TITLE: A Randomized, Double-Blind, Controlled Trial of Bright Light Therapy on All-Cause Excessive Daytime Sleepiness in Prader-Willi Syndrome

Unique ID: 2022-08-12

NCT# 05939453

Date: August 17, 2022

INTRODUCTION

The long-term goal of our center is to bring novel and effective treatment modalities for patients with Prader-Willi Syndrome (PWS). This study will address excessive daytime sleepiness (EDS), one of the key clinical issues that affect persons with PWS. There is extensive literature demonstrating the efficacy of light therapy (LT) in treating EDS and behavioral symptoms in other populations, with LT being accepted as an evidence-based treatment for seasonal depression. Bright light therapy improves day-night (circadian) rhythm and is known to have acute alertness promoting effect. Our hypothesis is that LT, as a sensory therapy, would improve sleepiness, mood, and behavior in patients with PWS. Research suggests that EDS is present independent of sleep apnea in patients with PWS. The limited availability of medication options further emphasizes the need to explore non-medication therapies for the management of EDS in PWS.

We propose to utilize a naturalistic approach to management of EDS independent of the presence of obstructive sleep apnea. Therefore, this study will examine the impact of LT on EDS defined as a score of 12 or more on the Epworth Sleepiness Scale (ESS) due to all causes in patients with PWS. Our specific aims are two-fold: 1) To determine the impact of LT on EDS in patients with Prader-Willi Syndrome (PWS). 2) To elucidate the effect of LT on mood, behavior, body weight, and hyperphagia in PWS patients.

BACKGROUND AND SIGNIFICANCE

Excessive daytime sleepiness or EDS is defined in the DSM-5 as “symptoms of excessive sleepiness associated with lapses into sleep, feeling unrefreshed despite adequate sleep time and difficulty waking in the morning despite adequate nighttime sleep”. In addition to sleep disturbance, EDS disrupts school performance and may be associated with irritability and behavioral problems seen in individuals with PWS. The etiology of EDS in PWS seems to be genetic and beyond what would be explained by the role of weight gain and low muscle tone leading to obstructive sleep apnea (OSA). This is evidenced by the persistence of EDS despite adequate treatment of OSA in patients with PWS. Several studies have demonstrated that SNORD116 plays a role in sleep. Rodent PWS mutant models have demonstrated that deletions in SNORD116 lead to an increased REM/NREM ratio, increased REM fragmentation, and increased amplitude of theta waves during REM sleep in the light phase. This speaks to the possibility that light exposure might have a modulating effect on the sleep abnormalities noted in PWS. While multiple studies provide evidence that light therapy is a simple, cost-effective modality with minimal side effects in other populations, there are no studies exploring its efficacy in treatment of EDS in patients with PWS.

Randomized controlled trials have shown that light therapy (LT) is associated with phase advances of the melatonin rhythm. Morning exposure to LT can suppress melatonin secretion resulting in the reduction of excessive daytime sleepiness and insomnia, as well as improving alertness. LT utilizes appropriately timed exposure to an artificial full spectrum lamp at 10,000 lux. It is thought to work by resynchronizing the biological clock (circadian system), enhancing alertness, and acting on serotonin, and other monoaminergic pathways.

The effects of LT are well-researched in several patient populations. As an example, EDS decreased significantly in the period from rising time to 3:00 P.M. with 2 hours/day of LT in nursing home patients with dementia. Additionally, LT has shown positive effects on mood, activity, and expressive language in patients with dementia. LT has also shown benefit in reducing fatigue in patients with traumatic brain injury. Interestingly, LT seems to have a dose-dependent effect on "threat-related brain function" by modulating amygdala-prefrontal reactivity and communication. This effect is consequential due to the known neurobiological correlates of PWS which contribute to increased impulsivity and reactive aggression. LT is an evidence-based treatment for both seasonal and non-seasonal depression and leads to significant improvement in circadian dysregulation. LT has been used as monotherapy as well as an adjunct in several depression trials. In addition to its effects of mood and behavior, LT has been shown to improve sleep architecture in patients with type 2 diabetes without PWS, suggesting that patients at risk for metabolic illnesses and EDS might benefit from this intervention. Significant reduction in night-time eating has been demonstrated with LT as well. Finally, there is some evidence suggesting that the addition of LT can alter body composition by significantly reducing body fat especially when combined with exercise.

