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Safety and acceptability of an organic light-emitting diode sleep mask as a potential therapy for retinal disease

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Learning Objectives

Upon completion of this activity, participants will be able to:

1. Assess the tolerability of organic light-emitting diode (OLED) therapy
2. Distinguish the most common reason for study withdrawal in the current trial of OLED therapy
3. Evaluate ocular outcomes among patients with diabetic macular oedema treated with OLED therapy
4. Analyze the effects of OLED therapy on symptoms of depression and sleep quality

Authors/Editors disclosure information

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CLINICAL STUDY

Safety and acceptability of an organic light-emitting diode sleep mask as a potential therapy for retinal disease

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Abstract

Purpose **The purpose of the study was to study the effect of an organic light-emitting diode sleep mask on daytime alertness, wellbeing, and retinal structure/function in healthy volunteers and in diabetic macular oedema (DMO).**

Patients and methods **Healthy volunteers in two groups, 18–30 yrs (A), 50–70 yrs (B) and people with DMO (C) wore masks (504 nm wavelength; 80 cd/m^2 luminance; ≤ 8 h) nightly for 3 months followed by a 1-month recovery period. Changes from baseline were measured for (means): psychomotor vigilance task (PVT) (number of lapses (NL), response time (RT)), sleep, depression, psychological wellbeing (PW), visual acuity, contrast sensitivity, colour, electrophysiology, microperimetry, and retinal thickness on OCT.**

Results **Of 60 participants, 16 (27%) withdrew, 8 (13%) before month 1, due to sleep disturbances and mask intolerance. About 36/55 (65%) who continued beyond month 1 reported ≥ 1 adverse event. At month 3 mean PVT worsened in Group A (RT (7.65%, $P<0.001$), NL (43.3%, $P=0.005$)) and mean PW worsened in all groups (A 28.0%, $P=0.01$, B 21.2%, $P=0.03$, C 12.8%, $P<0.05$). No other clinically significant safety signal was detected. Cysts reduced/resolved in the OCT subfield of maximal pathology in 67% Group C eyes. Thinning was greater at 3 and 4 months for greater baseline thickness (central subfield $P<0.001$, maximal $P<0.05$).**

Conclusion **Sleep masks showed no major safety signal apart from a small impairment of daytime alertness and a moderate effect on wellbeing. Masks were acceptable apart from in some healthy participants. Preliminary data suggest a beneficial effect on retinal thickness in DMO. This novel therapeutic approach is ready for large clinical trials.**

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Introduction

The increased oxygen demand in the outer retina in the dark, due mostly to the 140 million rods that double their oxygen intake in the dark adapted eye during sleep, may contribute to intraretinal hypoxic drive in a range of retinal vasculopathies including diabetic retinopathy (DR) leading to upregulation of the VEGF pathway.[1] If dark adaptation could be prevented or reduced, the reduction of intraretinal hypoxia may diminish the progression of DR and its complications.[2]

Light is a novel approach to modifying the hypoxia associated with dark adaptation.[3,4] Sleeping in an illuminated environment with light delivered through the closed lid has been tested in two small studies as a potential therapy for diabetic maculopathy.[5,6] Before light therapy can be more widely considered robust evidence on safety is required.

We developed a sleep mask containing a thin, flexible, organic light-emitting diode (OLED) to suppress dark adaptation therapeutically. We investigated if long-term nocturnal light exposure with this device could lead to sleep deprivation and effects on daytime alertness, psychological wellbeing, and retinal structure and function. We also studied safety in people with diabetic macular oedema (DMO).

Materials and methods

Healthy adult volunteers with good general health from two age groups (Group A: aged 18–30 years; Group B: aged 50–70 years) were

consented and recruited into a single-centre, prospective, longitudinal, non-commercial, interventional safety study with a 3-month dosing period followed by a 1-month post dosing assessment.

Key exclusion criteria were: disease that might affect the blood–retina barrier, unstable fixation on microperimetry, history of sleep disorders, depression or psychiatric disorders, psychomotor vigilance task (PVT), number of lapses (NL) ≥ 17 (see below), and use of psychoactive drugs.

The study complied with the Declaration of Helsinki was approved by the National Research Ethics Committee (13/WM/0011) and the Institutional Technical Devices Committee as a device study with a CE-marked device. It complied with the Declaration of Helsinki.

