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Blue-blocking glasses as additive treatment for mania: Effects on actigraphy-derived sleep parameters

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Abstract

Improvement of sleep is a central treatment goal for patients in a manic state. Blue-blocking (BB) glasses as adjunctive treatment hasten overall recovery from mania. This method is an evolvement from dark therapy and builds on the discovery of the blue-light-sensitive retinal ganglion cell that signals daytime to the brain. We report effects of adjunctive BB glasses on actigraphy-derived sleep parameters for manic inpatients as compared to placebo. Hospitalized patients with bipolar disorder in a manic state aged 18–70 years were recruited from five clinics in Norway from February 2012 to February 2015. The participants were randomly allocated to wearing BB glasses or placebo (clear glasses) as an adjunctive treatment from 18:00 to 08:00 hours for seven consecutive nights. Sleep and wake were monitored by actigraphy. From 32 eligible patients, 10 patients in each group qualified for the group analyses. The BB group's mean sleep efficiency was significantly higher at night 5 as compared to the placebo group (92.6% vs. 83.1%, p = .027). The 95% confidence interval (CI) was 89.4%–95.8% in the BB group and 75.9%–90.3% in the placebo group. There were fewer nights of interrupted sleep in the BB group: 29.6% versus 43.8% in the placebo group. The BB group received less-intensive sleep-promoting pharmacological treatment and showed significantly higher sleep efficiency and more consolidated sleep as compared to the placebo group. Our findings suggest sleep-promoting effects through deactivating mechanisms. Adjunctive BB glasses seem to be useful for improving sleep for manic patients in the hospital setting.

KEYWORDS

amber, bipolar disorder, chronotherapy, darkness, orange, virtual

1 | INTRODUCTION

Bipolar disorders (BDs) have traditionally been regarded as disorders of mood. Several coinciding symptoms, however, cycle in remarkable synchrony with the mood swings, in particular alterations in sleep and activity (Scott et al., 2017; Wehr et al., 1998).

Sleep disturbances are common in all states of BD, but usually exacerbated during episodes (Bauer et al., 2006; Gruber et al., 2011). The most dramatic changes in sleep patterns and subjective need for sleep occur during mania. Many patients report the first sign of an emerging manic episode as a sudden change in sleep, which predicts the onset of a mood episode with a latency of 1 day (Bauer et al., 2006). With hypomania, the subjective need for sleep and motivation for going to bed diminishes. At the transition to frank mania, activation, irritability and grandiosity rise even further. Grandiose psychosis usually interferes with the patients' insight and ability to comply with the treatment. Even with good cooperation from the patient, pharmacological restoring of sleep during mania can be challenging and may require high doses of antipsychotics, sedatives and hypnotics. This unsatisfactory clinical shortcoming may arise from an incomplete understanding of the mania-sustaining processes.

Converging evidence from several lines of research points to light as a major environmental influence in BD (Bauer et al., 2015; Esaki et al., 2019; Lewy et al., 1985). The effectiveness of chronotherapeutic interventions for BD strongly indicates that light plays a key role (Gottlieb et al., 2019). The first report on dark therapy for a severe case of rapid-cycling BD showed an almost instant transition from irregular to regular sleep concomitant with stabilization of mood (Wehr et al., 1998). The findings were replicated in another case report the following year, and the method was extended to manic inpatients in a very promising pilot study (Barbini et al., 2005; Wirz-Justice, Quinto, Cajochen, Werth, & Hock, 1999). The discovery of the daylight receptor (the intrinsically photo-responsive retinal ganglion cell; ipRGC), which is mainly blue-light sensitive, paved the way for the use of blue-blocking (BB) glasses as a means of creating a virtual darkness for the brain (Kayumov et al., 2005; Phelps, 2008).

Light at night may disrupt circadian rhythms and inhibit sleep Esaki et al., 2019; Green, Cohen-Zion, Haim, & Dagan, 2017). The retinal daylight receptors project directly to the circadian master clock, the suprachiasmatic nucleus (SCN) (LeGates, Fernandez, & Hattar, 2014). Additionally, the ipRGCs have projections to several other brain areas central to regulation of mood, cognition, emotion and arousal (Fernandez et al., 2018; LeGates et al., 2014; Vandewalle et al., 2010). Light in the blue and blue-green spectrum comprises a daylight signal and suppresses melatonin production via the ipRGC-SCN projections. Conversely, light depleted of wavelengths shorter than approximately 530 nm has a low capacity for stimulating the ipRGCs and hence allows melatonin production (Kayumov et al., 2005). Blue-blocking devices also protect from alerting effects of light in the evening (van der Lely et al., 2015).

Studies on the effects of blue-blocking (BB) interventions on sleep-related outcomes for BD patients are still few but very promising (Henriksen et al., 2014; Phelps, 2008). In the first case report on BB glasses used during mania, sleep was rapidly regularized. In this respect, the change in sleep was a replication of the preceding dark-therapy case observations. The patient showed fewer limb movements during sleep, which suggested deactivation. In the Virtual darkness as additive treatment in mania (VATMAN) trial (ClinicalTrials.gov, NTC01818622), we found a clear and rapid effect on overall Young Mania Rating Scale (YMRS) outcomes after intervention with adjunctive BB glasses, as compared to placebo (clear-lensed glasses) (Henriksen et al., 2016; Young, Biggs, Ziegler, & Meyer, 1978).