Sleep disorders are common and under-recognized in people with PWS. Excessive daytime sleepiness (EDS) affects over half of all individuals with PWS. The repercussions of EDS extend beyond sleep disturbance to other behavioral issues seen in PWS. The pharmacological strategies for the management of EDS in PWS include the use of stimulants, modafinil, and pitolisant. However, the prevalence of side effects and drug-drug interactions limit their use. Other than the use of continuous positive airway pressure (CPAP) in patients with co-morbid OSA, no other evidence-based non-pharmacologic management strategies for EDS in patients with PWS are available. LT, is a well-established, evidence-based non-pharmacological treatment to manage sleep disorders such as delayed sleep phase syndrome. Moreover, LT has shown efficacy for the management of EDS in patients with and without OSA. Despite the reported elevated risk of behavioral activation with LT, multiple studies evaluating its efficacy in the management of bipolar depressions have shown no significant risk of manic switching. LT has a well-known favorable safety profile.

Given the limited medication options, and their side effects, there is need to explore non-medication therapies for the management of EDS in PWS. Despite the ubiquity of EDS in PWS

and ample evidence of LT being an effective modality for the management of EDS in the general population, LT has not been studied in patients with PWS. This will be the first study looking at the efficacy and tolerability of LT in the management of all-cause EDS in patients with PWS.

STUDY OBJECTIVES

The **primary objective** of this study is to reduce EDS in PWS as evidenced by a significant reduction in the ESS score.

The **secondary objectives** include understanding the effect of LT on mood, behavior, body weight, and hyperphagia in the participants with PWS.

HYPOTHESIS

Our **hypothesis** is that LT, as a sensory therapy, would improve sleepiness, mood, and behavior in patients with PWS.

EXPERIMENTAL DESIGN AND METHODS

Study Design: Double-Blind Randomized Controlled Trial with Open Label Extension

Subjects: Children with Prader-Willi Syndrome

Eligibility Criteria:

Inclusion Criteria:

1) Subjects must be between 6 and 18 years of age
2) Diagnosis of PWS confirmed by genetic testing
3) Score of 12 or above on the Epworth Sleepiness Scale (ESS).

Exclusion Criteria:

1) Subjects with an eye condition that could be negatively affected by bright light such as patients with a history of retinal damage or patients needing photosensitizing medications
2) A history of previous treatment with LT
3) Patients presenting with active psychosis or mania

Note: Patients who have a documented history of OSA may be included as long as their regimen of treatment such as CPAP/BiPAP is unchanged for at least 4 weeks leading to the study and will remain so for the duration of the study.

Study Procedure: In order to make the study more accessible, and to minimize the risk of COVID-19 infection, all screenings and evaluations will be conducted utilizing a HIPAA-compliant video based tele-health platform. By utilizing over-the-counter materials which will be mailed to patients, all participants can be included in the study without any in-person visits. To duplicate real-world settings, patients will be using LT in the comfort of their homes without any invasive tests or physical examinations and without the risk of disrupting circadian rhythms due to travel. Despite the reported elevated risk of behavioral activation with LT, multiple studies evaluating its efficacy in the management of bipolar depressions have shown no significant risk of manic switching. However, a semi-structured psychiatric interview will be conducted at baseline to rule out mania and/or psychosis. A two-week period during which sleep schedule will be documented using a daily sleep log will be required after screening and enrollment and prior to randomization. Seven documented days in this 2-week pre-randomization period will be required to have a base-line evaluation of circadian rhythm.

