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Correcting delayed circadian phase with bright light therapy predicts improvement in ADHD symptoms: A pilot study

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a common condition with comorbid insomnia reported in >70% of children and adults. These patients demonstrate delays in sleep-wake rhythms, nocturnal rise in melatonin, and early morning rise in cortisol. Given that standard psychopharmacologic treatments for ADHD often do not completely control symptoms in participants with circadian rhythm delay, we sought to test whether bright light therapy (BLT) advances circadian rhythms and further reduces ADHD symptoms over standard treatments. In addition to standard of care, participants with ADHD diagnosis underwent 1 week of baseline assessment followed by 2-weeks of 30-min morning 10,000-lux BLT beginning 3 h after mid-sleep time. Participants minimized overhead light after 4 p.m., wore an actigraphy watch, and recorded BLT time on daily sleep logs. Dim Light Melatonin Onset (DLMO) was assessed at baseline and after 2-week treatment. ADHD symptoms were measured by the ADHD-Rating Scales (ADHD-RS). BLT significantly advanced the phase of DLMO by 31 min [mean time (SEM), 20:36 (0:21) advanced to 20:05 (0:20)] and mid-sleep time by 57 min [4:37 (0:22) advanced to 3:40 (0:16); paired t-tests, $p = 0.002$ and 0.004, respectively). Phase advances (in DLMO or mid-sleep time) were significantly correlated with decreased ADHD-RS total scores ($p = 0.027$ and 0.044) and Hyperactive-Impulsive sub-scores ($p = 0.014$ and 0.013, respectively). Actigraphy analysis for a subset of 8 participants with significant DLMO phase advance revealed no significant changes in total sleep time, sleep efficiency, wake after sleep onset, or percent wake during sleep interval. This is the first successful use of BLT for advancing melatonin phase and improving ADHD symptoms in adults. BLT may be a complementary treatment for both delayed sleep timing and ADHD symptoms in adults.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized by problems with attention, impulsivity and over-activity. The syndrome affects 4.5% of adults (Kessler et al., 2006), resulting in an estimated $3.6 billion loss in work costs (Birnbaum et al., 2005). More than 70% of children and adults with ADHD also report insomnia (Fargason et al., 2013; Fargason et al., 2011, Gruber et al., 2012; Kessler et al., 2006; Van der Heijden et al., 2005; Van Veen et al., 2010). The sleep disturbance is often due to circadian rhythm disruption characterized by delayed sleep in both children and adults, and psychiatric disorders, including ADHD, have been found to be associated with phase delay (Gamble et al., 2013; Lewy et al., 2006). Patients with ADHD demonstrate delays in: sleep-wake rhythms, nocturnal rise in melatonin, and early morning rise in cortisol (Baird et al., 2012; Novakova et al., 2011; Van der Heijden, Smits, 2005; Van Veen et al., 2010). Despite the significant comorbidity of ADHD and sleep disturbances, common treatment regimens such as stimulants do not address these sleep problems, and hence fail to achieve full symptom control of core ADHD symptoms. In fact, treatment with long-acting stimulant medications can shorten sleep duration, delay sleep-onset, and reduce circadian amplitude, all of which may negatively impact executive function and attention (Morash-Conway et al., 2017; Ironside et al., 2010). Additionally, circadian dysfunction and resultant disturbed sleep are associated with learning problems (Kopasz et al., 2010; Van der Heijden, Smits, 2005), poor driving

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performance (Anderson and Horne, 2013; Ftouni et al., 2013), depression (Lall et al., 2012; McCall et al., 2010; Taylor et al., 2005), and occupational dysfunction (Adan et al., 2012; Dagan, 2002), all of which are ADHD co-morbidities. As a result, there is an urgent need to develop non-pharmacological approaches to treat sleep disturbances, which often worsen attention deficits and impulsive behavior in adults with ADHD diagnosis.