Here we present the sleep outcomes from the same trial, as measured by wrist-worn actigraphs. We chose sleep efficiency as the primary outcome, and motor activity during the main sleep interval as the outcome most directly reflecting nightly activation. As secondary outcomes we analysed group differences in total sleep, wake after sleep onset, number of wake episodes, sleep fragmentation index, sleep onset, sleep offset and mid-time sleep. The sleep pattern characteristic mid-sleep awakening is descriptively presented. Finally, we discuss current theories relevant for possible mechanisms of action.

2 | METHODS

2.1 | Study design

The study was part of a multicenter randomized placebo-controlled single-blinded trial, recruiting patients from five hospitals in the southwest of Norway, latitude 58–59′N, in the time period February 2012 to February 2015 (Henriksen et al., 2016). The trial is registered with ClinicalTrials.gov: NTC01818622.

Eligible participants were patients in hospital with BD in a manic phase, aged 18–70 years. Adherence to the allocated intervention and valid actigraphy recordings for night 1 and night 5 qualified patients for inclusion in the statistical analyses of difference between the groups. For the description of nights with interrupted sleep, all nights of adherence to the protocol and with valid actigraphy recordings were used. Interrupted sleep was defined as one or more periods of active wake (wake and continuous motor activity) lasting 30 min or longer, within the main sleep interval.

2.2 | Ethics

The Regional Ethical Committee in Norway (REK registration 2011/1668) approved the procedures, which were in accordance with the Helsinki Declaration. All patients included in the study provided written informed consent.

2.3 | Randomization and masking

The included patients were randomly assigned to BB glasses or clear (placebo) glasses, by a manual draw performed by secretaries

not otherwise involved in the trial. All participants received identical information about the purpose of the study, which was testing the effectiveness of different glasses in reducing manic symptoms. The included patients had no previous knowledge of effects of BB glasses. No patients observed glasses of different color to their own.

2.4 | Procedures

Experienced psychiatrists trained in the use of the Mini International Neuropsychiatric Interview-Plus verified a diagnosis of 'bipolar disorder type I, current episode manic' (Sheehan et al., 1998). The patient's eyes were physically examined for transparency and vision by inspection of the red reflex and finger-count test.

2.5 | Interventions

The participants wore blue-blocking glasses (LowBlueLights.com, University Heights, OH, USA) or clear-lensed glasses (Uvex, Furth, Germany, and 3M, Austin, TX, USA) from 18:00 to 08:00 hours for 7 days. For transmittance of the intervention glasses, we refer to a previous publication from the trial (Henriksen et al., 2016). All patients received treatment as usual (TAU), individualized according to daily symptom levels, acceptance by patients, best medical judgement and law restrictions. The pharmacological TAU is shown in Table 1. Participants and nursing staff were instructed that neither type of glasses could be taken off unless turning out the light at bedtime. In the case of wake before 08:00 hours, the glasses should be put on. The participants could choose between different models of glasses according to individual comfort and preference of style.

2.6 | Measures

Motor activity, sleep and wakefulness were monitored continuously by actigraphy during the intervention (7 days or until dropout), with supporting data from daily nurse reports on sleep and wakefulness. All participants wore an actigraph device (Actiwatch Spectrum, Philips Respironics Inc.) on the wrist, left or right according to personal preference. Data were recorded in 30-s epochs. Start and end of major rest intervals were manually scored based on inspection of raw data supported by sleep logs, as recommended for actigraphy-derived sleep analyses (Smith et al., 2018). The inspection included both motor activity and light exposure. Wake thresholds and time of inactivity for calculating sleep onset and offset were set to medium sensitivity (40 counts/min) and 10 min, respectively (Actiware version 6.0, Philips Respironics Inc.). A detailed description of the criteria used for defining the major rest intervals is available in Appendix S1.

Habitual morningness or eveningness was assessed by the self-report Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) at the time of discharge (Horne & Ostberg, 1976). The patients were asked to recollect their habitual preferences when in a stable state. The MEQ constitutes 19 items: five items describing actual daily behaviour and 14 items referring to preferred timing in a self-regulated environment (i.e., preferred time of sleep and what time of day the person feels most competent to perform demanding tasks). MEQ scores between 59 and 86 indicate morning types, 42–58 indicates neither type and 16–41 indicates evening types.

The global seasonality score (GSS) derives from sub-scores in the Seasonal Pattern Assessment Questionnaire (SPAQ), which was originally made to assess seasonal affective disorder (SAD) (Melrose, 2015). The GSS measures seasonal variations in the items sleep, mood, weight, energy, social activity and appetite. Each of the six items is scaled 0–4, ranging from no seasonality to extremely marked seasonal variation, yielding a total score range of 0 to 24. We used an authorized Norwegian version of the questionnaire, translated by Dr Lingjaerde (Lingjærde, 1996). The cut-off levels of the GSS are usually set to 9–10 for sub-SAD and ≥11 for SAD (Melrose, 2015).

2.7 | Outcomes

The primary outcomes were sleep efficiency (percentage sleep during the main rest interval) and motor activity during sleep intervals. The secondary outcomes were total sleep (hours) during the main rest interval, wake after sleep onset (minutes), number of wake episodes, sleep fragmentation index (percentage active time in sleep interval + percentage inactive bouts of 1 min duration), sleep onset, sleep offset and mid-time sleep. For the descriptive presentation of nights with interrupted sleep, all valid night recordings from night 1 through to night 5 were included.

