the progression rate of dry AMD through modulating the visual cycle. For example, fenretinide (4-hydoxy[phenyl]retinamide) is a retinoid derivative that competes with retinol for binding to retinol binding protein 4 (RBP4), thus reducing the delivery of all-trans-retinol to the RPE.[66,67] In contrast, the treatment emixustat (a derivative of all-trans-retinylamine) is a retinol mimic that inhibits the action of isomerohydrolase RPE65,
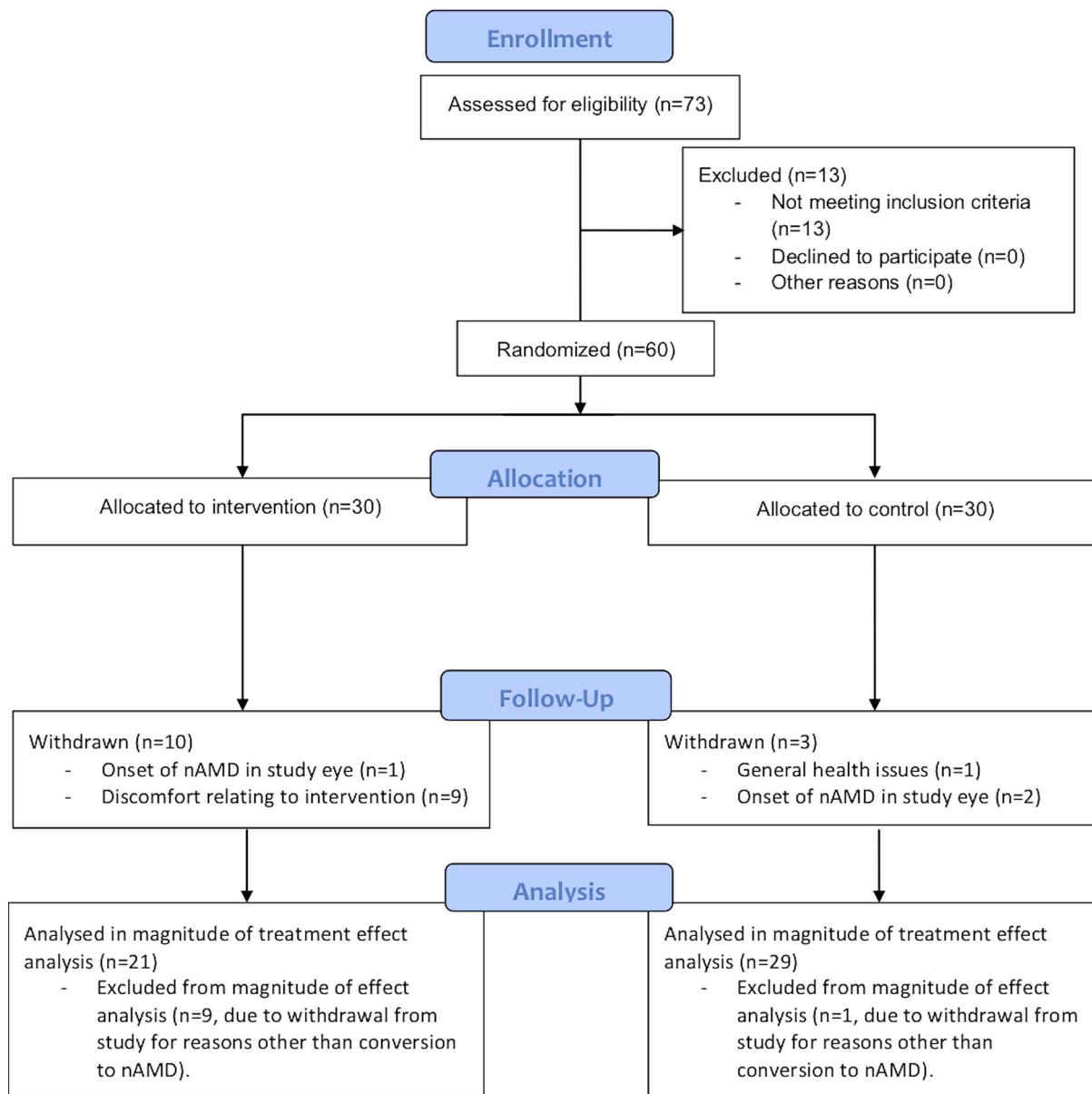
FIGURE 3. CONSORT flow diagram showing participant recruitment and follow-up (www.consort-statement.org/), with reasons for withdrawal at each stage.

