



Dark therapy for bipolar disorder using amber lenses for blue light blockade

James Phelps *

Corvallis Psychiatric Clinic, 3517 Samaritan Drive, Corvallis, OR 97330, United States

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Summary “Dark Therapy”, in which complete darkness is used as a mood stabilizer in bipolar disorder, roughly the converse of light therapy for depression, has support in several preliminary studies. Although data are limited, darkness itself appears to organize and stabilize circadian rhythms. Yet insuring complete darkness from 6 p.m. to 8 a.m. the following morning, as used in several studies thus far, is highly impractical and not accepted by patients. However, recent data on the physiology of human circadian rhythm suggests that “virtual darkness” may be achievable by blocking blue wavelengths of light. A recently discovered retinal photoreceptor, whose fibers connect only to the biological clock region of the hypothalamus, has been shown to respond only to a narrow band of wavelengths around 450 nm. Amber-tinted safety glasses, which block transmission of these wavelengths, have already been shown to preserve normal nocturnal melatonin levels in a light environment which otherwise completely suppresses melatonin production. Therefore it may be possible to influence human circadian rhythms by using these lenses at night to blunt the impact of electrical light, particularly the blue light of ubiquitous television screens, by creating a “virtual darkness”. One way to investigate this would be to provide the lenses to patients with severe sleep disturbance of probable circadian origin. A preliminary case series herein demonstrates that some patients with bipolar disorder experience reduced sleep-onset latency with this approach, suggesting a circadian effect. If amber lenses can effectively simulate darkness, a broad range of conditions might respond to this inexpensive therapeutic tool: common forms of insomnia; sleep deprivation in nursing mothers; circadian rhythm disruption in shift workers; and perhaps even rapid cycling bipolar disorder, a difficult- to -treat variation of a common illness.

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We humans have been cavalier with our environments in many ways, sometimes with a significant impact on medical illnesses. Although we have decreased the burden of suffering in remarkable ways, we have also increased it with some behaviors. Among these may be the use of electric light during hours that evolutionarily were dark, which

may have unintended circadian consequences, particularly in chronic mood disorders [1]. Yet the use of television and other bright light at night is now so ingrained in Western cultures that even obvious negative sequelae might not lead to spontaneous behavior change: witness for example the modern epidemic of obesity and metabolic syndrome, particularly in the United States, and the lack of response to calls for increased physical activity or decreased refined carbohydrate intake. A means

* Tel.: +1 541 829 9319 (office); fax: +1 541 768 6560.
E-mail address: jimp@PsychEducation.org

of addressing adverse circadian effects of electric light which people will find acceptable within the context of modern electronic environments would be of great interest.

This paper will integrate the recent discovery of circadian photoreceptors in humans with preliminary evidence from studies of darkness as a treatment for Bipolar Disorder. Using this illness as a paradigm, the feasibility of a simple device for creating "circadian darkness" in fully lighted environments is then demonstrated. If this device is effective for altering circadian rhythm, it could have profound implications for the treatment of many conditions affected by environmental light/dark cycles.

The human circadian photoreceptor

The human eye contains three photoreceptors, not just the familiar scotopic (rods) and photopic (cones) sensory cells. An independent system comprised of retinal ganglion cells has recently been described [2,3]. Fibers from this system project not to the visual cortex, but to the suprachiasmatic nucleus of the hypothalamus, location of the biological clock in humans. These newly-discovered photoreceptors are the primary means by which the human brain differentiates darkness from light, allowing the biological clock to synchronize with the natural day-light cycle. Interestingly, this circadian system utilizes a photopigment which responds primarily to light in the blue portion of the visual spectrum, wavelengths around 460 nm (blue to blue-green). Longer wavelengths are ineffectual except at very high intensities [4,5]. Thus it appears that for the human brain, darkness, at least from a circadian point of view, is effectively the absence of blue light.