2.8 | Statistical analyses

To characterize the sample, descriptive statistical methods were used. The effect of BB glasses at night 5 was assessed using the ANCOVA; that is, the linear regression for the outcome variable at night 5 depending on the group assignment adjusted for the outcome at night 1. We chose to analyse for group differences at night 5 because of two dropouts in the placebo group after this time-point. We considered these events to be not at random but a consequence of the allocation as described in the trial profile in a previous publication (Henriksen et al., 2016). At night 5, the integrity of the RCT design was, however, still sufficiently maintained.

In the graphical presentation, we used the raw data for each patient and the mean (95% confidence interval [CI]) at night 1 and night 5. Sleep efficiency, activity, wake after sleep onset, wake bouts and sleep fragmentation index were log-transformed before

TABLE 1 Individual medications for patients assigned to blue-blocking glasses or clear glasses (placebo)

Patient	Antipsychotics, mean dosage (mg/day)	Anticonvulsants, mean dosage (mg/day)	Lithium, mean dosage (mg/day)	Anxiolytics/hypnotics/sedatives, mean dosage (mg/day)
Clear glasses (placebo)				
1	Olanzapine 5.6 Quetiapine 600.0	Valproate 837.5		Diazepam 21.3 Zopiclone 15
2[a]	Quetiapine 200.0			
3		Valproate 3,300.0	Lithium sulphate 84.0	Zopiclone 7.5, Alimemazine 40.0
4	Haloperidol 6.25 Levomepromazine 50.0	Valproate 1,537.5		Diazepam 10.0, Zopiclone 7.5
5[a]	Haloperidol depot 50.0 (every 14 days) Chlorpromazine 162.5		Lithium sulpate 119.9	Diazepam 16.3
6	Haloperidol 0.75 Olanzapine 22.5	Carbamazepine 325.0		Diazepam 34.4
7	Olanzapine 20.0 Quetiapine 100.0		Lithium carbonate 1,200.0	Oxazepam 17.0 Zopiclone 3.3 Alimemazine 10.0, Cetirizine 10.0
8	Chlorprothixene 123.1 Olanzapine 23.6			Oxazepam 10.0
9	Levomepromazine 6.3, Olanzapine 3.8		Lithium sulphate 166.0	Diazepam 5.0 Melatonin 0.5
10	Aripiprazole 9.0 Quetiapine 30.0 Zuclopenthixol 10.0	Valproate 936.0		Cetirizine 10.0
Blue-blocking glasses				
11	Quetiapine 350.0 Zuclopenthixol 20.0		Lithium sulphate 84.0	
12	Olanzapine 20.0	Valproate 562.6		
13	Olanzapine 15.0			
14	Chlorpromazine 500.0		Lithium sulphate 166.0	Clonazepam 1.25 Cetirizine 10.0, Promethazine 25.0
15	Olanzapine 6.9 Quetiapine 600.0	Valproate 450.0		
16	Olanzapine 25.0	Lamotrigine 200.0	Lithium sulphate 192.6	Clonazepam 0.9
17	Aripiprazole 10.0			
18	Chlorprothixene 100.0, Olanzapine 40.0		Lithium sulphate 249.0	Buspirone 30.0, Clonazepam 2.25
19	Risperidone 0.6	Lamotrigine 162.5	Lithium sulphate 120.8	Alimemazine 3.75, Mirtazapine 24.4[b]
20	Olanzapine 15.0	Valproate 600.0		

[a]Patients 2 and 5 were administered ibuprofen 250 mg/day. Ibuprofen may affect melatonin production.

[b]Sedation is a recognized side-effect of the antidepressant mirtazapine

the regression analysis and computation of mean (95% CI). The significance level was set to 0.05. The computation was carried out in SPSS 25 and R 3.5.0 (R Team, 2018). The graphics were created using Matlab 9.0.

3 | RESULTS

Thirty-two patients were randomized to one of the two intervention groups (Figure 1). Two patients were unable to adhere to the protocol and six patients withdrew consent. One patient was excluded due to withdrawal symptoms and one patient's actigraphy recording failed. In the BB group, one patient dropped out after one night and for another patient the first night recording was invalid. In the placebo group, two patients dropped out after five and six nights, respectively. This yielded 20 patients for the ANCOVA analyses, 10 patients in the BB group and 10 patients in the placebo group.

Clinical characteristics of the current episode, previous medical history and measures of seasonality and morningness/eveningness