TABLE 3. Reported Issues Relating to Intervention Discomfort

Subjective Feedback	Reported, *n*	Withdrawn, *n*
Discomfort to temples	10	3
Facial overheating	6	1
Eyelid/eyelash irritation	2	1
Intolerance to light level	2	0
Discomfort to nasal bridge	9	3
Intolerance to odor of fabric housing	3	0
Intolerance to general sensation of mask wear	3	0
Intolerance to mask displacement during sleep	8	0
Increased dreaming since inception of mask wear	1	0
Increased periorbital darkening since inception of mask wear	1	0

The reported column specifies the total number of participants reporting each issue. The withdrawn column specifies the number of participants withdrawn from study reporting each reason as a key factor for their removal from study.
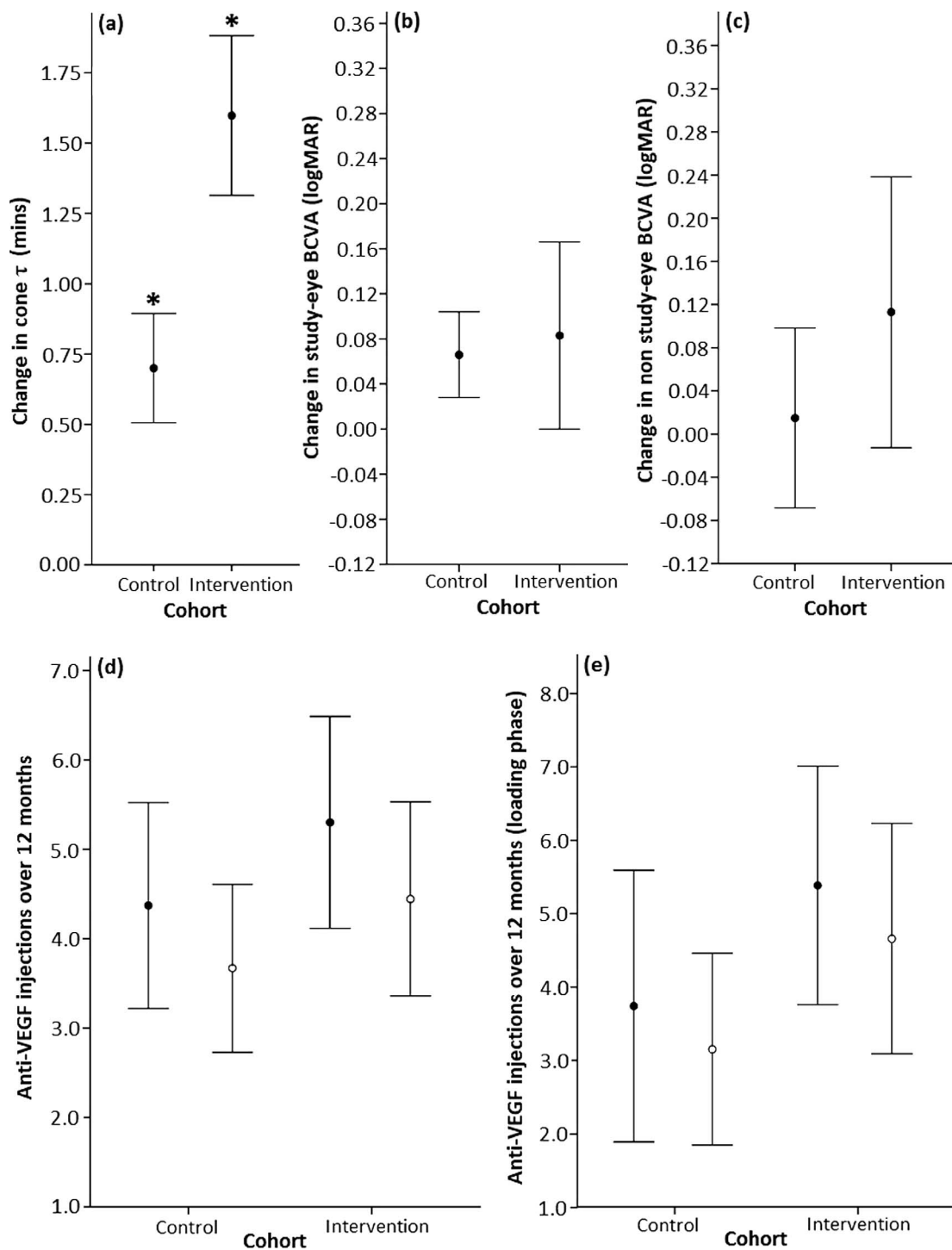
FIGURE 4. Mean plots showing change in rate of cone retinal adaptation (cone τ) (a) and BCVA (b, c) over 12 months. Plots (d) and (e) show the number of anti-VEGF injections administered over the study duration for the entire study cohort (d) and those recruited within their loading phase only (e). *Black circles* represent total injections (ranibizumab and aflibercept) and *white circles* represent those treated only with ranibizumab for the study duration. *Whiskers* denote 95% CIs. *Parameters that demonstrate a significant difference between study groups.

