Blue Light Blocking for Bipolar Disorder

Subjects: Neurosciences

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Light is by definition the electromagnetic radiation that corresponds to the perceptual limit of human eyesight. Light, being a form of electromagnetic radiation, is transmitted as a wave of energy particles from its source to the receiver, the human eye. A beam of light has a specific frequency, wavelength and energy. Frequency is measured in hertz (Hz), with one Hz corresponding to a wave passing a fixed point per second. The distance between two corresponding points of two consecutive waves is the wavelength and it is measured in meters. The energy that propagates with a particular beam of light is measured in photons, a hypothetical particle that corresponds to the smallest quantity of light energy at the given wavelength. The energy of a photon is thus variable, proportional to the frequency of the beam of light, inversely proportional to its wavelength, and expressed in electron volts (eV). Recently, following empirical findings, a few clinical studies have focused on the therapeutic potential for blue-light blocking in bipolar disorder (BD), reporting promising results.

bipolar disorder | blue-blocking glasses | amber glasses | mania | bipolar depression

1. Research Data So Far

1.1 Research Data

Table 1 presents the studies that were assessed in brief.

Table 1. Clinical studies involving blue light blocking glasses in bipolar disorder.

Study	Design	Patients	Intervention	Outcome Measure	Main Results	Conclusions
Phelps [1]	Case series	21 consecutive inpatients	Patients received BBG to wear from 20:00 h to bedtime. All had insomnia. Duration of treatment was undisclosed	Clinical Global Improvement Scale (CGI) score	52% of patients improved in CGI, most of them (42%) very much so. 38% did not respond	Results were promising but lack of control or placebo limited their significance
Esaki et al. [2]	RCT	43 outpatients with BD and insomnia	Research group received BBG and placebo	Visual Analog Scale (VAS) self-assessment of sleep quality,	No difference in VAS, sleep actigraphy or mood	BBG may be useful as adjunctive

Study	Design	Patients	Intervention	Outcome Measure	Main Results	Conclusions
		divided in two groups	group clear glasses to wear from 20:00 h to bedtime for 2 weeks	Morningness–Eveningness Questionnaire, sleep actigraphy, evaluation of mood	symptoms, improvement in sleep rhythm	treatment for BD
Henriksen et al. [3]	RCT	32 inpatients with BD divided in two groups, after drop-outs 12 patients in the research and 11 patients in the placebo group	Research group received BBG and placebo group clear glasses to wear from 18:00–20:00 h for 1 week	Young Mania Rating Scale (YMRS), actigraphy recording of motor activity [2][3]	Statistically significant difference in improvement of YMRS score in favor of research group	BBG are effective and feasible as add-on treatment for bipolar mania

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but with no control group [1]. Interestingly, the next study came some eight years later; Henriksen et al. [3] conducted a randomized controlled trial of 42 manic inpatients under pharmacological treatment and concluded that patients who wore blue-light blocking glasses (BBG) had higher sleep efficiency and a rapid decline of symptoms, assessed with the Young Mania Rating Scale (YMRS). Additionally, motor activity was assessed via actigraph recordings and this, along with the YMRS item scores related to increased activation, declined before the YMRS items related to symptoms of distorted thought and perception. This led the researchers to hypothesize that the primary anti-manic effect of BBG is deactivation. The intervention lasted for a week but improvement was evident from day one, with high effect sizes in general and the patients tolerating the BBG well.

Esaki et al. [2] assessed the impact of BBG in euthymic BD outpatients with insomnia who used them for two weeks, from 20:00 to bedtime. In a previous study where the research team examined the effectiveness of BBG against major depressive disorder, 40% of the participants reported pain or discomfort from wearing the BBG for an extended period of time [4]. The authors thus used BBG with a size-adjustable capability in this study. While the authors did not detect and changes in actigraph-recorded sleep parameters, mood symptoms or subjective sleep quality, there was a shift of the circadian rhythm towards the desired direction. However, the results were hampered by the low effect size and concomitant use of antidepressants in the BBG group.