When presented at the appropriate time-of-day, bright light therapy (BLT) has shown success for the treatment of a variety of sleep conditions (Crowley et al., 2004; Revell and Eastman, 2005; Smith et al., 2009; Wilhelmsen-Langeland et al., 2013, 2014; Wirz-Justice et al., 2013). A key characteristic of the endogenous circadian clock is the ability to synchronize 24-h rhythms to the light-dark cycle, such that early evening light exposure shifts wake-time to a later time (phase delay) while early morning light exposure shifts wake-time to an earlier time (phase advance) (Klein and Weller, 1970; Tamarkin et al., 1979). Well-timed light exposure can be used to shift sleep-wake rhythms earlier or later before/after transmeridian travel or before/after a change in shift schedule (Honma et al., 1991; Revell and Eastman, 2005). Therapeutic use of BLT in the morning to extend the light exposure period during the winter (mimicking summer-like conditions) alleviates depression in seasonal affective disorder (Burgess et al., 2004; Lieverse et al., 2011; Terman, 2006). Insomnia associated with delayed sleep phase syndrome is improved after administration of morning BLT (30 min) in a randomized controlled trial (Wilhelmsen-Langeland et al., 2013). Finally, combining BLT with total sleep deprivation and sleep phase advance ('Triple Chronotherapy') significantly reduced depression and suicidal ideation in an open-label, adjunctive therapy trial (Sahlem et al., 2014).

Our prior clinical trial demonstrated that delayed sleep timing (circadian phase delay) predicts ADHD symptom severity and that standard psychopharmacologic treatments for ADHD often do not completely control symptoms in participants with circadian rhythm delay (Gamble et al., 2013). These findings have not been translated into practical treatment applications such as BLT in patients with ADHD diagnosis. Thus, the aim of our study was to use BLT to manipulate the well-validated endogenous clock phase marker dim-light melatonin onset (DLMO) to explore the relationship between delayed circadian phase and ADHD symptoms. Understanding this relationship may highlight complementary or alternative mechanisms for clinical treatment.

2. Materials and methods

2.1. Participants

In this study, all participants were between ages 19 and 64 and met the DSM-IV-TR criteria for ADHD (more restrictive than DSM-5 criteria) with a mean age of 36.1 ± 13.2. Patients taking psychoactive medication for any condition other than ADHD or who were diagnosed with a co-morbid psychiatric disorder, sleep apnea, light-sensitive skin condition, ocular disorder or were shift-workers were excluded. Participants were recruited from the UAB Outpatient Psychiatry clinic during November 2013–March 2014. Clinic patients who qualified for the study were given a research brochure with research coordinator contacts in a neutral manner. A total of 28 potential participants were screened, with four meeting exclusion criteria (Fig. 1). One participant was lost to follow-up, and the remaining 23 participants gave written informed consent and were enrolled in the study, which was approved by the UAB institutional review board (IRB). Of the sample of 23, one participant withdrew due to an unrelated illness, three participants were not included due to protocol noncompliance with either the Actiwatch (N = 2) or the light therapy (N = 1). DLMO data from three participants were not analyzable due to low melatonin levels (N = 2) and light exposure during collection (N = 1), leaving a final sample of 16 participants who completed the protocol. The final sample (N = 16) included 7 (44%) men and 9 (56%) women with 15 (94%) Caucasian and 1 (6%) Hispanic participant. This was an adjunctive procedure to standard of care, including current stimulant medication (stable for ≥ 3 months), which varied in dosage and type. Patients presenting on medications for ADHD were allowed to continue standard regimens within PDR-approved dosage ranges (including, mixed amphetamine salts (MAS) and extended released MAS, or bupropion) provided all dosing occurred prior to noon. Participants on stimulant medication were strongly encouraged to take their medication by 8:00 am (Table 1).