In addition, as suggested by FPWR grant reviewers, we will utilize a wearable actigraphy device to record objective data. The device collects and downloads continuously, objective activity, sleep, and wake data from ambulatory subjects in one compact, professional-grade scientific device. The device chosen for both efficacy, history of being used in evidence-based research as well as cost-effectiveness was the latest iteration of a Fitbit Charge health tracker, the Charge 5. In addition to tracking sleep stages & quality, it also monitors Oxygen Saturation (SpO2), Heart Rate Variability, Breathing Rate, and dermal temperature Tracking Sleep Score & Sleep Stages all if which can help provide useful secondary data on the impact of LT on participants. It is designed to provide accurate and objective data recording to help assess activity, sleep, wake, and light-exposure in their subjects. Data collected through this single device, plus associated software, will also help us conveniently and reliably assess the impact of light therapy on PWS patients. The devices are water proof and can be worn safely throughout the day and night. The participants will be placing the device as recommended by the manufacturer on their non-dominant forearm to increase the sensitivity of the readings. Participants will be instructed to sync the data from all their devices using their respective apps on the tablet each day, within an hour of waking up. Additionally, a log will be provided to caregivers to manually enter any time period that the device was removed by the participant for any reason.

Phase 1: After the 2-week pre-randomization period, participants will be randomized in a 1:1 ratio to receive either 30 minutes of bright LT or dim-red light (sham) in gaze direction in the mornings (between 6 AM and 10 AM) and 30 minutes in the afternoon (between 2 PM and 6 PM) daily, i.e. 2 sessions per day, for a duration of 3 contiguous weeks. Bright LT will be provided using light box with an artificial full spectrum lamp providing 10,000 lux of illuminance, whereas, sham treatment will be provided from a light box with dim-red light spectrum lamp. The light box will be placed at least 70 cm and at most 90 cm away from the subject. A 90 cm string attached from

its side with a soft Velcro wrist band will be provided to ensure adherence to this distance. Detailed instructions will be provided to the participants, to assist with the proper exposure distance. Participants will be instructed to engage in any activity as long as the light source is within their gaze area and they are not sleeping. Daily sleep diary as well as LT administration log will be required to be filled by a consistent caregiver. Actigraphy records for the period will be retrieved. A total of 28 logged LT sessions will be required to qualify as completion of phase one. (see Table 1)

Phase 2: Upon completion of phase one, all participants will be given the option to continue into the open-label phase of the study. Participants will utilize LT for another 3 contiguous weeks. All instructions will remain the same as in phase one. A total of 28 logged LT sessions will be required to qualify as completion of this phase. (see Table 1)

Table 1: Schedule of Events

Study Events / Procedures	PHASE 1					PHASE 2			PHASE 2		
	Pre-randomization	Randomization	Main Phase			Participants who received sham in Phase 1			Participants who received LT in Phase 1		
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 6	Visit 7	Visit 8
	-14 days (2 weeks)	(Week 0)	(W 1)	(Week 2)	(Week 3)	(Week 4)	(Week 5)	(Week 6)	(Week 4)	(Week 5)	(Week 6)
Informed Consent and ESS	X										
Medical/Psychiatric Eval		X			X			X			X
Sleep diary		X	X	X	X	X	X	X	X	X	X
Scales (ESS, ABC, MOAS, HQ-CT)		X	X	X	X	X	X	X	X	X	X
CGI		X			X			X			X
Actigraphy reports		X	X	X	X	X	X	X	X	X	X
Review of AEs			X		X			X			X

Data Collection Procedures:

Weekly assessments will be conducted.

The scales utilized will include the following:

- ESS
- Hyperphagia Questionnaire (HQCT)
- Modified Overt Aggression Scale (MOAS)

- Clinical Global Impression- Severity and Improvement scales
- Aberrant Behavior Checklist scale

One study rater conducting the scales will remain blinded to the participants' LT vs sham assignment throughout the study.

Sleep diary and actigraphy reports will be reviewed and data recorded.

Data Analysis:

Data will be analyzed comparing participant outcomes in the two arms of phase one as well as within-participant data from the two phases. Instead of employing a full stepped-wedge design, which would require a larger sample size, data gathered from the open-label phase of this project will be analyzed through use of a paired t-test to compare the ESS scores between the treatment and open label phases for the control group to test for a significant effect of treatment in this group.