1.2 Quality of Evidence and Potential Confounders

While these results show some progress, there is a lack of a standardized procedure for this treatment, limited examination of potential confounder variables and the clinical potential may be underappreciated. Esaki et al. [2] screened outpatients whose type of BD or current mental status was not considered. Antidepressant use was considered as a confounder variable but there was no mention of mood stabilizer or antipsychotic use, nor was there a measure of sedation attributed to the drug regimen. The patients were instructed to wear BBG after 20:00 p.m. until bedtime. Henriksen et al. [3] recruited inpatients admitted with bipolar mania. Patients were instructed to use the glasses from 18:00 p.m. to 20:00 and were included in the analysis if they did so for at least one evening,

night and early morning. The dosages of the medication were reported in detail for each patient along with individual outcome with regard to the Young Mania Rating Scale score. Nearly all of the patients received a combination of antipsychotics and mood stabilizers.

It is clear from these two very early stage clinical trials that there is a multitude of related variables of which the possible effects should be taken into account while assessing the feasibility of using BBG in practice. There are practical issues, such as the actual effectiveness of the BBG units in their stated role to block blue light and patient comfort while wearing these BBG units. However, there also a significant number of key issues regarding patient's current state that would be appropriate for the treatment, including the type of BD (BD type I, II), phase of the disease (acute episode of mania, depression or mixed-episode, euthymic, hypomanic or dysthymic), and, the assessment of the appropriate time of day for wearing BBG and duration of wear. Finally, numerous potential confounders that include sleep routine, work shifts and current medication regime are relevant factors. These issues are becoming all the more important since the concept of BBG has been widely reported in the media to the extent that there is little chance of running a clinical trial with a placebo group, since BBGs are impossible to mask both from the patient and the researcher due to their characteristic amber hue. To a large extent, these gaps in the literature stem from an approach that is practical but with little linkage to research findings on the underlying psychophysiology.

2. Guidelines for Research and Practice

2.1. Research Setting

Studies so far have included both inpatients in a clinical setting and outpatients. A clinical setting may be more easily controlled and provides the opportunity for a control population who would not wear active lenses. Naturalistic settings involve patients in remission and should be organized during the same seasons and locations that do not vary considerably in latitude for all patients, so as to not have considerable variations in the day–night cycle between patients.

2.2. Study Populations

To summarize the very limited experimental data so far, the researchers should note that they point to the possibility of a specific endophenotype of BD patients who are more prone to circadian-rhythm disruption. This should correspond to patients with a specific pattern of disruption in their corresponding genes, one that could provide a slight benefit in reducing the need compensatory sleep in milder, subclinical cases, as was demonstrated in the unaffected siblings of patients with BD. Hence, a first guideline would be to further expand research on unaffected siblings of patients with BD. Although the genetic burden would be variable, the reduced number of confounder variables in unaffected individuals makes it worthwhile. If unaffected siblings are tested early enough in their lifespan, there is a possibility that in due time they could be diagnosed with BD. These data will be of additional importance compared to senior siblings who are not diagnosed with BD.

2.3. Type, Phase and Age of Onset of BD

An important parameter in any study of BD patients is the diagnostic consistency of the disease. A recent comprehensive review of published articles found a mean prospective consistency of 77.4% and a retrospective consistencies of 67.6% [5]. The results are acceptable as a whole, yet the inclusion of patients with a first-time episode in a study would be best avoided. The type and phase of BD is most likely of lesser importance in a cross-sectional study but monitoring a patient longitudinally as he/she transitions from a manic episode to a euthymic state would provide useful data in how the BBG affects circadian variability in the long term. So far, data have been available from the acute phase of BD and while they are interesting from a clinical viewpoint, they are fraught with confounder variables, including pharmacologic-treatment modalities. Typically, the BBG are considered to be an add-on treatment and thus patient treatment varies greatly. Refractory-to-treatment patients could have multiple confounding factors at play and could mask the results, including rapid-cycling episodes. A better alternative would be a separate study on patients with rapid-cycling or refractory to treatment-as-usual but in an euthymic state while under study. While a BD type I diagnosis typically has a large percentage of interrater reliability and wide acceptance, this is not the case for a BD type II diagnosis where considerable controversy exists on whether patients should be simply classified as being in a bipolar spectrum [6]. So far, the experimental studies have grouped all BD diagnoses together and no discerning elements have been reported between BD types. It is unclear whether the I and II subtypes would be somehow differentiated by severity of circadian dysfunction, although a depressive episode in both major depression and bipolar depression may be treated with blue-light exposure. More comparative research would be helpful.