2.2. BLT procedure and actigraphy

Participants were recruited by internal referral, fliers and local campus media. Trained research assistants performed a standard pre-screen interview when contacted by prospective participants. Qualifying individuals were invited for a screening visit. The initial screening visit included the consenting procedure; establishment of ADHD diagnosis by ADHD-RS and psychiatric clinical evaluation using DSM-IV-TR criteria; physical examination, and a Brief Sleep Disorder Screening Questionnaire. Research assistants conducted the Mini International Neuropsychiatric Interview for psychiatric conditions, and the HAM-A and HAM-D to exclude participants with depression or anxiety not in full remission (i.e. HAM-D score ≤7, HAM-A score ≤5 required). During this 3-week intervention study, consenting participants underwent one week of baseline assessment followed by 2-weeks of 30-min morning BLT to advance sleep timing. A wrist accelerometer (Actiwatch Spectrum, Philips, Andover, MA) was worn continuously throughout the study for use in conjunction with a sleep-wake diary (Manber et al., 1996) to monitor sleep-wake cycles for a baseline week and the two-week light treatment period. The intervention required home use of a standard UV-protected 10,000-lux Bright light therapy box (EnergyLight HF3318/60, Philips, Andover, MA) every morning. Data from the participant's actigraphic baseline assessment week was used to determine the mid-sleep time as a basis for scheduling timing of morning light box use (3-h after their calculated mid-sleep time). Participants were instructed to: (i) use the light box daily (for two weeks) for 30 min at the instructed time and record light box usage times on daily sleep logs (Manber et al., 1996), (ii) minimize overhead light and wear blue-wavelength blocking glasses outside after 4 p.m. to prevent Blue-wavelength light (460–480 nm range) from suppressing melatonin onset, and (iii) adhere to their usual schedule and record reasons for deviations in their sleep diary. For both baseline and post-light treatment DLMO assessment periods, participants stayed overnight in the UAB Hospital Research Unit to allow for strict control of light exposure, temperature and oral intake factors that could alter melatonin levels. Participants provided 2–3 ml of saliva on an hourly basis from 7 p.m. to 2 a.m., which were stored for DLMO assessment, and completed other outcome measures at both overnight visits. A daily sleep and light exposure diary was maintained for the entire study period. One subject did not complete sufficient sleep diary entries, resulting in N = 15 for subsequent sleep analysis. Primary outcome measures included timing of the calculated Dim-light melatonin onset (DLMO) (see result section) obtained from salivary melatonin samples collected while in the temperature and light-controlled research unit and mid-sleep time by actigraphy (the mid-time point between sleep start and end time–an accurate measure of the circadian phase of sleep). Secondary validated outcome measures included: 1) The ADHD-Rating Scale (ADHD-RS); 2) PSQI-sleep quality scale (25); 3) sleep quality measures by actigraphy,

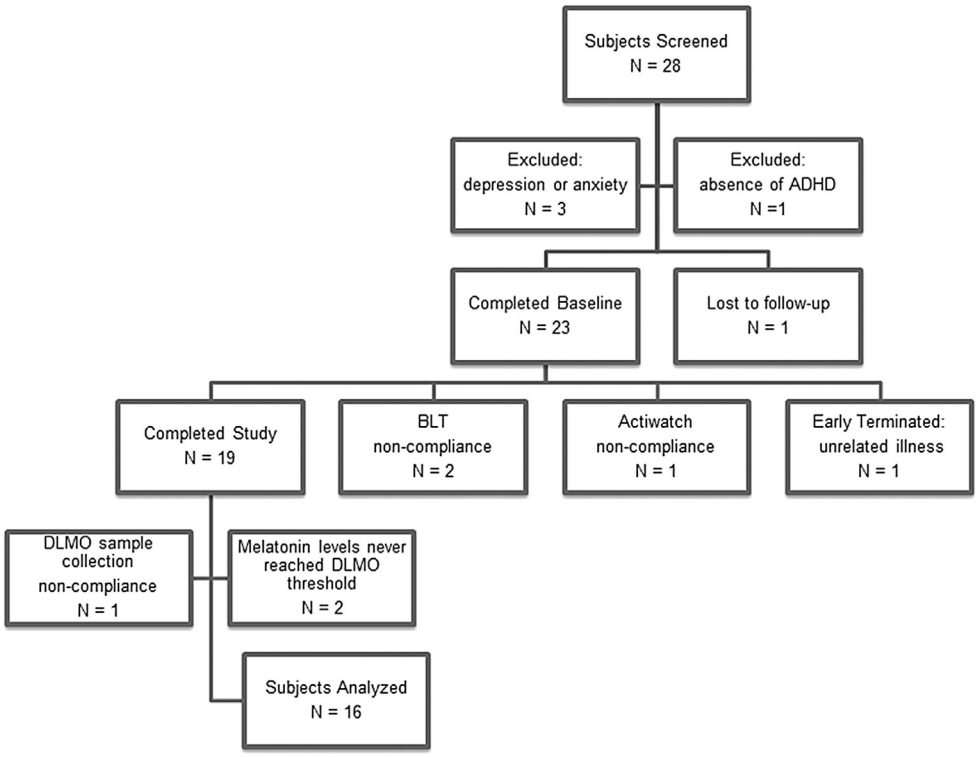

Fig. 1. Twenty-eight potential participants were screened. Three were excluded for depression or anxierty diagnoses, and one was excluded for absence of ADHD diagnosis. One participant was lost to follow-up, and the remaining 23 participants were enrolled in the study. Of the sample of 23, one withdrew due to unrelated illness, and three participants were not included due to protocol noncompliance with either the Actiwatch (N = 2) or the light therapy (N = 1), leaving a final sample of 19 participants who completed the protocol.

Table 1
Demographics.