REFERENCES

1. Rastad C, Ulfberg J, Lindberg P. Improvement in Fatigue, Sleepiness, and Health-Related Quality of Life with Bright Light Treatment in Persons with Seasonal Affective Disorder and Subsyndromal SAD. Depress Res Treat. 2011;2011:543906. doi: 10.1155/2011/543906. Epub 2011 Jun 13. PMID: 21747994; PMCID: PMC3123908.

2. Videnovic A, Klerman EB, Wang W, Marconi A, Kuhta T, Zee PC. Timed Light Therapy for Sleep and Daytime Sleepiness Associated With Parkinson Disease: A Randomized Clinical Trial. JAMA Neurol. 2017 Apr 1;74(4):411-418. doi: 10.1001/jamaneurol.2016.5192. PMID: 28241159; PMCID: PMC5470356.

3. Hiroe Y, Inoue Y, Higami S, Suto Y, Kawahara R. Relationship between hypersomnia and respiratory disorder during sleep in Prader-Willi syndrome. Psychiatry Clin Neurosci. 2000 Jun;54(3):323-5. doi: 10.1046/j.1440-1819.2000.00697.x. PMID: 11186096.

4. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991 Dec;14(6):540-5. doi: 10.1093/sleep/14.6.540. PMID: 1798888.

5. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

6. Lassi G, Priano L, Maggi S, Garcia-Garcia C, Balzani E, El-Assawy N, Pagani M, Tinarelli F, Giardino D, Mauro A, Peters J, Gozzi A, Grugni G, Tucci V. Deletion of the Snord116/SNORD116 Alters Sleep in Mice and Patients with Prader-Willi Syndrome.

Sleep. 2016 Mar 1;39(3):637-44. doi: 10.5665/sleep.5542. PMID: 26446116; PMCID: PMC4763347.

7. Pail G, Huf W, Pjrek E, Winkler D, Willeit M, Praschak-Rieder N, Kasper S. Bright-light therapy in the treatment of mood disorders. Neuropsychobiology. 2011;64(3):152-62. doi: 10.1159/000328950. Epub 2011 Jul 29. PMID: 21811085.

8. Ito T, Yamadera H, Ito R, Endo S. [Effects of bright light on cognitive disturbances in Alzheimer-type dementia]. Nihon Ika Daigaku Zasshi. 1999 Aug;66(4):229-38. Japanese. doi: 10.1272/jnms.66.229. PMID: 10466338.

9. Srisurapanont K, Samakarn Y, Kamklong B, Siratrairat P, Bumiputra A, Jaikwang M, Srisurapanont M. Blue-wavelength light therapy for post-traumatic brain injury sleepiness, sleep disturbance, depression, and fatigue: A systematic review and network meta-analysis. PLoS One. 2021 Feb 4;16(2):e0246172. doi: 10.1371/journal.pone.0246172. PMID: 33539446; PMCID: PMC7861530.

10. Adhikari P, Pradhan A, Zele AJ, Feigl B. Supplemental light exposure improves sleep architecture in people with type 2 diabetes. Acta Diabetol. 2021 Sep;58(9):1201-1208. doi: 10.1007/s00592-021-01712-y. Epub 2021 Apr 14. PMID: 33851274.

11. Sene-Fiorese M, Duarte FO, de Aquino Junior AE, Campos RM, Masquio DC, Tock L, de Oliveira Duarte AC, Dâmaso AR, Parizotto NA, Bagnato VS. The potential of phototherapy to reduce body fat, insulin resistance and "metabolic inflexibility" related to obesity in women undergoing weight loss treatment. Lasers Surg Med. 2015 Oct;47(8):634-42. doi: 10.1002/lsm.22395. Epub 2015 Jul 29. PMID: 26220050.

12. Patel VP, Patroneva A, Glaze DG, Davis K, Merikle E, Revana A. Establishing the content validity of the Epworth Sleepiness Scale for Children and Adolescents in Prader-Willi Syndrome. J Clin Sleep Med. 2021 Aug 26. doi: 10.5664/jcsm.9632. Epub ahead of print. PMID: 34437052.