People attending for monitoring of DMO were assessed (Group C). Additional inclusion criteria: best corrected visual acuity (BCVA) ≥ 73 ETDRS letters, retinopathy $\leq$ ETDRS grade 47, DMO meeting definition of clinically significant macular oedema, mean subfield thickness ≥ 2 SD in any central five OCT subfields.

OLED sleep masks developed by Polyphotonix Medical Ltd (Figure 1) comprised a soft cushioned fabric mask containing a plastic 'Pod' containing the light sources emitting light into the eyes through closed lids. The OLED spectrum with a peak of 504 nm was designed to closely match the scotopic response curve for selective activation of rods and to deliver a light intensity of 2 scotopic Trolands at the retina to suppress dark adaptation.[6] Touching a capacitive sensor activated the mask for a maximum 8 h controlled by an internal clock with delivered dose recorded by internal sensors (hours of wear/month).

After training, participants were instructed to wear the mask each night for 3 months and record sleep times and experiences in a diary. Participants attended monthly for 4 months and were replaced if they withdrew before completing the month 1 visit. A small honorarium and reimbursement of expenses were provided.

Study procedures (all visits)

The PVT measured loss of concentration and alertness caused by sleep deprivation as increasing response time (ms) (PVT-RT) and NL (failure to respond) (PVT-NL). Using normative data we derived upper limits of normal (mean+2 SD): NL ≤ 16; RT ≤ 459, ≤ 359.[7] The Karolinska Sleepiness Scale (KSS) (range 1–9 (worst))[8] and the Pittsburgh Sleep Quality Index (PSQI) (range 0–21 (worst))[9] questionnaires assessed level of sleepiness and sleep quality. PVT-NL, PVT-RT, KSS, and PSQI served as co-primary outcomes.

Self-reported symptoms of depression were assessed using the Centre for Epidemiologic Studies Depression scale (CESD) (abnormal ≥ 16)[10] and psychological wellbeing using the General Health Questionnaire (GHQ12) (range 0–36, >15 evidence of distress, >20 severe distress).[11]

The following were also assessed: medical and ocular history, ophthalmological examination, BCVA (ETDRS letters at 1 m), Pelli Robson contrast sensitivity (CS), colour vision Cambridge colour test ((CCT); Cambridge Research Systems (Rochester, Kent, UK), normal thresholds $<100\times10^{-4}$ $u'v'$ protan and deutan, $<150\times10^{-4}$ $u'v'$ tritan[12]) 19-segment multifocal electroretinogram[13] (mfERG, Roland Retiscan, Brandenburg an der Havel, Germany), electrooculogram (EOG), microperimetry (MP, Nidek MP1, Padova, Italy), mean central subfield thickness on spectral domain optical coherence tomography (SD-OCT). For Group C mean thickness was also recorded for subfield with maximal OCT pathology with a qualitative assessment of response to therapy.

Adverse events including discomfort, sleep disturbance, mood alterations, daytime wakefulness, and

Figure 1 Principal components of OLED sleep mask. Left panel: plastic pod containing OLED light source delivering light at 504 nm peak for a maximum of 8 h with dose delivery sensor. Right panel: soft cushioned fabric mask that houses the plastic pod.

reasons for withdrawal were recorded and reviewed independently for relatedness (SPH, TG).

Statistical analysis

Groups of 20 were selected for the healthy cohort based on accepted guidance for paired *t*-tests in the lack of previously published data. Demographics and baseline variables were compared across groups using two-sided 2-sample *t*-test where variances were equal; if the unequal variances *t*-test was used, then this was reported in the results.

Analysis used STATA 13.1 (StataCorp LP, Timberlake, Richmond, UK) with log-transformations for non-normal distributions and linear regression where the dependent variable was change from baseline to 3 (primary analysis) and 4 months with hours of mask wear as a covariate (centred by average). The resultant regression intercept represented the mean change from baseline to month 3 (or 4) for the average amount of mask wear.

A 2-step method adjusted values of α for multiple comparisons of change of our four co-primary variables only: (1) standard Bonferroni for a family-wise error rate (change from baseline to month 3 in each of four co-primary outcomes) equivalent to 0.05: $0.05/4 = 0.013$ (2) Holm–Bonferroni to compare ordered *P*-values for the two hypotheses in each group (Groups A and B) giving corrected significance levels of 0.013 and 0.0063. *P*-values are presented uncorrected and interpreted against these revised values of α.