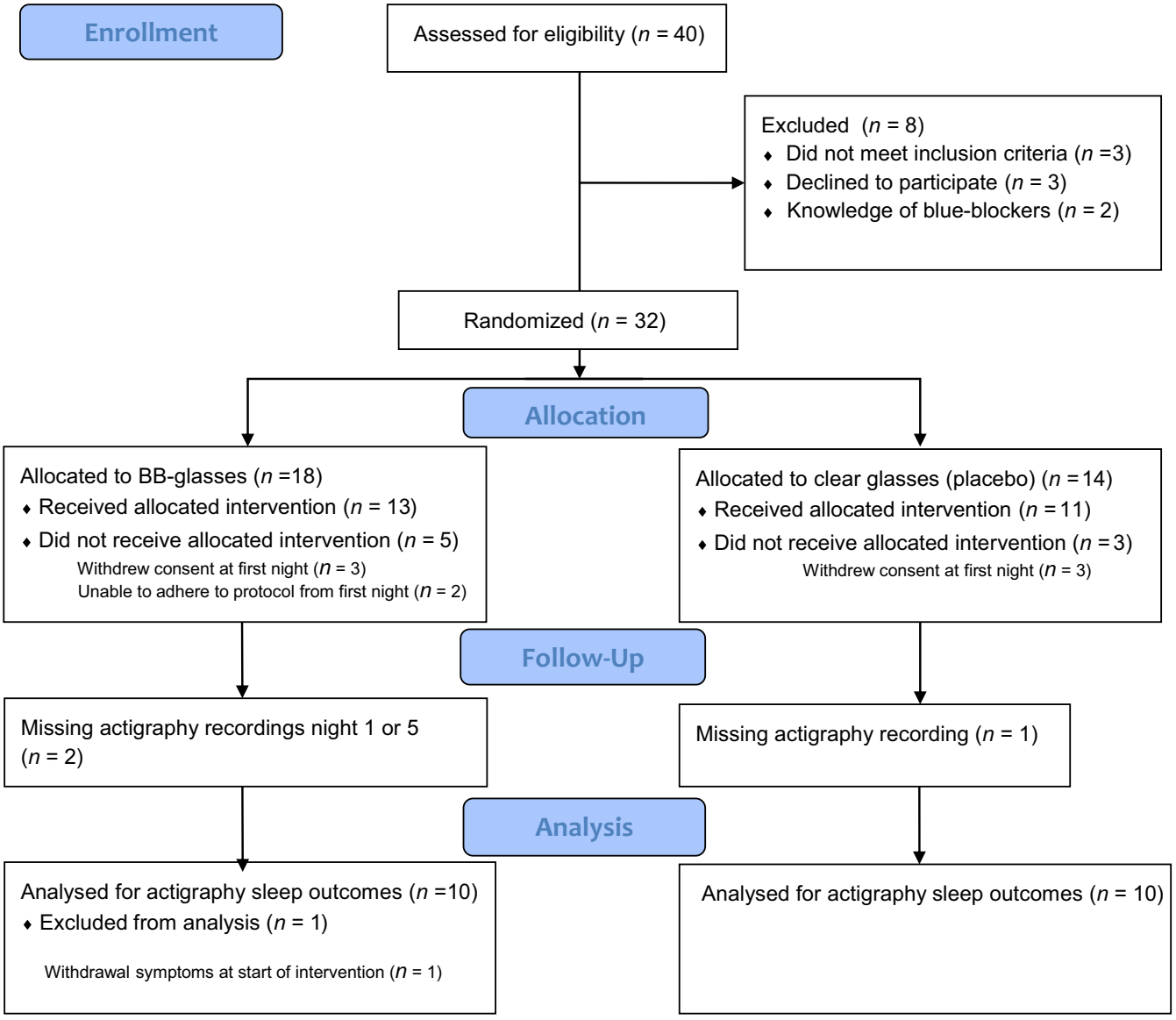

FIGURE 1 Trial profile

are shown in Table 2. The placebo group was somewhat older (mean 48.8 years vs. 43.9 years) and had a modestly higher mean YMRS total score at the start of the intervention (26.8 vs. 23.9). The placebo group scored on average as more morning type than the BB group (MEQ: 60.4 ± 5.8 vs. 52.4 ± 14.8, respectively). The data on seasonality were similar across the groups; mean GSS scores were under the cut-off for sub-SAD for both the placebo and the BB groups (8.1 vs. 7.3, respectively). Approximately the same proportion of patients in the two groups reported a seasonal change in sleep of 1 hour or more.

The BB group received less medication per TAU than the placebo group. Only 3/10 patients in the BB group received two or more different types of antipsychotics, versus 8/10 in the placebo group. For anxiolytics, hypnotics or sedatives, the ratios were 4/10 for the BB group and 9/10 for the placebo group (Table 1).

After five nights of intervention, the BB group's mean sleep efficiency was significantly higher as compared to the placebo group (p = .027). The mean sleep efficiency in the BB group increased from day one (88.1%; 95% CI, 82.4%–93.8%) to night 5 (92.6%; CI, 89.4%–95.8%), whereas the placebo group's mean sleep efficiency showed little change from night 1 (83.4%; CI, 71.2%–95.6%) to night 5 (83.1%; CI, 75.9%–90.3%) (Figure 2, Table S1).

The BB group showed lower activity counts per epoch (one epoch = 30 s) during the main sleep interval at night 5 compared to the placebo group (p = .007). In the BB group, the mean activity during the main sleep interval declined from night 1 (20.0; CI, 9.1–30.9) to night 5 (11.7; CI, 5.6 – 17.8), whereas the placebo group's mean activity during the sleep period increased markedly from night 1 (33.3; CI, −0.1–66.6) to night 5 (47.4; CI, 17.5–77.3).

Wake after sleep onset at night 5 was significantly lower in the BB group (p =.010), for which the wake time nearly halved from night 1 (60.7 min; CI, 23.6–97.7 min) to night 5 (33.5 min; CI, 19.8–47.1 min). The placebo group's wake time increased from night 1 (64.8 min; CI, 14.7–114.9 min) to night 5 (79.2 min; CI, 48.0–110.3 min) (Figure 3, Table S1).

