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Title:

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

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ABSTRACT

Aims: 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).

Methods: Healthy volunteers in 2 groups, 18-30 yrs (A), 50-70 yrs (B) and people with DMO (C) wore masks (504nm wavelength; 80cd/m^2 luminance; ≤8 hours) 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, retinal thickness on OCT.

Results: Of 60 participants, 16 (27%) withdrew, 8 (13%) before month 1, due to sleep disturbances and mask intolerance. 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 $p<0.05$).

Conclusions: 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 to some healthy participants. Preliminary data suggest a beneficial effect on retinal thickness in DMO. This novel therapeutic approach is ready for large clinical trials.

The increased oxygen demand in the outer retina in the dark, due mostly to the 140 million rods which 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).

METHODS

Healthy adult volunteers with good general health from 2 age groups (group A: aged 18 to 30 years; group B: aged 50 to 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), 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 ≤ETDRS grade 47, DMO meeting definition of clinically significant macular oedema, mean subfield thickness ≥2 standard deviation (SD) in any central 5 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 504nm 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 hours 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 (msec) (PVT-RT) and number of lapses (failure to respond) (PVT-NL). Using normative data we derived upper limits of normal (mean +2SD): 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 (CES-D) (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 metre), Pelli Robson contrast sensitivity (CS), colour vision (CCT; Cambridge Research Systems, 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), electrooculogram (EOG), microperimetry (MP, Nidek MP1), 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, 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 2-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 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: i) 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 ii) Holm-Bonferroni to compare ordered p values for the 2 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

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 to 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. 8 withdrew after completing month 1. Numbers completing all study visits were: A 17, B 17, C 12. Reasons for withdrawal are listed in Table 1. Light intolerance and sleep disturbance were cited by 1 participant in Group A and 5 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 hours) 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 while 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 to 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 $p=0.006$).

Safety

Tables 2 and 3 show changes in study variables at months 3 and 4 compared to baseline for participants who completed 3 months of sleep mask wear (A 17, B 17, 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 while 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 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.

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.

40/45 (95%) healthy participants and 13/15 (87%) DMO patients completed sleep diaries during the dosing period (61% for all three months). 33 reported mask discomfort and slippage. 3 participants (none in Group C) reported the light as an issue and then only at month 1; all 3 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 (see 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). 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 10µm 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 approximately 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.

Neurobehavioral 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 msec) 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. 8 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 number of lapses 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, 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 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 CES-D.

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 to 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 to 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. 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 4 light emitting diodes with similar parameters as in our OLED.[6] 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 was 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 provides 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.

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Conflicts of interest: IG is the Medical and Scientific Adviser to Polyphotonix Medical Ltd. MH is the Operations Director at Polyphotonix Medical Ltd. No conflicting relationships exist for other authors.

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LEGENDS FOR FIGURES

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

Figure 2. Boxplots for total hours of mask wear in those participants (Group A n=17, Group B n=17, 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 hours in month 2, patient 31 138 hours in month 3, patient 34 129 hours in month 3).

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

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. Data are presented as means with standard deviation (SD) or 95% confidence intervals, corrected for hours of mask wear. P values refer to paired t-test of change in outcome (month 3 minus baseline), are uncorrected and should be interpreted against adjusted values of α (see text).

	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***	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***	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 (msec)	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

* *= statistically significant*

Legend: BCVA = best corrected visual acuity; CCT = Cambridge color vision test; CESD = The Centre for Epidemiologic Studies Depression scale; GHQ12 **General Health Questionnaire of psychological wellbeing**; CS = contrast sensitivity; EOG = electro-oculogram; 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

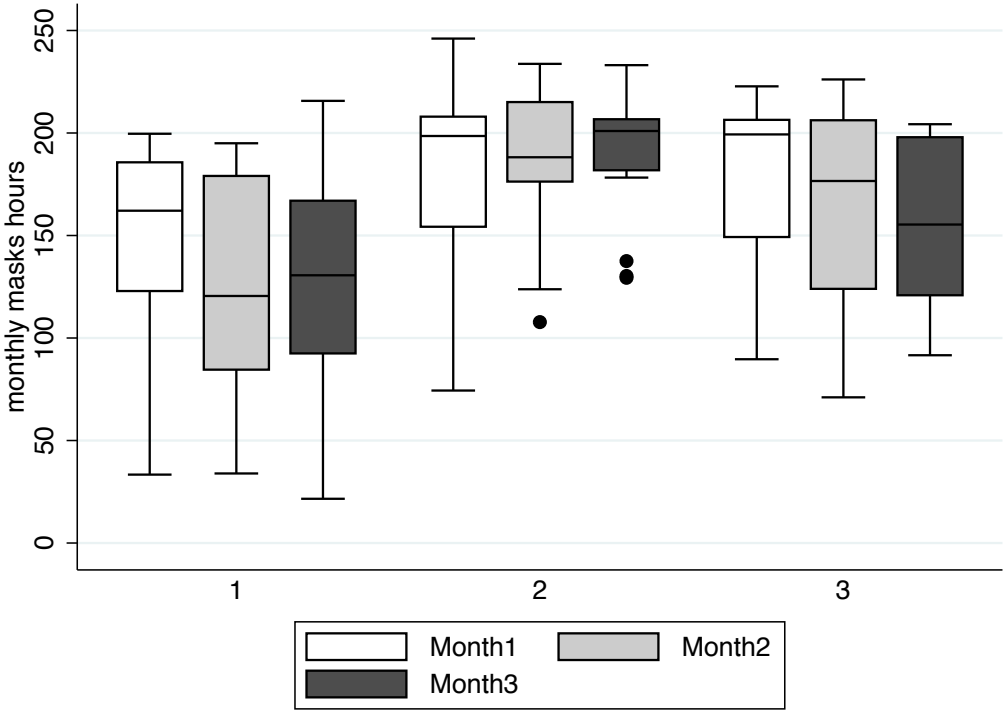
Table 3: Changes in alertness, sleep quality, psychological wellbeing, and ocular function and structure 1 month after discontinuing sleep mask wear in 46 participants who completed 3 months of wear. EOG was not recorded at this visit. Data are presented as means with standard deviation (SD) or 95% confidence intervals, corrected for hours of mask wear. Data on the effect of mask wear is also presented as effect of 100 hours wear. P values are uncorrected and should be interpreted against adjusted values of α (see text).

	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 3 (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 (msec)	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

* *= statistically significant*

Legend: BCVA = best corrected visual acuity; CCT = Cambridge color vision test; CESD = The Centre for Epidemiologic Studies Depression scale; GHQ12 **General Health Questionnaire of psychological wellbeing**; CS = contrast sensitivity; EOG = electro-oculogram; 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


monthly masks hours
0
50
100
150
200
250
1
2
3
Month1
Month2
Month3