Results

About 45 healthy volunteers were recruited, 21 Group A (18–30 years) and 24 Group B (50–70 years), and 15 participants to Group C. Patient demographics and baseline variables are presented in Supplementary Table 1. All daytime alertness, psychological wellbeing, and retinal structure/function variables were worse in Group C compared with Group B (similar mean ages), significant for CCT (2-sample *t*-test with unequal variances: protan and deutan $P<0.01$, tritan $P<0.001$) and PSQI (Tukey pairwise, $P=0.05$).

Of 60 recruited participants, 8 withdrew before month 1 and were replaced. Eight withdrew after completing month 1. Numbers completing all study visits were: A 17, B 17, and C 12. Reasons for withdrawal are listed in Table 1. Light intolerance and sleep disturbance were cited by one participant in Group A and five in Group B.

Figure 2 shows mean hours of sleep mask wear, equivalent to exposure to light therapy. Time of mask wear from baseline to month 3 (mean ± SD) was lower in Group A (410 ± 125 h) than Groups B (559 ± 87.4, $P<0.001$, ANOVA) and C (495.8 ± 139.1, $P=0.002$). In Group A mask wear was more variable but stayed stable, whereas in Group B it improved and became more consistent with time. On average younger healthy participants received 56% of the available light dose (with wider variability) compared with 76% in older participants (2-sample *t*-test with unequal variances $P<0.001$). Patients with DMO also had a wide variation in hours worn per month, which dropped off by month 2 (2-sample *t*-test with unequal variances $P=0.006$).

Table 1 Reasons given for withdrawal of 16 participants by study visit

Reported reason for withdrawal	*Group A*	*Group B*	*Group C*
Before month 1			
Intolerance of light and sleep disturbances	0	3	0
Unable to attend follow-up	1	0	1
Could not perform study investigations	0	0	1
No reason given	0	1	1
After month 1			
Intolerance of light and sleep disturbances	0	2	0
Unrelated medical event	0	0	1
At month 2			
Intolerance of light and sleep disturbances	1	0	0
Could not perform study investigations	0	1	0
Unable to attend follow-up	2	0	0
No reason given	0	0	1

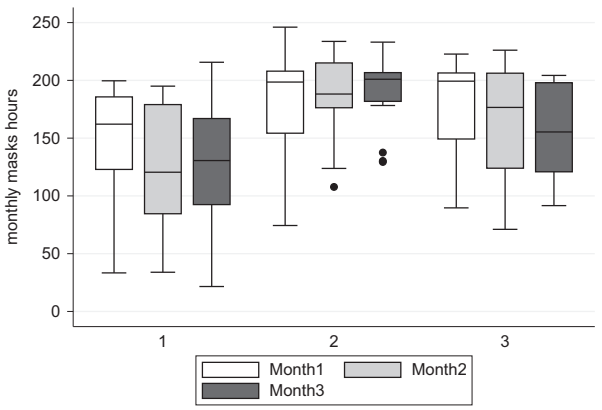

Figure 2 Boxplots for total hours of mask wear in those participants (Group A $n=17$, Group B $n=17$, and Group c $n=12$) who completed 3 months of the study. Median is shown as horizontal line with upper and lower quartile as box, and range minima and maxima at ends of vertical lines; outliers with single months with reduced mask wear shown as single points (patient 29 108 h in month 2, patient 31 138 h in month 3, and patient 34 129 h in month 3).

Safety

Tables 2 and 3 show changes in study variables at months 3 and 4 compared with baseline for participants who

Table 2 Changes in alertness, sleep quality, psychological wellbeing, and ocular function and structure at month 3 in 46 participants who completed 3 months of sleep mask wear