Age of onset is an understudied variable. BD has been shown to have either a trimodal (early onset, mid-onset and late-onset) or a bimodal age of onset in a recent review [7]. The average age of early onset was 17.3 years (SD = 1.19) corresponding to 45% of total cases, for mid-onset 26.0 years (SD = 1.72) with 35% of total cases and for late onset 41.9 years (SD = 6.16) in 20% of total cases. For the bimodal distribution, the average age of early onset was 22.5 years (SD = 7.32) with 63% of total cases and for late onset was 40.8 years (SD = 16.89) in 37% of total cases. Regarding age of onset of BD, the researchers cannot at this point in time hypothesize as to whether it would be a parameter that could discern patients who would respond better to BLB treatment. Unfortunately, the experimental studies so far failed to either record this variable or compare responders to non-responders on it. The researchers would, however, expect an earlier age of onset to be predictive of response, since a genetic disturbance would manifest its negative effects early. Additionally, with the preponderance of sources of blue light in the modern-day environment, it is plausible that an additive negative effect could affect patients who would otherwise remain asymptomatic for longer. Thus, sources of blue light in the living environment need to be taken into account and neutralized with appropriate solutions. Thankfully, there is a number of alternatives both for lighting but also for the use of digital screens in general with applications that change the color temperature of screens. Hence, this variable needs to be both researched and controlled for in any given research and clinical setting.

2.4. Patient History Taking

A complete patient history should include exhaustive information regarding his/her chronotype, social rhythms and seasonality. Patients should be matched to controls regarding matters that are outside the patient's control, such as type of work and especially regularity of work shifts while sleep patterns and activity need to be recorded. Seasonality is an element that can be easily extracted from patient's history and has not been reported in larger studies so far. It should be taken into account when conducting a clinical trial; this may be challenging considering that typical studies may be extended for a span of time that encompasses two seasons or more.

2.5. Recording of Patient Pharmacological Treatment

A very important confounder variable is current treatment. As reported above, lithium and, to a lesser extent, sodium valproate, have been linked with circadian-rhythm regulation. The presence of these agents in the treatment regime could mask the full effect of BBG treatment. A study comparing treatment efficacy for lithium between patients who responded to BBG and non-responders may yield interesting data. Antipsychotics and benzodiazepines have not been reported to have meaningful effects in the circadian rhythm. However, given the sedentary nature of a number of compounds, they could indirectly affect the results by affecting sleep and alertness. Antidepressants that affect dopaminergic, serotoninergic or melatoninergic transmission may directly affect the circadian rhythms of patients as well. Discerning between the type of antidepressants and response to BBG may also provide some interesting research data.

2.6. Laboratory and Neuropsychological Testing

A comprehensive test battery that can be used to determine the elements in the presumed endophenotype of BD patients with circadian-rhythm dysfunction by examining response to BBG treatment may be a potential research goal. This should include reliable measures of cortisol, melatonin, sleep quality and latency, impulsivity, risk-taking behaviors, arousal, aggression and hostility. Cortisol measurement may be carried out using hair for an up-to-three-month retrospective assessment or saliva to record current variation during the waking day, as carried out elsewhere [8]. Saliva melatonin measurement can be a useful supplement to saliva cortisol measurement [9]. While these elements are negatively affected in all BD patients, it would be interesting to see whether there are meaningful differences between BBG responders and non-responders. If BBG responders have worse scores than non-responders, it is possible that causation flows from the direction of circadian dysregulation to the general dysfunction of dopaminergic regulation and is not a mere correlate. The issue of cost and scalability comes into play. Administering a neuropsychological test battery to assess behavioral aspects is a relatively easier process and does not require a sleep laboratory. Measuring cortisol, melatonin or/and dim light melatonin onset are more expensive but also more exact methods. Actigraph recordings of activity are becoming cheaper with the advent of microtechnologies, with a large number of commercial products already offering some level of activity monitoring. Lately, a number of state-of-the-art machine-learning approaches have been proposed to assess the circadian time from a single blood sample [10][11]. Researchers will soon be offered new tools with great potential.

