PROJECT TITLE: **EFFECTS OF BRIGHT LIGHT TREATMENT ON DAYTIME SLEEPINESS AND NOCTURNAL SLEEP IN PATIENTS WITH PARKINSON'S DISEASE**

PI: **Aleksandar Videnovic, M.D.**

ABSTRACT

This is a randomized, parallel group study of bright light treatment versus dim-red light treatment (control group) in Parkinson's disease (PD) patients with excessive daytime sleepiness. Study objectives are to determine the efficacy, safety and tolerability of bright light treatment in PD patients with daytime sleepiness. Thirty PD patients will be enrolled and equally randomized to bright light or dim-red light treatment. Objective (actigraphy) and subjective (sleep logs/scales) sleep measures will be collected through the baseline and intervention phases of the study. The primary outcome measure will be the change in the Epworth Sleepiness Scale (ESS) comparing the bright light treatment with dim-red light treatment. Secondary outcome measures will include the Multiple Sleep Latency Test (MSLT), global Pittsburg Sleep Quality Index (PSQI) score, Parkinson's Disease Sleep Scale (PDSS) score, and actigraphy measures. A variety of exploratory analyses will examine the effects of bright light treatment on fatigue, depression, quality of life, cognition, and motor disability.

Corresponding Address:

Aleksandar Videnovic, MD, MSc, FAAN, FAASM

Director, Program on Sleep, Circadian Biology, and Neurodegeneration
Movement Disorders Unit and Division of Sleep Medicine
Massachusetts General Hospital

Associate Professor of Neurology
Harvard Medical School

MGH Neurological Clinical Research Institute
165 Cambridge Street, Suite 600
Boston, MA 02446
phone: 617.724.3837
fax: 617. 643.3558
e-mail: avidenovic@mgh.harvard.edu

BACKGROUND AND SIGNIFICANCE

Sleep disturbances are common in Parkinson's disease (PD). In particular, excessive daytime sleepiness and nocturnal sleep fragmentation are frequently observed sleep complaints, affecting up to 90% of advanced PD patients [1, 2]. Sleep disturbances reduce quality of life, impair daytime functioning, and are associated with motor vehicle accidents in PD [3-5]. The chronic nature of sleep disturbances in PD, coupled with the side effects of medications, limits the usefulness of pharmacological treatment strategies. Therefore, there is a great need to develop non-pharmacological treatment approaches for the prevention and management of sleep disorders in PD population.

The etiology of sleep disturbances in PD has largely been attributed to the symptoms of PD [6, 7], side effects of antiparkinson medications [8], and primary neurodegeneration of central sleep regulatory areas [9]. However, disruption of circadian rhythms, which can also result in sleep fragmentation and daytime somnolence [10, 11], has not been well studied in PD population.

Circadian rhythms are physiologic or behavioral cycles that occur on a 24-hour cycle, and are generated by a circadian pacemaker located in the suprachiasmatic nucleus of the hypothalamus [12, 13]. Circadian rhythms are synchronized (entrained) to the environmental light/dark and social/activity cycles by so called "zeitgebers" (German for "time-giver") [14]. Light represents the most effective zeitgeber of the circadian timing system [15, 16].

There is a negative correlation between environmental light intensity and sleep disturbances in the elderly [17-19]. Older people are exposed to reduced illumination levels in their daily lives, but have a maintained responsiveness of the circadian pacemaker to light [20]. Supplementary exposure to morning bright light has shown beneficial effects on sleep quality and daytime vigilance [21-23]. Therapeutic exposure to bright light has also been shown to consolidate sleep-wake cycle and rest-activity rhythms in patients with dementia [24-29].

To the best of our knowledge only one short-term study examined the effects of bright light exposure in PD population [30]. In this study, 40 PD patients were exposed to bright light, with subsequent decrease in rigidity and bradykinesia and improvement in overall motor function. We are not aware of any study that assessed the effects of bright light exposure on daytime sleepiness and nocturnal sleep in PD population.

Clear guidelines for the optimal dosing and duration of light therapy do not exist. Most commonly used light intensities are between 2,500 to 10,000 lux, administered in burst of 1 to 2 hours [31]. Side effects are mild and transient, and include headache, nausea, vomiting, and hypomania [32].