	Group A (n = *17*)		*Group B* (n = *17*)		*Group C* (n = *12*)	
	Baseline (SD) range	*Change at month 3 (95% CI) P-value*	*Baseline (SD) range*	*Change at month 3 (95% CI) P-value*	*Baseline (SD) range*	*Change at month 3 (95% CI) P-value*
PVT-NL (number)	4.53 (4.69) 0–18	1.96 (0.63, 3.64) **0.005**[a]	4.30 (5.44) 0–24	−0.17 (−1.15, 1.11) 0.75	6.08 (5.42) 1–21	−0.8 (−1.99, 1.82) 0.93
PVT-RT (ms)	336.41 (36.62) 270.89–418.43	24.39 (13.35, 39.12) **<0.001**[a]	332.10 (50.5) 276.1–456.6	25.39 (6.71, 42.34) **0.02**	346.95 (13.37) 208–430	6.93 (−9.67, 23.53) 0.19
KSS (score)	3.41 (1.80) 1–7	0.74 (−0.33, 1.86) 0.16	2.41 (1.12) 1–5	0.47 (−0.16, 1.10) 0.13	2.92 (1.62) 1–7	0.08 (−1.41, 1.58) 0.90
PSQ (score)	2.65 (2.32) 0–8	0.82 (−0.16, 1.81) 0.09	3.60 (2.23) 1–9	0.06 (−1.23, 1.35) 0.92	4.58 (2.87) 1–11	0.5 (−0.57, 1.57) 0.32
CESD (score)	4.30 (3.87) 0–16	1.35 (−0.52, 3.23) 0.15	4.20 (4.50) 0–13	−0.88 (−3.13, 1.37) 0.42	6.33 (6.23) 0–20	1.25 (−1.92, 4.42) 0.40
GHQ12 (score)	6.71 (2.02) 4–11	1.88 (0.51, 3.25) **0.01**	6.94 (2.51) 3–12	1.47 (0.20, 2.74) **0.03**	7.83 (2.72) 5–14	1.00 (0.02, 1.94) **0.046**
BCVA (letters)	90.65 (3.32) 85–96	1.59 (−0.02, 3.19) **0.05**	89.18 (3.28) 83–95	1.17 (−0.10, 2.45) 0.07	85.92 (5.18) 79–93	−0.33 (−2.37, 1.70) 0.73
CS (letters)	41.29 (1.36) 37–42	0.35 (−0.37, 1.08) 0.32	41.18 (1.51) 36–42	0.17 (−0.64, 0.99) 0.65	35.0 (3.74) 30–41	1.0 (−0.67, 2.67) 0.11
CCT protan (u′v′)	60.29 (19.47) 22–95	−3.41 (−12.35, 5.52) 0.43	61.56 (14.47) 40–86	−7.75 (−19.93, 4.43) 0.19	141.64 (89.35) 42–353	−37.14 (−90.14, 15.85) 0.15
CCT deutan (u′v′)	53.47 (18.57) 26–97	2.59 (−5.69, 10.87) 0.51	66.56 (19.19) 45–122	−13.00 (−22.73, −3.27) **0.01**	133.25 (99.47) 59–411	−32.75 (−96.45, 30.95) 0.28
CCT tritan (u′v′)	64.12 (22.51) 33–106	−2.47 (−16.02, 11.08) 0.70	78.06 (36.58) 29–158	−4.06 (−28.84, 20.71) 0.73	233.0 (131.55) 34–488	−46.5 (−129.3, 36.3) 0.24
mfERG amp 1 (μV)	68.98 (16.02) 41.5–108	0.39 (−8.43, 9.21) 0.92	64.25 (12.22) 44.9–88.6	1.45 (−3.99, 6.91) 0.58	56.17 (9.76) 38.2–70.1	0.73 (−7.17, 8.65) 0.84
mfERG lat 1 (ms)	35.81 (2.19) 31.5–40.2	−1.18 (−2.14, −0.22) **0.02**	36.25 (1.72) 33.4–39.2	−0.29 (−1.05, 0.48) 0.44	38.18 (2.05) 35.4–41.3	−0.35 (−1.33, 0.62) 0.44
EOG (light rise ratio)	2.36 (0.40) 1.66–3.00	0.16 (−0.68, 0.99) 0.70	2.22 (0.42) 1.60–3.00	0.19 (−1.08, 1.47) 0.75	2.46 (0.60) 1.7–3.6	−0.12 (−0.42, 0.18) 0.19
MP1 (dB)	19.45 (1.13) 15.6–20	0.25 (−0.28, 0.78) 0.33	19.41 (1.05) 16.6–20	−0.06 (−0.73, 0.61) 0.86	13.7 (3.19) 6.6–17.8	1.95 (−0.39, 4.29) 0.09
OCT CST (μm)	274.53 (16.72) 238–308	−0.53 (−2.60, 1.54) 0.60	286.53 (20.88) 255–319	−2.82 (−5.62, −0.02) **0.05**	320.50 (35.34) 274–389	−6.25 (−20.40, 7.90) 0.35
OCT maxST (μm)					365.33 (34.69) 327–439	−12.00 (−28.80, 4.80) 0.14

Abbreviations: BCVA, best corrected visual acuity; CCT, Cambridge color vision test; CESD, The Centre for Epidemiologic Studies Depression scale; CS, contrast sensitivity; EOG, electrooculogram; GHQ12, General Health Questionnaire of psychological wellbeing; KSS, Karolinska Sleep Scale; mfERG, multifocal electroretinogram; MP1, microperimetry; OCT CST, optical coherence tomography mean central subfield thickness; OCT maxST, mean thickness of OCT subfield with maximal pathology; PSQI, Pittsburgh Sleep Quality Index; PVT-NL, psychomotor vigilance task (PVT) number of lapses; PVT-RT, PVT response time.