2.7. Type of BBGs

Finally, there is a practical element that should not be overlooked. The clinician should bear in mind that not all blue-blocking glasses are created equal. Amber lenses may have the higher potential for blocking blue wavelengths and are useful for outdoor use or for use in a controlled clinical setting but they cannot be employed indoors and they skew the perception of color, leading to potential personal safety risks. Most commercially available blue-blocking glasses are tinted amber but also attempt to preserve color perception, which leads to compromises. A recent survey [12] of seven commercially available blue-blocking glasses found the actual reduction ranging from 6–43% while circadian sensitivity was reduced by 4–27%. While all glasses provided a degree of protection against photochemical retinal damage, it is unclear as to the actual meaningful impact on the circadian system would be. Circadian sensitivity was calculated as a function of the spectral sensitivity of the ipRGC cells. To date, there is no experimental study that compares the spectral sensitivity of the ipRGC cells of BD patients to controls, thus the optimum degree of reduction is unknown. Lens transmittance alone cannot determine the circadian impact completely, due to idiosyncratic factors (e.g., pre-existing eyesight issues that require the use of corrective lenses and the transmittance of ocular media). In an experimental setting where the subjects were exposed to evening bright-light LED to a resetting of the circadian pacemaker, a mere 1% dosage of light achieved a level of response comparable to 50% of the full dosage [13]. Thus, the potential of using blue-blocking lenses that do not hinder color perception yet impart a meaningful effect on circadian rhythm appears good. A numerical index, the Non-Linear Circadian Index, has been proposed recently to summarize the impact of the transmitted light on the circadian cycle [14]. The authors suggested that further research should be carried out with retinal cells in vitro and the researchers would expand on this suggestion in that additional research should be carried out in the field with BD patients wearing specific lenses during a specific time of day and level of activity. A summary of the main findings can be found on **Table 2**.

Table 2. Suggestions for future research by research variable.

Research Variable	Suggestion
Setting	A clinical setting may be more easily controlled and provides the opportunity for a control population. Naturalistic settings should be organized during the same seasons and locations that do not vary considerably in latitude for all patients.
Population	Ideally, non-affected siblings of BD patients. If a patient population, then refractory-to-treatment patients and patients with mixed episodes should be examined separately. Include age of onset and duration of untreated and treated disease as confounders if matching on these variables is unfeasible.
Type of bipolar disorder	Bipolar I or II, provided the diagnosis has already been established and the patient has been followed previously to avoid issues with diagnostic accuracy.
Phase	Manic or depressive episode in clinical settings, euthymic in naturalistic settings.
Patient history	Record information on chronotype, social rhythms, seasonality, line of work and work shifts. For patients studied in a naturalistic setting, this information should ideally be unchanged for the duration of the study. Record any changes in this information in clinical patients prior to the latest episode.

Research Variable	Suggestion
Current treatment	Careful recording of type and duration of current treatment. Record separate variables for lithium, valproate, antidepressants and sedating medication. Record previous treatment regime if discontinued prior to relapse and level of response.
Laboratory tests	Cortisol secretion via measurement in hair and saliva, saliva melatonin measurement, activity, portable actigraph measurements of sleep quality and latency; new machine-learning approaches may assess circadian time from blood samples and will become widely available in the near future.
Neuropsychological examination	Measures of impulsivity, risk-taking behavior, arousal, aggression and hostility.
Type of blue-blocking glasses	Amber lenses for a clinical setting, appropriate lenses that do not skew color perception for naturalistic settings. Any type of lenses should be assessed for its effectiveness.

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