13. De Cock VC, Diene G, Molinas C, Masson VD, Kieffer I, Mimoun E, Tiberge M, Tauber M. Efficacy of modafinil on excessive daytime sleepiness in Prader-Willi syndrome. Am J Med Genet A. 2011 Jul;155A(7):1552-7. doi: 10.1002/ajmg.a.34047. Epub 2011 Jun 10. PMID: 21671379.

14. Pullen LC, Picone M, Tan L, Johnston C, Stark H. Cognitive Improvements in Children with Prader-Willi Syndrome Following Pitolisant Treatment-Patient Reports. J Pediatr Pharmacol Ther. 2019 Mar-Apr;24(2):166-171. doi: 10.5863/1551-6776-24.2.166. PMID: 31019411; PMCID: PMC6478354.

15. Gillett ES, Perez IA. Disorders of Sleep and Ventilatory Control in Prader-Willi Syndrome. Diseases. 2016 Jul 8;4(3):23. doi: 10.3390/diseases4030023. PMID: 28933403; PMCID: PMC5456282.

16. Epperson CN, Terman M, Terman JS, Hanusa BH, Oren DA, Peindl KS, Wisner KL. Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. J Clin Psychiatry. 2004 Mar;65(3):421-5. doi: 10.4088/jcp.v65n0319. PMID: 15096083.

17. Fetveit A, Bjorvatn B. Bright-light treatment reduces actigraphic-measured daytime sleep in nursing home patients with dementia: a pilot study. Am J Geriatr Psychiatry. 2005 May;13(5):420-3. doi: 10.1176/appi.ajgp.13.5.420. PMID: 15879592.

18. Fisher PM, Madsen MK, Mc Mahon B, Holst KK, Andersen SB, Laursen HR, Hasholt LF, Siebner HR, Knudsen GM. Three-week bright-light intervention has dose-related effects on threat-related corticolimbic reactivity and functional coupling. Biol Psychiatry. 2014 Aug 15;76(4):332-9. doi: 10.1016/j.biopsych.2013.11.031. Epub 2013 Dec 19. PMID: 24439303.

19. Manning, K. E., Tait, R., Suckling, J., & Holland, A. J. (2017). Grey matter volume and cortical structure in Prader-Willi syndrome compared to typically developing young adults. NeuroImage. Clinical, 17, 899–909. https://doi.org/10.1016/j.nicl.2017.12.027

20. Wirz-Justice A, Bader A, Frisch U, Stieglitz RD, Alder J, Bitzer J, Hösli I, Jazbec S, Benedetti F, Terman M, Wisner KL, Riecher-Rössler A. A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. J Clin Psychiatry. 2011 Jul;72(7):986-93. doi: 10.4088/JCP.10m06188blu. Epub 2011 Apr 5. PMID: 21535997.

21. McCune AM, Lundgren JD. Bright light therapy for the treatment of night eating syndrome: A pilot study. Psychiatry Res. 2015 Sep 30;229(1-2):577-9. doi: 10.1016/j.psychres.2015.07.079. Epub 2015 Jul 29. PMID: 26239768.

22. Figueiro MG. Delayed sleep phase disorder: clinical perspective with a focus on light therapy. Nat Sci Sleep. 2016 Apr 6;8:91-106. doi: 10.2147/NSS.S85849. PMID: 27110143; PMCID: PMC4830627.

23. Soreca I. The role of circadian rhythms in Obstructive Sleep Apnea symptoms and novel targets for treatment. Chronobiol Int. 2021 Sep;38(9):1274-1282. doi: 10.1080/07420528.2021.1929281. Epub 2021 May 24. PMID: 34027758.

24. Stucky B, Clark I, Azza Y, Karlen W, Achermann P, Kleim B, Landolt HP. Validation of Fitbit Charge 2 Sleep and Heart Rate Estimates Against Polysomnographic Measures in Shift Workers: Naturalistic Study. J Med Internet Res. 2021 Oct 5;23(10):e26476. doi: 10.2196/26476. PMID: 34609317; PMCID: PMC8527385.