Data are presented as means with SD or 95% confidence intervals, corrected for hours of mask wear. *P*-values refer to paired *t*-tests of change in outcome (month 3 minus baseline), are uncorrected and should be interpreted against adjusted values of α (see text). Levels of $P \leq 0.05$ are shown in bold.

[a]Indicates statistically significant co-primary variable.

completed 3 months of sleep mask wear (A 17, B 17, and C 12). At month 3, the PVT-RT deteriorated in both healthy groups (A 24.39 (7.25%), B 25.39 (7.65%)), statistically significant for Group A ($P<0.001$). PVT-NL deteriorated significantly in Group A (1.96 (43.27%), $P=0.005$). RT stayed depressed at month 4 whereas NL recovered. Group C had worse baseline levels of PVT than Group B but both older age groups showed no statistically significant change during the study.

Interpreting our secondary outcomes requires some caution due to multiple comparisons. Psychological wellbeing (GHQ12) worsened in all the groups at month 3 (A 28.0%, $P=0.01$; B 21.2%, $P=0.03$; C 12.7%, $P<0.05$) with a small but statistically significant greater effect with increasing mask wear.

In older participants there was a consistent improvement in CCT thresholds at month 3, statistically significant for deutan (13.00 (19.5%) $P=0.01$). There were small increases in BCVA at month 4: Group A +2.44 letters ($P<0.001$), Group B +1.59 letters ($P=0.025$). No change was detected in Group C at month 3 in BCVA, CS, mfERG, EOG, or for any other variables in any group. We detected no clinically important effect on primary or secondary variables associated with duration of recorded mask wear apart from GHQ12.

Table 3 Changes in alertness, sleep quality, psychological wellbeing, and ocular function and structure 1 month after discontinuing sleep mask wear in 46 participants who completed 3 months of wear