TABLE 2 Characteristics of patients with mania assigned to blue-blocking (BB) glasses or placebo glasses (mean/*SD*)

	Placebo *n* = 10	BB glasses *n* = 10
Age (years)	48.8 (14.1)	43.9 (11.8)
Sex (male)	8/10	6/10
Current episode		
Days from admittance to start of intervention[a]	5 (1–21)[b]	6 (1–20)
YMRS day 0	26.8 (7.5)	23.9 (8.7)
Change in YMRS day 0 to day 1	−1.7 (1.6)	−5.5 (2.9)
Change in YMRS day 0 to day 5	−3.8 (9.1)	−12.9 (7.5)
Data on season, seasonality, morningness/eveningness		
Season for data collection		
Spring (March–May)	3/10	2/10
Summer (June–August)	2/10	1/10
Autumn (September–November)	2/10	5/10
Winter (December–February)	3/10	2/10
Global seasonality score (GSS)	8.1 (5.5)	7.3 (4.6)
Seasonal sleep variability 1 hr or more	5/9	7/10
Morningness–Eveningness Questionnaire (MEQ)	60.4 (5.8)	52.4 (14.8)
Clinical characteristics, medical history		
Self-reported age at first affective episode	22.3 (9.5)	23.4 (12.0)
Duration of illness (years)	24.0 (12.5)	18.1 (11.7)
Lifetime medication use		
Antidepressants	2/10	7/10
Antipsychotics	8/10	09/10
Anticonvulsants	7/10	8/10
Lithium	7/10	5/10
Hypnotics/sedatives	7/10	7/10
Anxiolytics	4/10	6/10

[a]Median/range.

[b]Without patient with extreme value of 535 days, *n* = 9.

For the secondary outcome measures total sleep time, sleep maintenance, sleep fragmentation index and wake bouts, the BB group improved and the placebo group worsened, but the differences were not statistically significant in this sample (Figure 3, Table S1).

Descriptively, there were fewer nights of biphasic or polyphasic sleep in the BB group as compared to the placebo group, when counting number of nights with one or more periods of active wake for 30 min or longer. During the first five nights of actigraphy monitoring, 29.6% (16/54) of valid night recordings for the BB group showed interrupted sleep, compared to 43.8% (21/48) in the placebo group (Table S2). Because the observation of less biphasic or polyphasic sleep in the BB group was made during the course of the study, without an *a priori* hypothesis, we chose to merely describe this without pursuing statistical testing.

We also observed that several patients in both groups showed irregular sleep timing during the intervention. High day-to-day variability of the length of the sleep interval, centred on a relatively stable mid-sleep time, was a characteristic sleep–wake pattern in several patients, as shown in data on sleep outcomes for the full 7 days of observation (Figure S1). For several patients, every other night's sleep interval was either short or contained one or more long active wake periods. This pattern could be seen in both groups, but seemed to be most prominent in the placebo group (Figure 4). The 48-hr-like rhythm is also recognizable in the overview of data for the 7 days shown in Figure S1.

4 | DISCUSSION

In this paper, we present data from the first study on change in actigraphy-derived sleep outcomes and sleep patterns during intervention with BB glasses for BD patients in a manic episode as compared to clear-lensed placebo glasses. Data on the effect on overall manic symptoms have been published previously (Henriksen et al., 2016).

Sleep efficiency increased and mean motor activity in the sleep interval decreased in the BB group. For both primary outcomes, the BB group significantly improved as compared to the placebo group by night 5. Time in wakefulness after sleep onset was also significantly lower in the BB group. For the remaining measures of sleep fragmentation, there were no significant group differences.

Several patients showed a 48-hr-like rhythm of a night of longer sleep alternating with a night of shorter sleep with mid-sleep–wake periods. This pattern could be seen in both groups, but seemed to be more pronounced in the placebo group (Figure 4). Many authors have previously described a distinct 48-hr pattern of activity in bipolar patients, but after a burst of papers in the 1970s the interest faded (Wehr, Goodwin, Wirz-Justice, Breitmaier, & Craig, 1982). It has recently been suggested that the 48-hr-like rhythm of interrupted sleep in bipolar disorder might reflect an amplified dopamine tone, as a footprint of a pathologically prolonged dopamine ultradian oscillator (DUO) rhythm (Blum et al., 2014). In mice, a similar 48-hr activity rhythm is provoked by pharmacologically increasing the availability of dopamine (Blum et al., 2014). Based on the observed decline in Young Mania Rating Scale items reflecting dopamine function in the BB group of the VATMAN trial, we have previously hypothesized that the BB intervention may decrease dopamine tone (Henriksen et al., 2016). The multiple examples of 48-hr-like activity patterns in this sample are interesting in relation to the theory of DUO-influenced sleep disturbance in mania (Blum et al., 2014). More research is needed to establish whether the rhythm of motor activity bursts can serve as a proxy for dopamine tone in humans.