Chronobiologic strategies, such as bright light could potentially improve sleep related impairments in daytime function in PD patients. Such behavioral strategies would be highly desirable since pharmacological interventions for sleep disturbances in PD have been of modest benefit, and may cause unacceptable side effects [33].

HYPOTHESIS

Bright light exposure will diminish daytime sleepiness and improve night-time sleep in PD patients with daytime sleepiness.

SPECIFIC AIMS

1. to assess the effects of bright light treatment on daytime sleepiness and nocturnal sleep in PD patients with daytime sleepiness
2. to assess the feasibility and tolerability of bright light therapy in PD patients with daytime sleepiness.

STUDY DESIGN

This is a randomized, parallel group study of bright light treatment versus dim-red light treatment (control group) in PD patients with excessive daytime sleepiness. Thirty subjects will be enrolled and randomized 1:1 to bright light or dim-red light exposure.

STUDY SUBJECTS

Subjects will be screened and recruited from the Northwestern University Parkinson's Disease and Movement Disorders Center, which evaluates over 700 PD patients annually, and the Rush University Movement Disorders Center, which evaluates over 1000 PD patients annually. The study protocol will be approved by the Institutional Board Reviews of Northwestern and Rush University. All study related procedures / visits will take place at Northwestern University. Written consent will be obtained from all subjects prior to enrollment.

Inclusion criteria will be: diagnosis of idiopathic PD as defined by the United Kingdom Parkinson's Disease Society Brain Bank Criteria; Hoehn and Yahr stage of 2 to 4 in the "on" state; excessive daytime sleepiness as defined by the Epworth Sleepiness Scale (ESS) score of greater than or equal to 12 points; stable PD medication regimen for at least 4 weeks prior to study screening; a reliable bed partner / caregiver who can observe the patient during the night.

Exclusion criteria will be: atypical parkinsonian syndromes; significant sleep disordered breathing (defined as an apnea-hypopnea index >15 events/hr of sleep on screening PSG), significant periodic limb movement disorder (defined as a PLM arousal index>10 events/hr of sleep on screening PSG), and REM sleep behavior disorder (based on the presence of both clinical symptomatology as well as intermittent loss of REM atonia on screening PSG); cognitive impairment indicated by the mini-mental status examination (MMSE) score of less than 24; untreated hallucinations or psychosis (drug-induced or spontaneous); use of hypno-sedative drugs for sleep or stimulants during the daytime; use of antidepressants unless the patient has been on a stable dose for at least three months; visual abnormalities that may interfere with light therapy, such as significant cataracts, narrow angle glaucoma or blindness; travel through 2 time zones within 90 days prior to study screening.

STUDY PROTOCOL

Screening visits

At screening, potential study subjects will be evaluated for inclusion and exclusion criteria. Subjects meeting entrance criteria will be invited to participate and sign informed consent. All subjects will have neurological and ophthalmologic examination, Hoehn and Yahr staging, The United Parkinson's Disease Rating Scale (UPDRS) and MMSE. Subjects will also complete a set of questionnaires, including ESS, The Parkinson's Disease Sleep Scale (PDSS), The Pittsburgh Sleep Quality Index (PSQI), The Berlin Questionnaire, The Fatigue Severity Scale (FSS), The Beck Depression Inventory (BDI) and The PDQ38 (PD-specific quality of life scale). Subjects will subsequently be scheduled for a polysomnogram (PSG) and the Multiple Sleep Latency Test (MSLT) at the General Clinical Research Center at Northwestern Memorial Hospital. PSG will be conducted using standard nocturnal polysomnographic procedures. MSLT will be conducted the following day. PSG will be reviewed and if subjects continue to qualify for the continuation of the study protocol they will be scheduled for the baseline visit.

Baseline visit

During this visit subjects will be educated how to use an actigraphy monitor and complete daily sleep log and visual analog scale.

Baseline phase – weeks 1 and 2

During the baseline phase all subjects will wear an actigraphy monitor with integrated light sensor

(Actiwatch-L, Mini-Mitter Co., Inc., Bend, OR, USA), on their non-dominant wrist, 24 hours a day, seven days a week. The Actigraphy monitor will record their activity in epochs of one minute. This monitor has a photosensor that will record light exposure, and therefore allow us to monitor compliance with timed light exposure. Subjects will also complete a sleep log every day, noting time of "lights off", estimated time of sleep onset, any awakenings during the night (>5min), final awakening, and "lights on" time in the morning. Subjects will also complete visual analog scale for daytime sleepiness on Mondays, Wednesdays and Fridays, every two hours, starting at 8am for total of 12 hours.