which is responsible for generating 11-cis retinol from all-trans-retinyl ester in RPE cells.[67,68] The hypothesis with both of these treatments, and other visual cycle modulating agents, is that, through slowing the visual cycle and the consequent reduction in formation of the toxic bisretinoid fluorophore A2E found in RPE lipofuscin, AMD progression will be slowed.[66,67,69–71] Trial results for fenretinide did not show a statistically significant difference in geographic atrophy lesion size compared with placebo and the trend toward reduced lesion growth rates in those where RBP levels dropped below 2 mg/dL was also not statistically significant.[66] Similarly, a phase 2b/3 trial of emixustat in the treatment of geographic atrophy failed to reach its primary endpoint.[71] In common with the current study, these interventions resulted in an apparent (but not symptomatic) delay in dark adaptation[72,73]; however, the mechanism of action is very different. That is, the low-level

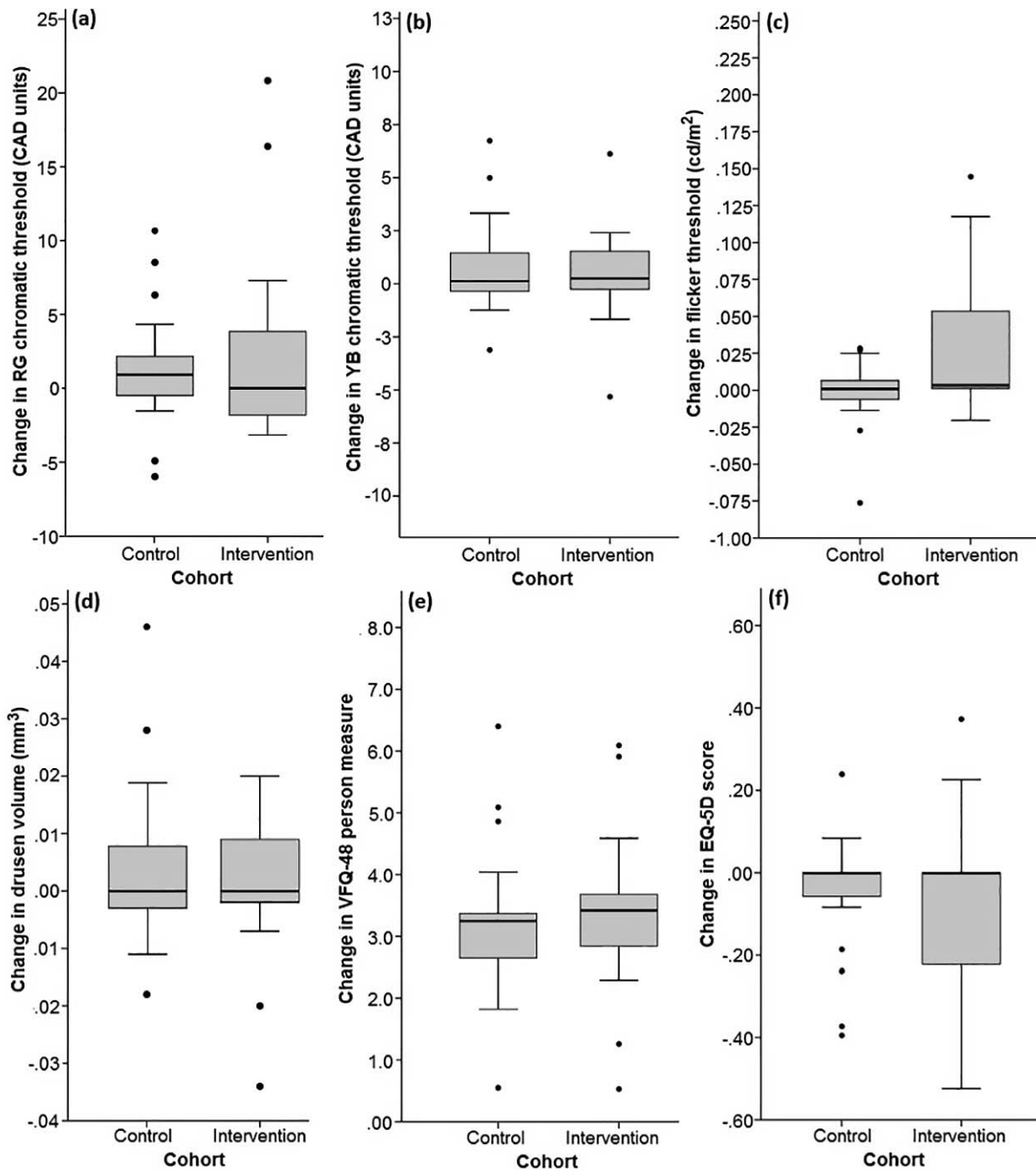Investigative Ophthalmology & Visual Science