N = 16	N (%) or Mean ± SEM
Age	35.25 ± 3.39
Gender	9 (56%) Female
	7 (44%) Male
Race/Ethnicity	15 (94%) White,
	1 (6%) Hispanic
Medication[a]	4 (25%) no medication
	1 (6.25%) Bupropion XL
	5 (31.25%) short-acting mixed-amphetamine salt
	4 (25%) long-acting mixed amphetamine salt
	2 (12.5%) lisdexamfetamine

[a] Single morning dose only.

and also; 4) “sleepiness” ratings on the daily sleep diary.

2.3. Data collection

DLMO was assessed at baseline and after the 2-week treatment in the UAB Hospital Research Unit in order to control light exposure (<10 lux) and oral intake factors. Hourly saliva samples (2–3 ml) from 7pm to 2am were assayed (Buhlmann Direct Saliva Melatonin ELISA 01-EK-DSM, ALPCO Diagnostics, Salem, NH) and DLMO defined as the time at which the melatonin exceeded a baseline threshold of 4 pg/ml and remained above that level. The precise clock time between sampling time-points was determined by linear interpolation (Voultsios et al., 1997; Crowley et al., 2016). Actigraphy data were determined after bed and wake times were entered into the Actiware analysis program, and used to determine sleep quality, efficiency, and fragmentation according to the software algorithms. Additional outcome measures were: mid-sleep time (the mid-time point between bed-time and wake-up time, according to the sleep diary); the ADHD-Rating Scale (ADHD-RS; DuPaul et al., 1998); actigraphy sleep measures (Gamble et al., 2013); sleep diary ‘sleepiness’ construct (Manber et al., 1996); and the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989).

2.4. Data analysis

Demographics and other data analysis were completed using SPSS 22. To compare any statistically significant changes between pre- and post-BLT outcomes, pairwise comparisons of the change from baseline were used. Following this initial analysis, correlations between the size of the phase shift (in either mid-sleep time or DLMO) and the reduction in ADHD symptoms were determined using a Pearson's product moment correlation.

3. Results

A total of 19 participants completed the protocol. DLMO data from 3 participants were not analyzable due to low melatonin levels (N = 2) and light exposure during collection (N = 1). As predicted, BLT advanced the phase of DLMO by 31 min [mean time (SEM), 20:36 (0:21) advanced to 20:05 (0:20)] and mid-sleep time by 57 min [4:37 (0:22) advanced to 3:40 (0:16); paired t-tests, $p = 0.002$ and 0.004, respectively; Fig. 2). The net effect of these two outcomes produced a significantly more narrow phase angle between DLMO and mid-sleep time [mean time (SEM), 8:11 (0:25) hours decreased to 7:44 (0:22) hours; paired t-tests, $p = 0.001$). Phase advances (in DLMO or mid-sleep time) were significantly correlated with decreased ADHD-RS total scores ($r = -0.55$ and $r = -0.53$, $p = 0.027$ and 0.044, respectively; Fig. 3) and

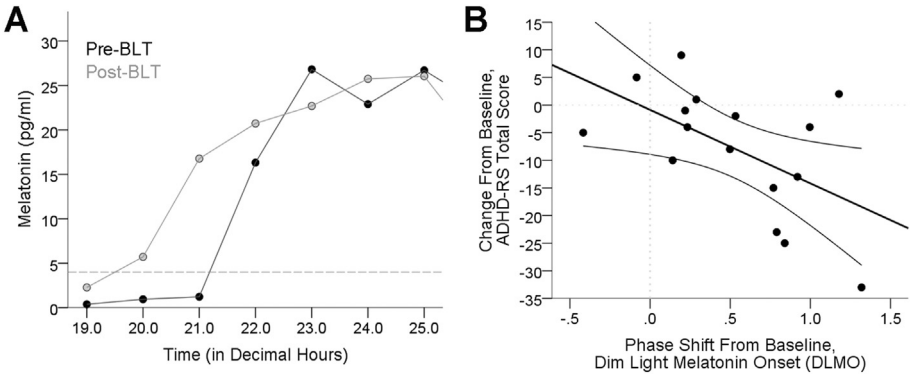

Fig. 2. A) Chart showing time of DLMO Pre-BLT and Post-BLT for a representative participant. DLMO was determined for each participant according to the linear interpolation procedure described in the Methods. B) Chart demonstrating a significant association between the DLMO phase shift from baseline and corresponding change in ADHD-RS total score.