It is also of note that during the first five nights the placebo group's sleep worsened on all outcomes related to activated sleep. Our findings add to the growing literature on poor sleep quality for

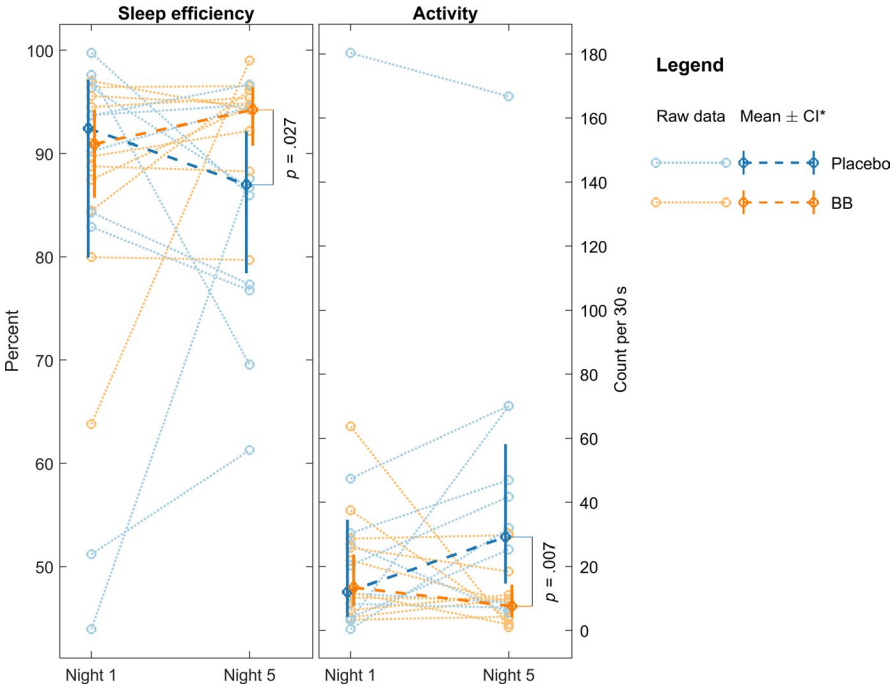

FIGURE 2 Sleep efficiency and motor activity during the sleep interval (counts per 30 s) for the patients included in the ANCOVA analysis at night 5. Raw data and the retransformed means for the blue-blocking glasses (BB) group (n = 10) and the placebo group (n = 10) are shown, and 95% confidence interval (CI), for which the 1-log transformation still applies

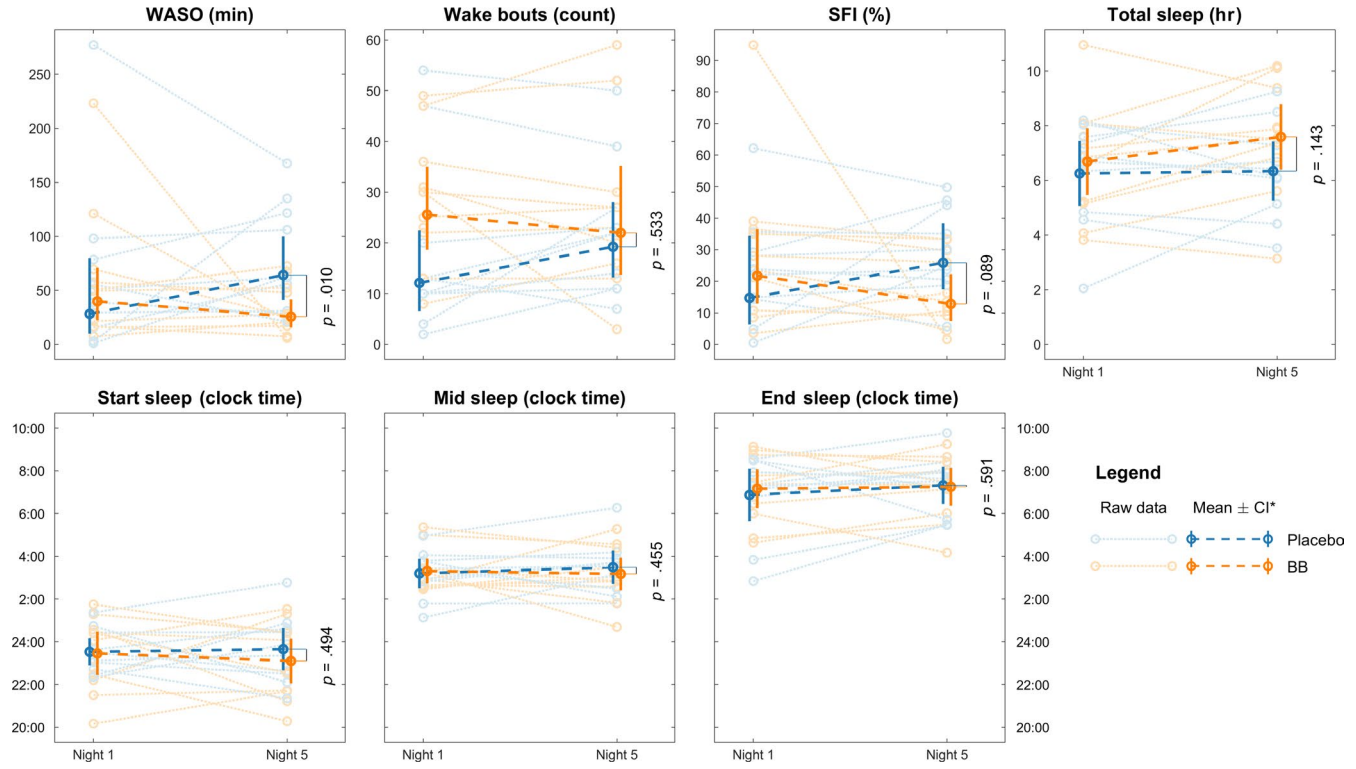

FIGURE 3 Secondary sleep outcomes for the patients included in the ANCOVA analysis. For the outcomes wake after sleep onset (WASO), wake bouts, sleep fragmentation index (SFI) and total sleep, the means were 1-log transformed for the analysis and retransformed for the figure, whereas the 95% confidence intervals (Cis) are still 1-log transformed