The discovery of this circadian photoreceptor system has already led to a minor revolution in treatment modalities for mood disorders. Light therapy for seasonal affective disorder has heretofore been conducted with large "light boxes", most of which are the size of a small suitcase. Discovery of the blue-light dependence of the circadian system led to the development and testing of a light box which emits only blue light, enabling a much smaller and less expensive design, which has since been shown to have efficacy similar to that previously demonstrated for the larger light-boxes [6].

For further exploration of the roles of light and darkness in human illness, one particular mood condition, Bipolar Disorder, might be ideal. Clinicians have long recognized the pro-manic effects of sleep deprivation, but recent data have under-

scored the central role of circadian rhythms in Bipolar Disorder (formerly "manic-depressive illness"). For example, one of the mechanisms of action of lithium appears to be a direct role in regulating the molecular cascade of events which function as a biological clock in animals from fruit flies to humans, through the enzyme glycogen synthase kinase [7]. More recently it was shown in mice that knocking out the CLOCK gene, which codes for a crucial molecule in the 24-h sleep/wake cycle, leads to a behavioral state very similar to mania, which reverts to normal with lithium treatment [8]. Amongst patients with bipolar depression, a particular allele variation of the CLOCK gene is associated with higher activity levels in the evening, delayed sleep onset, and reduced amount of sleep at night, relative to patients with the more common allele; and these differences diminish with lithium treatment [9].

Thus evidence strongly suggests that manipulations of circadian rhythm in Bipolar Disorder may have therapeutic potential. As an illustration of the potential role of darkness as a treatment tool, perhaps relevant to other conditions as well, consider the preliminary experience with "dark therapy" as a treatment for Bipolar Disorder.

Dark therapy

If light therapy is an effective antidepressant for some patients, as has clearly been demonstrated, might darkness potentially act as a "mood stabilizer" in some circumstances, akin to lithium? Limited evidence suggests this may be so. A remarkable case report from the NIMH in 1998 presents a man with rapid cycling Bipolar Disorder which responded dramatically to "enforced darkness" [10]. This gentleman was treated with no medications, only a regimen in which he was routinely placed in a completely dark room every night from 6 p.m. to 8 a.m. the following morning. Despite a pattern of severe and unremitting rapid cycling for several years prior to the initiation of this treatment, he experienced a complete cessation of cycling within several weeks. His response was so dramatic that he was able to taper gradually to a total of 10 h of darkness nightly, from 10 p.m. to 8 a.m., and remained well on this regimen alone for over a year. A single-case replication using this "dark therapy" followed shortly after this publication with similar results [11].

More significantly, a small controlled trial tested the same concept in patients hospitalized with mania [12]. Patients were randomized to receive treatment as usual (TAU), or TAU plus "dark therapy",

using the NIMH protocol. Although the adjunctive circadian treatment was administered for only three nights, patients receiving it experienced a significantly more rapid reduction in YMRS scores (interestingly, however, this result held only for those whose mania had lasted for two weeks or less). Those receiving dark therapy required a lower dose of anti-manic drugs and were discharged from the hospital earlier than those receiving TAU alone.

The importance of regular circadian rhythms has also been underscored in a bipolar-specific psychotherapy called Social Rhythm Therapy. In this treatment, patients are instructed to maintain regular bedtimes and rise times, as well as a regular schedule of other daytime activities. Randomized trials of this approach have demonstrated lower relapse rates for patients receiving social rhythm therapy, relative to treatment as usual [13,14].

Yet in the author's clinical experience, patients strongly resist instructions which might curtail their use of television and/or computers in the late evening. These forms of entertainment are endemic in Western society, although ironically, they emit a very blue light (as patients well know: they can tell when their neighbors are watching television because of the blue color of the light on the window shades, for example). Obviously this is precisely the wrong wavelength to be receiving just before bedtime: it is as though patients expose themselves to circadian "high noon" then expect to be able to turn off the TV and fall asleep quickly. (Might this effect of television even play some role in the popularity of somnogenic medications such as zolpidem and eszopiclone?)