FIGURE 5. Boxplots showing 12-month change in RG chromatic threshold (a), YB chromatic threshold (b), 14-Hz flicker threshold (c), drusen volume (d), VFQ-48 person measure (e), and EQ-5D score (f). For change in drusen volume, three outliers (two control [−0.058, 0.120] and one intervention [−0.120]) have not been included, to aid visualization.

light therapy aims to reduce the oxygen demand of the retina by reducing the dark current, so alleviating hypoxia, rather than targeting bisretinoid accumulation in the RPE and the associated photo-oxidative damage. The efficacy of these different modes of treatment is not, therefore, likely to be directly comparable.

In this study, we found the potential influence of light therapy on ranibizumab retreatment rate to be limited. However, the variation in how long patients had been on treatment at the start of the study is likely to have been a key confounding factor. As retreatment rates were generally low,

this will have further affected any likelihood of significant reductions being observed.

The retinal illuminance provided by the mask was well tolerated by 90% of participants. The overall withdrawal rate as a result of mask issues alone (26%) and compliance rate (70%) were in agreement with data reported by Sahni et al.[28] (withdrawal rate, 21%; compliance rate, 76%), in which a similar intervention was assessed in patients with diabetic macular edema ($n = 15$) and healthy controls over two age groups (18–30 years, $n = 45$ and 50–70 years, $n = 24$). As 75% of withdrawals caused by mask issues occurred within 64 days

post randomization, future studies may expect a low withdrawal rate beyond 3-months wear.

In the present study, disruption to compliance was minimal and primarily caused by ranibizumab administration. The complaints relating to mask discomfort reported by those who had completed the full study duration were not reflected in the PSQI analysis of sleep quality. According to data obtained with the PSQI, the nightly delivery of low-level light therapy had no measurable effect on sleep quality (duration or latency). This is in agreement with other studies that also reported no SAEs associated with mask wear.[27–29]

The strengths of the study include the robust randomized controlled trial design, the successful masking of treating ophthalmologists, the high level of compliance, and the relatively low rate of withdrawal after the initial period of adaptation. A weakness was that an eligibility criteria change was required to improve the recruitment rate, thus potentially reducing the power of the analysis with respect to rate of injection in the eye with nAMD. This study focused on progression defined by increased drusen volume or conversion to nAMD. It may be valuable for any future trial to also include the development or progression of atrophic changes. A further major limitation of the trial with respect to the assessment of efficacy was the small sample, which was appropriate for a phase I/II safety evaluation but was powered only to detect a relatively large effect size.

In conclusion, this exploratory study has collected important information about the safety and acceptability of the OLED sleep mask in this patient cohort and the potential magnitude of the treatment effect for powering future trials. Further phase I and II trials are required to explore the finding of a greater delay in cone dark adaptation in the treated group, to determine the origin and longevity of this effect, and to investigate the potential safety implications of this finding. Thereafter, assuming that the safety issues are addressed, a larger cohort will be required to determine whether the small (statistically insignificant) effect of the intervention on risk of progression of early AMD at 12 months was a chance finding. Further work is also required to determine the potential effect of the treatment on the progression and retreatment rates for nAMD, as well as the possible effect of treatment extending beyond 12 months.

Acknowledgments

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