	Group A (n = *17*)		*Group B* (n = *17*)		*Group C* (n = *12*)	
	Baseline (SD) range	*Change at month 4 (95% CI)* P-*value*	*Baseline (SD) range*	*Change at month 4 (95% CI)* P-*value*	*Baseline (SD) range*	*Change at month 4 (95% CI)* P-*value*
PVT-NL (number)	4.53 (4.69) 0–18	0.59 (−0.26, 11.28) 0.07	4.30 (5.44) 0–24	1.39 (−0.95, 5.27) 0.27	6.08 (5.42) 1–21	1.25 (−7.93, 4.43) 0.41
PVT-RT (ms)	336.41 (36.62) 270.89–418.43	28.02 (10.24, 46.70) **0.005**	332.10 (50.5) 276.1–456.6	27.66 (10.11, 46.10) **0.01**	346.95 (13.37) 208–430	10.03 (−5.70, 25.77) 0.09
KSS (score)	3.41 (1.80) 1–7	0.41 (−0.68, 1.50) 0.44	2.41 (1.12) 1–5	0.29 (−0.33, 0.92) 0.33	2.92 (1.62) 1–7	−0.58 (−1.81, 0.64) 0.32
PSQ (score)	2.65 (2.32) 0–8	0.12 (−0.73, 0.97) 0.77	3.60 (2.23) 1–9	0.71 (−0.63, 2.04) 0.28	4.58 (2.87) 1–11	0.92 (−0.82, 2.66) 0.27
CESD (score)	4.30 (3.87) 0–16	1.38 (−1.05, 3.80) 0.24	4.20 (4.50) 0–13	0.19 (−2.65, 3.02) 0.88	6.33 (6.23) 0–20	3.67 (−1.19, 8.52) 0.12
GHQ12 (score)	6.71 (2.02) 4–11	0.94 (−0.39, 2.27) 0.15	6.94 (2.51) 3–12	1.06 (−0.79, 2.91) 0.24	7.83 (2.72) 5–14	2.08 (−0.19, 4.36) 0.07
BCVA (letters)	90.65 (3.32) 85–96	2.44 (0.68, 4.20) **0.001**	89.18 (3.28) 83–95	1.59 (0.23, 2.95) **0.025**	85.92 (5.18) 79–93	0.00 (−2.56, 2.56) 1.00
CS (letters)	41.29 (1.36) 37–42	0.56 (−0.26, 1.39) 0.17	41.18 (1.51) 36–42	0.06 (−0.47, 0.59) 0.82	35.0 (3.74) 30–41	2.57 (0.84, 4.33) **0.01**
CCT protan (u′v′)	60.29 (19.47) 22–95	−8.88 (−9.78, 2.01) 0.10	61.56 (14.47) 40–86	−2.19 (−14.14, 9.76) 0.70	141.64 (89.35) 42–353	−37.56 (−95.04, 19.92) 0.18
CCT deutan (u′v′)	53.47 (18.57) 26–97	−1.29 (−11.68, 9.10) 0.80	66.56 (19.19) 45–122	−10.00 (−19.14, 2.55) 0.11	133.25 (99.47) 59–411	−46.17 (−114.1, 21.77) 0.16
CCT tritan (u′v′)	64.12 (22.51) 33–106	−3.47 (−22.11, 15.16) 0.70	78.06 (36.58) 29–158	0.19 (−18.07, 18.44) 0.98	233.0 (131.55) 34–488	−54.83 (−125.5, 15.8) 0.12
mfERG amp 1 (μV)	19.45 (1.13) 15.6–20	0.10 (−0.28, 0.48) 0.59	19.41 (1.05) 16.6–20	0.30 (−0.14, 1.14) 0.30	55.73 (9.42) 38.2–70.1	−2.71 (−10.75, 5.33) 0.47
mfERG lat 1 (ms)	68.98 (16.02) 41.5–108	1.70 (−7.35, 10.75) 0.70	64.25 (12.22) 44.9–88.6	7.81 (0.88, 14.74) **0.03**	38.20 (1.95) 35.4–41.3	−0.72 (−1.94, 0.49) 0.21
MP1 (dB)	35.81 (2.19) 31.5–40.2	−1.22 (−2.14, −0.30) **0.01**	36.25 (1.72) 33.4–39.2	0.08 (0.84, 1.01) 0.85	13.7 (3.19) 6.6–17.8	2.29 (0.18, 4.41) **0.04**
OCT CST (μm)	274.53 (16.72) 238–308	0.24 (−1.41, 1.88) 0.77	286.53 (20.88) 255–319	1.24 (−3.18, 5.65) 0.56	320.50 (35.34) 274–389	−7.58 (−22.08, 6.91) 0.27
OCT maxST (μm)					365.33 (34.69) 327–439	−15.58 (−32.93, 1.76) 0.07

Abbreviations: BCVA, best corrected visual acuity; CCT, Cambridge color vision test; CESD, The Centre for Epidemiologic Studies Depression scale; CS, contrast sensitivity; EOG, electrooculogram; GHQ12, General Health Questionnaire of psychological wellbeing; KSS, Karolinska Sleep Scale; mfERG, multifocal electroretinogram; MP1, microperimetry; OCT CST, optical coherence tomography mean central subfield thickness; OCT maxST, mean thickness of OCT subfield with maximal pathology; PSQI, Pittsburgh Sleep Quality Index; PVT-NL, psychomotor vigilance task (PVT) number of lapses; PVT-RT, PVT response time.
EOG was not recorded at this visit. Data are presented as means with SD or 95% confidence intervals, corrected for hours of mask wear. Data on the effect of mask wear are also presented as effect of 100 h wear. *P*-values are uncorrected and shown in bold if ≤ 0.05.

About 75% participants in Groups A and B and 40% in Group C who wore the sleep mask for ≥ 1 month reported ≥ 1 adverse event (Supplementary Table 2). Events were mostly attributed to the fabric mask housing the 'Pod'. One SAE deemed unlikely to be related to the sleep mask occurred in Group C.

About 40/45 (95%) healthy participants and 13/15 (87%) DMO patients completed sleep diaries during the dosing period (61% for all 3 months). Thirty-three reported mask discomfort and slippage. Three participants (none in Group C) reported the light as an issue and then only at month 1; all three completed the study.