One could even wonder whether evening/late-night blue light exposure from electric lights, televisions, and computers contribute to Attention Deficit Hyperactivity Disorder (ADHD). In an interesting case example consistent with this concern, an 11-year-old with ADHD and apparent delayed sleep phase (bedtime later than 1 a.m. 80% of the time) was taken off methylphenidate and treated with morning light. The intent was to cause a "phase advance", shifting his circadian rhythm toward an earlier bedtime. In one week, his sleep onset had advanced by 2 h, and his Conner's Teacher Global Index score (a standard measure of ADHD severity) had improved from 64 to 45 [15]. An open trial of light therapy for ADHD found similar results in 29 adults [16].

How then to deliver "darkness" when patients are so inclined toward light at night (especially blue light in the form of television)? In psychiatry we already labor against patients' disinclinations on so many fronts (acceptance of diagnosis, side effects, long-term risks, stigma, need for exercise, weight

control) that battling their television and computer use may seem too daunting to pursue. But what if there was a means of delivering "virtual darkness", through the absence of blue light, without any other constraints? (Remember, because of the wavelength preference of the human circadian photoreceptor, the absence of blue light appears to be equivalent to darkness.) Preliminary experience with such an approach will be presented below, after one more diversion into basic science.

Melatonin, light, and blocking blue wavelengths

Melatonin, a hormonal marker of biological night [17], characteristically rises at the onset of sleep and remains elevated through the night, decreasing to near-zero levels at awakening. In an important experiment, healthy subjects were invited to spend the night in a sleep lab, with melatonin levels measured every 30 min. When instead of darkening the lab, the lights were left on all night, subjects' normal melatonin production was completely blunted: no increase at all took place at sleep onset or later, even though most of them slept much of the night. However, when these same subjects wore amber-tinted safety lenses all night, their melatonin levels followed the normal pattern of increase and decrease with sleep onset and offset despite the lights having been left on [18]. A study of similar design replicated this finding [19].

Why amber-tinted safety lenses? This simple device, if the proper hue and density, can block more than 90% of blue wavelengths, allowing transmission of the rest of the visual spectrum [20]. Like the little blue light box, these lenses represent a direct application of the discovery that the circadian photoreceptor system appears to rely entirely on blue light. Thus, blocking those wavelengths creates a "virtual darkness", which the experimental results above demonstrate has a physiologic effect equivalent to true darkness, at least at the level of melatonin synthesis.

An obvious next step is to investigate whether restoring more "natural" melatonin production using these amber lenses, in the face of electrically lit nocturnal environments, might reverse the drift toward delayed sleep phase and circadian disruption which may be associated with this unnatural light exposure in some patients. The simplest way to demonstrate this would be to examine whether patients with a prolonged sleep latency suggestive of a delayed sleep phase might experienced a reduction in this initial insomnia if wearing amber lenses while exposed to electric light in the evening.

Amber lenses for virtual darkness

As a preliminary test of this concept, a series of patients were given amber-tinted plastic safety glasses in the context of outpatient treatment for Bipolar Disorder. Those selected for this trial had initial insomnia at minimum; many had an additional evidence of circadian rhythm disruption, such as highly fragmented sleep. Consecutive outpatients with a clinical diagnosis of Bipolar Disorder by DSM-IV [21] criteria (5% Bipolar I, 43 % Bipolar II, 52% BP NOS) were offered a trial of this approach. Given the simplicity of the intervention and the private outpatient setting, Institutional Review Board approval was not sought. Exclusion criteria included ongoing substance use, personality disorder as a primary diagnosis, and inability to understand the rationale behind the intervention. All patients continued their prior pharmacotherapy.

Amber-tinted lenses of the same design used in the study of melatonin preservation [18] were obtained from a light research team at John Carroll University (www.lowbluelights.com). A fit-over design allowed use of regular glasses if needed. Patients were instructed to begin use of the lenses around 8 p.m., removing them at bedtime after all artificial lighting was extinguished.

One of the most striking findings was patients' willingness to try this approach once they understood the background research. None refused, suggesting that treatment using restoration of a more "natural" light environment has strong appeal. Although 0.5 mg of melatonin at dusk likely has the same biological effect and might be preferred by many patients (Alfred Lewy, personal communication, 2006), clearly the amber lenses are easily accepted; most patients were eager to try them.