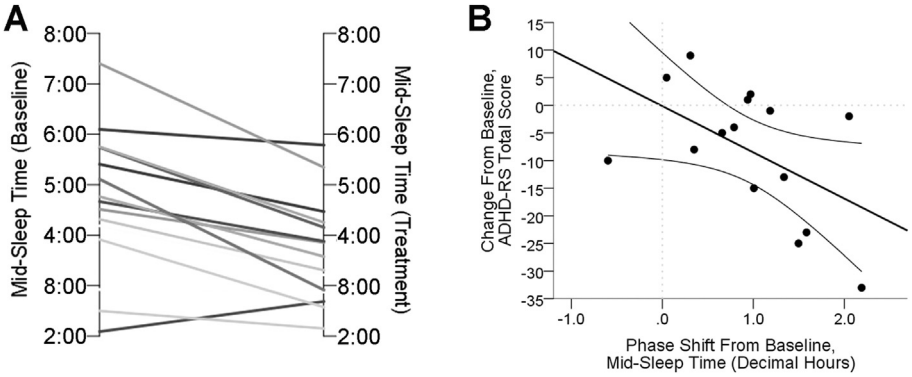

Fig. 3. A) Chart comparing Mid-Sleep Time for each participant pre-BLT and post-BLT. B) Chart demonstrating a significate association between the shift in Mid-Sleep Time from baseline and corresponding change in ADHD-RS total score.

Hyperactive-Impulsive sub-scores (r = −0.60 and r = −0.62, $p = 0.014$ and 0.013, respectively). However, reductions in total and Hyperactive-Impulsive ADHD-RS scores were not correlated with decreased DLMO: mid-sleep phase angle (r = 0.18 and r = 0.26, $p = 0.515$ and 0.356, respectively). Actigraphy analysis for a subset of 8 participants with significant DLMO phase advance ($p = 0.01$) revealed no significant changes in total sleep time, sleep efficiency, wake after sleep onset, or percent wake during sleep interval (Table 2). Although not statistically significant, there was a tendency for participants to have earlier sleep start times, wake-up times (sleep end), and increased sleep fragmentation (Table 2).

Table 2
Actigraphic sleep parameter estimates.

	Baseline		BLT		p
	Mean	SE	Mean	SE	
Sleep start (h)	0:34	0:33	23:59	*0:21*	*0.075*
Sleep end (h)	7:47	0:34	7:04	*0:20*	*0.064*
Mid-sleep time (h)	4:11	0:32	3:31	0:18	**0.048**
Total sleep duration (h)	7.2	0.4	7.1	0.4	0.677
Sleep efficiency (%)	81.3	2.9	77.4	3.0	0.333
% Wake	7.4	0.9	8.0	0.7	0.243
Wake After Sleep Onset (WASO)	30.7	4.6	32.3	4.0	0.627
Fragmentation Index (%)	14.7	2.4	18.9	*2.3*	*0.078*
DLMO (time; hours:min)	19:49	0:14	19:21	0:16	**0.028**

Note: Sleep timing and duration are calculated based on the primary sleep session/day, excluding naps. All data were compared using paired samples t-tests (N = 8), with significance indicated in bold ($p < 0.05$) or trends indicated in italics ($p < 0.10$).

Interestingly, 'sleepiness' ratings from the sleep dairy (Manber et al., 1996) were significantly reduced (mean ± SEM, 2.97 ± 0.13 to 2.63 ± 0.21; $p = 0.033$), and subjective sleep quality was improved as assessed by the PSQI (mean ± SEM, 10.1 ± 1.2 to 6.1 ± 1.3; $p < 0.001$).

4. Discussion

Despite the association of delayed sleep timing with ADHD symptom severity and the inadequacy of standard psychopharmacologic treatments for ADHD in participants with circadian rhythm delay (Gamble et al., 2013), the effectiveness of BLT as a treatment for patients with ADHD diagnosis has not previously been assessed. As hypothesized, BLT advanced DLMO and mid-sleep in adults with ADHD, and these advances were associated with decreased ADHD symptoms, including hyperactive-impulsive symptoms. This demonstrates the importance of addressing sleep-timing delays in preventing symptoms of impulsivity or hyperactivity (Gamble et al., 2013). This also supports BLT as a possible complementary treatment for both delayed sleep timing and ADHD symptoms in adults, especially given that the average reduction in ADHD-RS scores observed after BLT was ~8 points, which is comparable to other non-stimulant FDA approved agents determined from recent meta-analyses (Li et al., 2016).