DMO

For Group C all measures of retinal function and structure showed no statistically significant improvement or change with increasing hours of mask wear (Tables 2 and 3); however there were trends for improvement across all measures. There was a near significant OCT effect for the field of maximal pathology at month 4 ($P = 0.07$). About 10/15 (67%) showed a reduction/clearance of cysts in the maximum pathology subfield.

Statistically significant greater changes in mean thicknesses per 1 μm change in baseline thickness were seen for CST and maxCT at 3 and 4 months: month 3:

CST: −0.77 (−1.03, −0.53), $P<0.001$; month 4: CST: −0.79 (−1.05, −0.53), $P<0.001$; maxST: month 3: −0.44 (−0.87, −0.02), $P=0.05$, month 4: −0.62 (−0.96, −0.28), $P<0.01$. For the subfield of maximal pathology, for each 10 μm increase in baseline thickness, there was a corresponding greater reduction of thickness of 4–6 μm.

Discussion

This is the first safety study, to our knowledge, of a sleep mask containing an OLED device designed as a potential therapy for retinal diseases.

We designed a stimulus aimed at evenly reducing the rod dark current without stimulating cones. Previous work has used LED light, which has a narrow spectral bandwidth and is directional.[5,6] Emission from our OLED was close to Lambertian and homogenous across the plane of the OLED, ensuring even illumination of the retina and minimising the effect of eye movement during sleep. This allowed the brain to adapt to the presence of the light through Troxler's fading.[14] After attenuation of the output spectrum by the lid and ocular media, mesopic retinal illumination drops from 80 candelas/m^2 to a level of around 2 candelas/m^2.[15] The effect of this wavelength on the melanopsin containing retinal ganglion cells responsible for circadian synthesis could suppress and shorten melatonin onset and duration, and potentially impact sleep, thermoregulation, blood pressure, and glucose homeostasis.[16,17]

Sleep disturbance and intolerance to light appeared to be the principal reasons given for withdrawal, especially in older volunteers; in younger people withdrawal was associated with lack of compliance with mask wear and/or attendance. The level of light intolerance of 5–10% appears acceptable as light therapy moves into efficacy trials. Further dose calibration experiments changing intensity or with shorter duration may be justified depending on future efficacy trials.

The significant withdrawal rate of 24% (11% in the first month of usage) and the self-reported adverse event rate of ~75% all indicate that further modifications of mask design are needed for home compliance to become optimal. Patients with DME reported less adverse events possibly due to higher motivation in participants with treatable disease.

Neurobehavioural function as a measure of sleep disturbance was reduced at month 3 in PVT-RT for both age groups and PVT-NL for younger participants. The delays in RT of 24.39 (younger) and 25.39 (older) were within the SD of typical response times for healthy non-sleep-deprived participants (40–100 ms) in our and other published data.[9,18] PVT-NL showed a larger 43% mean change in younger participants but changed little in older participants; impaired PVT-NL has been reported in sleep-deprived young men but not older men.[19,20] The worsening in NL returned to normal by month 4.

Although our results are generally reassuring we believe that PVT is an important safety measurement and should be included in dark adaptation blocking therapy trials. Eight of our participants developed loss of performance during the study (Supplementary Tables 3 and 4). NL rose as high as 40 in one participant and in 3 there was concordance between worsening NL and RT. Worsening reaction times and NL have been observed after extended periods of wakefulness[21] and associated with poor driving performance.[22] We developed age-specific upper criteria, extrapolated from published normative data,[7] useful in future clinical trials (<52 years: NL = 17; 52–64 years: NL = 26; >64 years: NL = 31).

Some secondary outcomes (BCVA, OCT, mfERG latency, and CCT deutan) showed statistically significant changes at month 3 but none were in an unsafe direction.

The GHQ12 evidence of worsening wellbeing is of some concern. GHQ12 was a secondary outcome; so the findings should be interpreted with caution but the worsening was significant in all the groups (28% reduction for younger healthy controls) and some participants moved from the no distress to the some distress or severe distress categories. There were no significant changes in depressive symptoms on CESD.

We extended our safety study to a cohort of people with DMO primarily to study safety but also to investigate an effect on macular oedema. These participants performed worse across all study variables including daytime alertness, psychological wellbeing, and retinal structure/function when compared with healthy volunteers with similar ages (Group B). This is not unexpected for retinal structure and function, especially colour dysfunction[23] but less familiar to ophthalmology for poor wellbeing and alertness. Visually impaired people have reported lowered alertness and performance parameters[24] and people with diabetes suppressed neuropsychological test scores compared with age-matched controls.[25]

All study parameters that measured retinal function and structure improved by month 3 apart from EOG. Improvements persisted into month 4 but only reached statistical significance for CS and MP1. The depression scores improved but psychological wellbeing worsened at month 3 as in the healthy cohort.