The author's subjective assessment of patient response (Clinical Global Improvement Scale, CGI) is shown in Table 1.

Over half of the participants showed some evidence of response. Both patients who worsened

disliked the treatment because it made them fall asleep earlier than they wished, interfering with television or computer game use. Both were adamant that they strongly disliked the effect of the lenses, and discontinued them within less than five days. Comments from responders included:

- "When I have trouble going to bed at a decent hour (2AM or later isn't decent!) I start wearing them in the evening. I usually notice a difference by the third evening, and am able to start getting to bed around 11PM. Sometimes I feel like going to bed even earlier."
- "Almost better than lorazepam, much easier to fall asleep; with exercise and the glasses I'm almost guaranteed of a good night's sleep."
- "I go right to sleep when I have those on. My sleep is calmer. On the nights I don't wear them, I feel more jittery and it takes me longer to get to sleep."

Most patients who responded have discovered that if they stop using the lenses, their sleep pattern begins to relapse; reinstating them decreases sleep latency. One patient was able to discontinue her use of zolpidem and lorazepam entirely; others were able to reduce their doses of hypnotics.

Discussion

In this preliminary study of blue light blockade as an adjunct to medication treatment of Bipolar Disorder, targeting initial insomnia, some patients appear to have experienced a robust response. The lack of any control condition, and the strong potential for placebo response given the apparent appeal of the concept to patients, suggest caution in the interpretation of these results.

Potential risks of this approach include disturbance of circadian sleep phase. Although in seasonal depression the most common circadian derangement is a delayed sleep phase, a significant subset have an advanced sleep phase, and depression in the latter group can worsen with further sleep advance [22]. In theory, use of amber lenses to produce evening "virtual darkness" should produce a circadian phase advance, and therefore might worsen seasonal depression in some patients. One patient in the series herein may have had this experience during the transition from summer to late fall, responding to early evening light treatment instead of the amber lenses at that point.

Because blocking blue wavelengths at night theoretically produces a light environment more akin to that in which humans evolved, it is difficult to

Table 1 Consecutive patients' response to amber lenses for initial insomnia

Clinical Global Improvement Scale Score	N	%
3 Very much improved	9	42
2 Much improved	1	5
1 Slightly improved	1	5
0 No response	8	38
-1 Slightly worse	1	5
-2 Much worse	1	5
-3 Very much worse	0	0

imagine other risks. Use of these lenses while driving (e.g. in an attempt to maintain circadian rhythm in shift workers) is obviously unwise, given their presumed mechanism of action. Because preliminary evidence suggests that blue light improves cognitive performance [23], patients using these lenses at night may need to be warned of the potential for a relative cognitive impairment.

At minimum, explaining to patients the importance of circadian rhythm, and the possible importance of blue light, helps reinforce for patients the importance of regular sleep patterns in the treatment of Bipolar Disorder. Randomized trials are warranted to determine if a direct effect on patients' circadian rhythms is possible using a simple pair of amber-lensed safety glasses to create "virtual darkness". If so, this approach could be useful for patients with initial insomnia; postpartum mothers for nocturnal breast-feeding; shift workers trying to preserve a regular circadian pattern of light and dark exposure; and perhaps even patients with rapid cycling Bipolar Disorder, using amber lenses to deliver dark therapy in a manner more practical than enforcing complete darkness. Specialists in other fields may wish to consider circadian disruption as a complicating factor in the illnesses they treat, particularly if we have at hand such a simple means of addressing this problem, at least for some patients.

Statement on conflict of interest

Dr. Phelps is on speakers bureau for GlaxoSmithKline, AstraZeneca, and Abbott Labs; owns no stock in these or other pharmaceutical companies; and has posted an extended discussion of these relationships on his website, PsychEducation.org. He receives royalties from a book for patients and families based on the bipolar spectrum concept. He has no financial connection to lowbluelights.com or Photonics LLC.

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