hospitalized patients, and how the hospital environment may even worsen sleep (Horne, Hay, Watson, & Anderson, 2018; Lei et al., 2009; Muller, Olschinski, Kundermann, & Cabanel, 2016; Veale, 2019). Several factors in the hospital setting could have an impact on sleep; for example, noise, regular nightly inspection rounds and light flashes. Because the sole intervention in this study was to alter light exposure in the evening and night, it is plausible that the BB group was protected from the activating effects of light at night, whereas the placebo group was not.

The placebo group received more intensive pharmacological treatment than the BB group, as reported in a previous paper from the trial and shown in Table 1 (Henriksen et al., 2016). The design was strictly

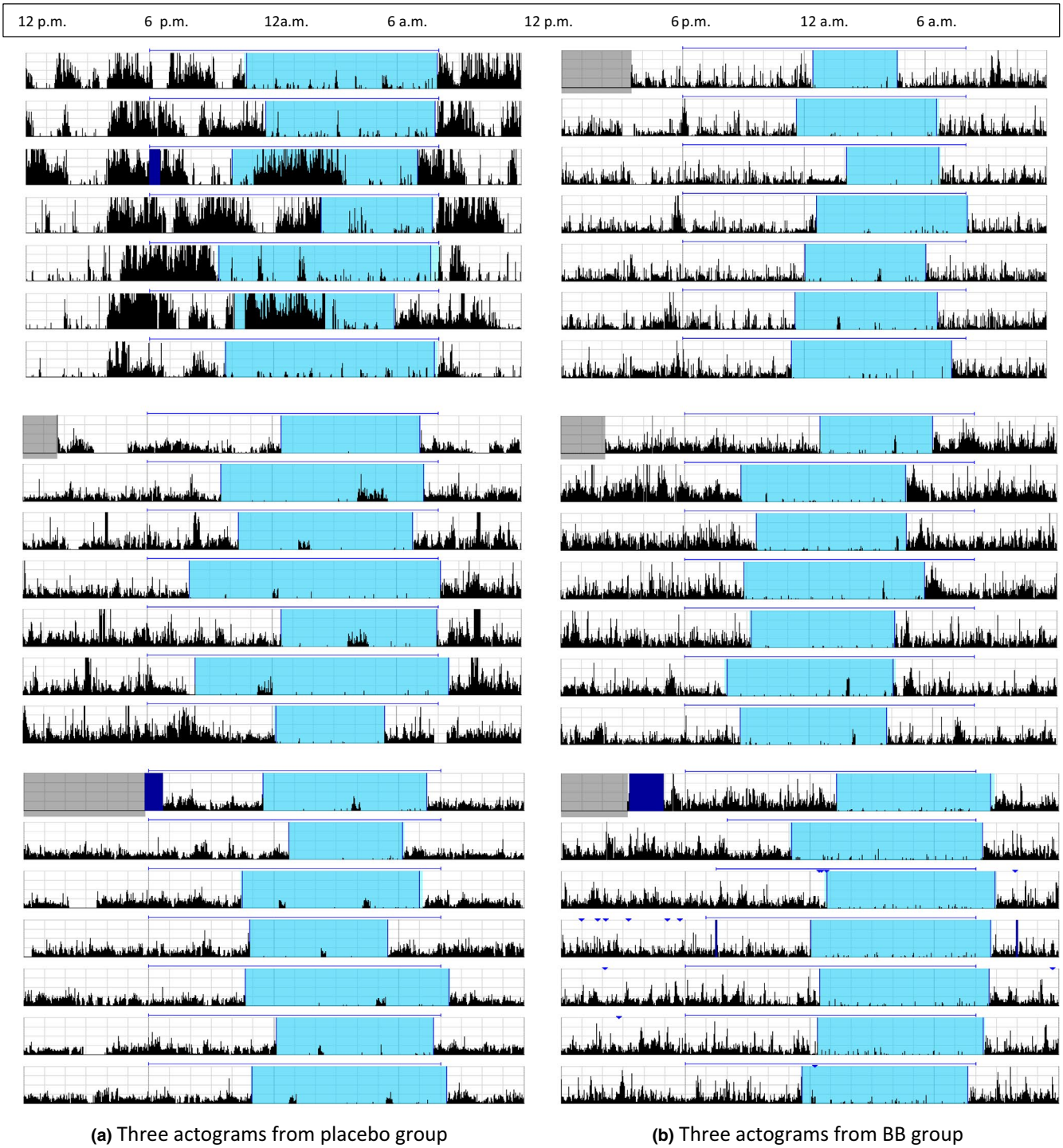

FIGURE 4 Seven-day actograms (one column, 24 hr) of three patients in the placebo group column (a, left) and three patients in the blue-blocking glasses (BB) group column (b, right). Black bars show activity counts; epoch 30 s, scale 1,000 counts maximum. Background colour: dark blue, excluded interval; light blue, main rest interval. Blue lines indicate verified use of glasses or indoor lights off. Note the more pronounced wake periods and irregular sleep–wake cycles of the three patients in the placebo group (column a, left)

naturalistic, except for the interventions, which indicates that the treating doctors regarded sleep as less of a problem for the BB group. We regard the less intensive pharmacological treatment for the BB group as a very important and clinically relevant observation.