Visit #1

After 14 days of actigraphy monitoring and subjective data collection subjects will return to the office and actigraphy data will be downloaded using the Actiware Software (Mini-Mitter Co., Inc., Bend, OR, USA). Subjects will be equally randomized to bright light and dim-red light treatment. Randomization will employ a random-length permuted block design, with blocks of length 2 and 4. The randomization scheme will be generated in advance, using computer generated, pseudo-random numbers. Subjects will be educated how to use the light box during this visit.

Intervention phase – weeks 3 and 4

Subjects will receive one hour of morning (within 9:00-11:00 am) and afternoon (within 5:00-7:00 pm) bright light (10,000lux) or dim red light exposure (<300 lux in gaze direction), daily for two weeks. All subjects will be instructed to keep their face directed towards the light box, without prolonged eye closure. The box will be placed 0.5-1 meter away from the subject. Subjects will record the light exposure duration and timing daily. "SunRay" light boxes (The SunBox Co., Gaithersburg, MD, USA) will be used for light-treatment administration. During the intervention phase all subjects will continue to wear an actigraphy monitor, maintain sleep log, and complete visual analog scale for daytime sleepiness on Mondays, Wednesdays and Fridays, every two hours, starting at 8am for total of 12 hours. After the first week of treatment all subjects will be contacted via phone to screen for potential adverse events.

Visit #2

At the end of the intervention phase, all subjects will have final MSLT at the General Clinical Research Center at Northwestern Memorial Hospital.

Visit #3

After the completion of the MSLT subjects will return for a follow up evaluation. They will have examination, including the UPDRS and complete ESS, PDSS, PSQI, FSS, BDI and PDQ38. Actiwatches will be returned during this visit and collected data will be downloaded. In order to examine for the carry over effects of initial response to bright light treatment all subjects will continue to maintain sleep logs, and complete visual analog scale for daytime sleepiness on Mondays, Wednesdays and Fridays, every two hours, starting at 8am for total of 12 hours, for additional two weeks.

Visit #4

During the final visit sleep diary and visual analog scales will be collected and study subjects will complete ESS, PSQI, PDSS, FSS, BDI and PDQ38.

OUTCOME MEASURES

Primary endpoint

The primary outcome measure will be the change in the ESS comparing the bright light exposure with dim-red light exposure.

Secondary endpoints

Secondary outcome measures will include MSLT, the global PSQI score, PDSS score, and actigraphy measures including total sleep time, sleep efficiency, sleep fragmentation index, frequency of naps, and mean activity level (a measurement of daytime function).

A variety of exploratory analyses will examine the effects of bright light exposure on FSS, BDI, quality of life, cognition, and motor disability.

STATISTICAL ANALYSIS

Primary endpoint

The distribution of the change scores of the treatment groups will be compared using the Wilcoxon rank-sum test or student's 2-sample *t*-test, as appropriate. The test will be two-sided, with α=0.05.

Secondary endpoint

The distribution of the change scores of the treatment groups will be compared using the Wilcoxon rank-sum test or student's 2-sample *t*-test, as appropriate. Actigraphy measures will be calculated using the software analysis program provided by Mini-Mitter (Bend, OR) and checked against the daily sleep logs maintained by the subjects. Two-factor repeated measures ANOVA with day of study as the within-subject factor (three time points) and group membership as the between-subject factor will be conducted for actigraphy output measures.

Sample size and power

The absence of precise preliminary data from previous studies of light therapy in PD using sleep outcomes precludes precise power calculation. With 15 participants per treatment group completing the study protocol, we will have 80% power against an effect size of 1.1(α=0.05, two sided, two sample t-test). This corresponds to a mean difference in change scores of around 4.6 on the ESS, if we project a within-group SD of 4 points. The projection is conservatively based on a study of modafinil for the treatment of daytime sleepiness in PD, in which Adler et al. [34] reported within group standard deviations for the change scores ranging from 2.1 to 4.2. We are planning to enroll 15 subjects per treatment group to allow for 20% dropout rate.