We detected a small beneficial effect of mask wear on DMO as measured by OCT. This effect was larger for those with more severe thickness, may be clinically relevant, was statistically significant and comprised a 10–20% reduction in thickness. Arden *et al*[6] reported 6-month OCT and BCVA changes in an uncontrolled patient population with bilateral DMO where one eye was treated with a light mask with four light-emitting diodes

with similar parameters as in our OLED. The authors reported a reduction in number of retinal cysts and detected no adverse events, claiming the therapy to be safe and acceptable. Their study had a number of limitations in the *post hoc* statistical analysis and no safety data were collected. However our results are consistent with their findings. Faced with a global epidemic of diabetes a readily available, inexpensive, non-invasive home therapy that can be used at the earliest stages of disease development, would be a major therapeutic asset.

Our study detected no major safety signal and allows a move to phase 3 clinical trials of light therapy during sleep for retinal diseases. Data from our DMO cohort provide useful additional pilot evidence of a potential beneficial effect. We believe that the therapy will be acceptable to most potential patients including older people and people with diabetes. However it will be challenging for some individuals, with a small but acceptable proportion likely to be intolerant beyond a few days. Including behavioural and psychological investigations of the effect on sleep disturbance in future clinical trials will be important including carefully designed monitoring and exit criteria. Usefulness will depend on improvements in mask design for compliance, tolerability, and acceptability.

Summary

What was known before

- Light therapy has been proposed as a potential therapy for retinal diseases.
- Dark adaptation during sleep increases oxygen demands in the retina.

What this study adds

- Organic light-emitting diode sleep masks show no major safety signal.
- Light therapy is acceptable apart from in some healthy participants.
- Daytime alertness and psychological wellbeing should be monitored during light therapy.
- Preliminary data suggest a beneficial effect on diabetic macular oedema.

Conflict of interest

IG is the Medical and Scientific Adviser to Polyphotonix Medical Ltd. MNH is the Operations Director at Polyphotonix Medical Ltd. The remaining authors declare no conflict of interest.

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Safety and acceptability of an organic light-emitting diode sleep mask as a potential therapy for retinal disease

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1. You are assessing a 63-year-old woman with diabetic macular oedema, and you are considering treatment with an organic light-emitting diode (OLED) at night to slow the progression of her disease. Which of the following statements regarding the tolerability of OLED therapy in the current study is ***most*** accurate?

   A Only half of the cohort completed the study
   B An estimated 90% of participants who dropped out did so in the first month
   C Intolerance of light and sleep disturbance were the most common reasons for study withdrawal
   D Headaches were the most common reason for study withdrawal

2. What were the effects of OLED therapy on attention tests in the current study?

   A No group experienced a difference in psychomotor vigilance testing during or after treatment
   B The cohort with diabetic macular oedema experienced an improvement in psychomotor vigilance testing with treatment
   C Response time decreased among young adults, and this population continued to experience depression at 1 month after OLED treatment
   D OLED therapy slowed response times most among the cohort with diabetic macular oedema

3. In the current study, which ophthalmologic outcome was ***most*** improved with OLED therapy among adults with diabetic macular oedema?

   A Best corrected visual acuity
   B Cambridge color vision test
   C Optical coherence tomography mean central subfield thickness (CST)
   D Electrooculogram

4. According to the results of the current study, what should you tell this patient about OLED therapy and the risks for depression and problems with sleep?

   A OLED therapy significantly improved depression overall
   B OLED therapy significantly worsened sleep quality overall
   C There was no significant change in depression or sleep scores during treatment
   D Depression scores worsened, but sleep quality improved during treatment

Activity evaluation

1. The activity supported the learning objectives.

Strongly disagree				Strongly agree
1	2	3	4	5

2. The material was organized clearly for learning to occur.

Strongly disagree				Strongly agree
1	2	3	4	5

3. The content learned from this activity will impact my practice.

Strongly disagree				Strongly agree
1	2	3	4	5

4. The activity was presented objectively and free of commercial bias.

Strongly disagree				Strongly agree
1	2	3	4	5