Light at night may interfere with sleep through several mechanisms. The original two-process model of sleep regulation describes two independent synergistic processes regulating sleep propensity (Borbely, 1982). Process S describes the homeostatic build-up of sleep debt during wake. Process C refers to the circadian rhythm component (Borbely, 1982). This model still holds ground, but the original model of two independent factors has recently been revised (Xu & Lang, 2018). New research has revealed multiple

reciprocal interactions between these two processes; examples are reduced circadian amplitude and altered clock functioning by increased sleep homeostatic pressure (Borbely, Daan, Wirz-Justice, & Deboer, 2016). Hubbard et al. go further and suggest an expansion of the two-process model to also include the influence of ambient light as a third separate process (Hubbard, Ruppert, Gropp, & Bourgin, 2013).

In modern society, light exposure is a concomitant of wakefulness. Picture a manic patient waking up at 03:00 hours feeling rested. This patient will surely not stay in bed in a dark room but rather reach for the light switch and suddenly feel even more awake and energetic. In this example, wake and light form a reinforcing feedback loop, directly and rapidly affecting the sleep-regulation processes. Short-wavelength light through the ipRGC system counteracts and withholds the effects of the sleep-promoting factor S (sleep depth), through activating wake-promoting projections to the hypothalamus, and via SCN-hypothalamic and brainstem-hypothalamic projections (Hattar et al., 2006; LeGates et al., 2014; Saper & Fuller, 2017). Light also exerts effects on factor C, the circadian rhythm, through change in timing and amplitude of the incoming daylight signal to the SCN and suppression of melatonin secretion (LeGates et al., 2014).

Conversely, BB glasses should have the potential to reduce the nightly sleep-inhibiting effects of the third factor, light, on both process S and process C. Elimination or reduction of the daylight signal in the evening and at night allows for less light-mediated activation and thereby stronger sleep-promoting influence from the homeostatic factor S. Several patients spontaneously reported a sudden awareness of feeling calm, tired or sleepy after putting on the BB glasses. Patients in a manic state are relatively sleep deprived and in this state may be particularly sensitive to the activating effects of light (Gold & Sylvia, 2016; Henriksen et al., 2016).

The previously reported YMRS and activity data from the RCT suggested that deactivation was the first and foremost effect of the BB intervention (Henriksen et al., 2016). The findings on sleep outcomes supported the interpretation of reduced activation in the BB group, seen as effects on sleep efficiency and reduced nightly limb movements.

In the analyses of the sleep outcomes related to circadian factors (process C), such as phase shift of rest and activity rhythm, no effect was found. Synergistic contributions to improved sleep efficiency through effects on melatonin, circadian phase, amplitude and rhythmicity are likely, but need to be tested in larger samples with longer observation.

As described in a previous publication, the interventions were visible to the participants and the nursing staff (Henriksen et al., 2016). No patients observed any intervention other than their own. We instructed the nursing staff to present a uniform approach towards the two groups; that is, encourage equally the use of the glasses according to the protocol. The study was undertaken before there was any knowledge in the patient population on the effects of BB glasses, so we regard clear glasses as a valid placebo at the time of the data collection. The patients could choose the position of the Actiwatch (left or right wrist). We did not note the individual choices, but previous studies have shown no significance of position of the actigraph regarding sleep outcomes (Littner, Kushida, Anderson, Bailey, & Berry, 2003).

The sample was small for analysing actigraphy data, making the study susceptible to type II errors. Two patients dropped out towards the end of the intervention because they were allocated to the placebo condition and not to the BB intervention (worsening of symptoms and no subjective effect). This limited the interpretation of the outcomes in the placebo group after night 5. The lack of baseline data is, however, the most serious limitation, preventing precise effect-size calculations. Based on previous observations, it is likely that some effects were present already on the first night (Henriksen et al., 2014).

From this actigraphy study on the effects of BB glasses on sleep as an adjunctive treatment for mania, we found that the BB group had significantly higher sleep efficiency and lower motor activity in sleep intervals during the course of treatment, as compared to the placebo group. The BB group received substantially less sleep-promoting medication than the placebo group. The outcomes suggest a primary sleep-promoting effect through deactivating mechanisms. Our findings support the suggestion that BB glasses are useful for improving sleep in hospitalized patients in a manic state.

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CONFLICT OF INTEREST

Tone E. G. Henriksen is a shareholder in Chrono Chrome AS. The disclosure does not apply to the planning and data collection for the VATMAN trial.

AUTHOR CONTRIBUTION

TEGH has contributed substantially to the conception and design, literature search, the acquisition of data, processing, analysis and interpretation of data, and drafting and revision of the manuscript. OBF and AL have contributed substantially to the design, interpretation of data and revision of the manuscript. HS, IL and JBB have contributed substantially to the acquisition of data and revision of the manuscript. JG has contributed substantially to the processing, analysis and interpretation of data, and drafting and revision of the manuscript. JA has contributed substantially to the analysis and interpretation of data, and drafting and revision of the manuscript. KY has contributed substantially to the interpretation of data, and drafting and revision of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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