One interesting outcome of this study is that the phase angle difference between evening DLMO and mid-sleep time significantly narrowed with BLT treatment. The "ideal" phase angle has been previously reported to be ~6 h (Lewy et al., 2006). Before BLT, our

delayed participants showed larger phase angles of ~8 h, varying from 6 h to over 12 h. Participants with very large phase angles tended to have very late mid-sleep times (e.g., 5:30am). The change in mid-sleep time was greater than the change in DLMO, resulting in the timing of sleep occurring closer to DLMO than before BLT. Thus, we found that BLT was an effective treatment for restoring alignment between DLMO and mid-sleep phases even in extreme delayed types.

Consistent with these findings, symptoms of ADHD correlate with circadian disruption at multiple levels. Adults with ADHD diagnosis report excess daytime sleepiness, later bed/wake-up times, and have documented sleep-activity cycles that are delayed with reduced amplitude, suggesting that these physiological impairments may be due to deficits in the underlying circadian (24-h) clock (Bioulac et al., 2015; Van Veen et al., 2010; Voinescu et al., 2012). Circadian rhythms in sleep-wake cycles, physiology, and hormones are intrinsically driven by a central clock in the hypothalamus (the suprachiasmatic nucleus). Cortisol and melatonin are the best markers of endogenous circadian phase in humans (Moore-Ede et al., 1982). Both the nocturnal rise in melatonin (measured as DLMO) and the early morning rise in cortisol appear later in children and adults diagnosed with ADHD, indicating a delayed circadian clock phase (Baird et al., 2012; Imeraj et al., 2012; Novakova et al., 2011; Van der Heijden K.B., 2005; Van Veen et al., 2010). Additional evidence suggests that ADHD is associated with circadian impairment at the genetic/molecular level. For example, rhythmic expression of the circadian 'clock genes' (*i.e.*, *BMAL1* and *PER2*, the molecular 'gears' of the intracellular clock) is flattened in white blood cells from ADHD participants, and the amplitude of these oscillations is significantly correlated with increased nocturnal hyperactive behavior and delayed cortisol rhythms (Baird et al., 2012). Indeed, genetic polymorphisms of several circadian clock genes are associated with ADHD diagnosis (Brookes et al., 2006; Cao et al., 2012; Kissling et al., 2008; Xu et al., 2010). As result of a weakened and delayed intrinsic circadian clock, patients suffering from ADHD may experience difficulty waking up in the morning and going to bed at night, explaining why more than 70% of adults with ADHD have insomnia (Kessler et al., 2006) compared to estimates of around 30% in the adult, U.S. population (Roth et al., 2007). Unfortunately, insomnia associated with ADHD is largely unaddressed by current treatment regimens (Hamblin, 2007; Walsh, 2006), and is often exacerbated by administration of stimulants in the late day/evening (Fargason et al., 2011, 2013). Taken together, this suggests that a delayed central circadian pacemaker underlies insomnia due to delayed sleep/activity rhythms in individuals with ADHD.

In the present study, BLT was found to be a feasible treatment for delayed sleep timing in adults with ADHD. ADHD symptoms sometimes make adherence to treatment difficult, and one subject was noncompliant with BLT and not included in the study. Participants used the light box ~10 out 14 days on average, and on these days, they were ~90% compliant with using the box within 9–12 h of DLMO, which is necessary to produce a phase advance (Revell and Eastman, 2005). Participants also reported less subjective sleepiness and improved subjective sleep quality. This demonstrates the viability of using BLT with adults with ADHD.

Limitations of this study include small sample size, some variability in treatment adherence and lower than desirable adherence. The lack of a placebo control is also a limitation; however, it is important to note that this was a pilot study. Additionally, the treatment response was significantly associated with the size of shift in DLMO, an intrinsic response, suggesting that the effect was not due to placebo. Finally, true blind placebo controls for light therapy are a major challenge for the chronobiology research with few alternatives that do not induce phase changes or introduce the possibility of incidental light exposure. Despite these limitations, this intervention still induced a modest (~half hour) phase advance in DLMO for the majority of the participants primarily due to frequent usage of the light within 9–12 h of DLMO.

This study demonstrates the utility of BLT when assessed with an objective circadian phase marker (DLMO). Future research should assess the effectiveness of using a morning BLT intervention to advance circadian phase of adults with ADHD and improve ADHD symptoms while reducing stimulant side effects.

5. Conclusion

This open-label pilot study suggests that BLT is a feasible treatment for adults with ADHD and may be a successful complementary treatment for delayed sleep timing and symptoms of ADHD in adults. A randomized, placebo-controlled trial is needed to assess futher treatment effects.

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