REFERENCES

1. Lees AJ, Blackburn NACampbell VL: The nighttime problems of Parkinson's disease*. Clin Neuropharmacol* 11(6), 512-519 (1988).
2. Tandberg E, Larsen JPKarlsen K: A community-based study of sleep disorders in patients with Parkinson's disease*. Mov Disord* 13(6), 895-899 (1998).
3. Karlsen KH, Tandberg E, Arsland D et al.: Health related quality of life in Parkinson's disease: a prospective longitudinal study*. J Neurol Neurosurg Psychiatry* 69(5), 584-589 (2000).
4. Scaravilli T, Gasparoli E, Rinaldi F et al.: Health-related quality of life and sleep disorders in Parkinson's disease*. Neurol Sci* 24(3), 209-210 (2003).
5. Meindorfner C, Korner Y, Moller JC et al.: Driving in Parkinson's disease: mobility, accidents, and sudden onset of sleep at the wheel*. Mov Disord* 20(7), 832-842 (2005).
6. Factor SA, McAlarney T, Sanchez-Ramos JR et al.: Sleep disorders and sleep effect in Parkinson's disease*. Mov Disord.* 5(4), 280-285. (1990).
7. Stocchi F, Barbato L, Nordera G et al.: Sleep disorders in Parkinson's disease*. J Neurol* 245 Suppl 1S15-18 (1998).
8. Paus S, Brecht HM, Koster J et al.: Sleep attacks, daytime sleepiness, and dopamine agonists in Parkinson's disease*. Mov Disord* 18(6), 659-667 (2003).
9. Rye DB, Bliwise DL, Dihenia B et al.: FAST TRACK: daytime sleepiness in Parkinson's disease*. J Sleep Res.* 9(1), 63-69. (2000).
10. Lockley SW, Skene DJ, Arendt J et al.: Relationship between melatonin rhythms and visual loss in the blind*. J Clin Endocrinol Metab.* 82(11), 3763-3770. (1997).
11. Myers BLBadia P: Changes in circadian rhythms and sleep quality with aging: mechanisms and interventions*. Neurosci Biobehav Rev.* 19(4), 553-571. (1995).

12. Moore RYEichler VB: Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. *Brain Res* 42(1), 201-206 (1972).
13. Dijk DJLockley SW: Integration of human sleep-wake regulation and circadian rhythmicity. *J Appl Physiol* 92(2), 852-862 (2002).
14. Moore-Ede MC, Czeisler CARichardson GS: Circadian timekeeping in health and disease. Part 2. Clinical implications of circadian rhythmicity. *N Engl J Med* 309(9), 530-536 (1983).
15. Czeisler CA, Allan JS, Strogatz SH et al.: Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. *Science* 233(4764), 667-671 (1986).
16. Wever RA, Polasek JWildgruber CM: Bright light affects human circadian rhythms. *Pflugers Arch.* 396(1), 85-87. (1983).
17. Van Someren EJ, Riemersma RFSwaab DF: Functional plasticity of the circadian timing system in old age: light exposure. *Prog Brain Res.* 138205-231. (2002).
18. Shochat T, Martin J, Marler M et al.: Illumination levels in nursing home patients: effects on sleep and activity rhythms. *J Sleep Res.* 9(4), 373-379. (2000).
19. Mishima K, Okawa M, Shimizu T et al.: Diminished melatonin secretion in the elderly caused by insufficient environmental illumination. *J Clin Endocrinol Metab.* 86(1), 129-134. (2001).
20. Klerman EB, Duffy JF, Dijk DJ et al.: Circadian phase resetting in older people by ocular bright light exposure. *J Investig Med.* 49(1), 30-40. (2001).
21. Kobayashi R, Kohsaka M, Fukuda N et al.: Effects of morning bright light on sleep in healthy elderly women. *Psychiatry Clin Neurosci.* 53(2), 237-238. (1999).
22. Kaida K, Takahashi M, Haratani T et al.: Indoor exposure to natural bright light prevents afternoon sleepiness. *Sleep* 29(4), 462-469 (2006).
23. Phipps-Nelson J, Redman JR, Dijk DJ et al.: Daytime exposure to bright light, as compared to dim light, decreases sleepiness and improves psychomotor vigilance performance. *Sleep* 26(6), 695-700 (2003).
24. Schindler SD, Graf A, Fischer P et al.: Paranoid delusions and hallucinations and bright light therapy in Alzheimer's disease. *Int J Geriatr Psychiatry.* 17(11), 1071-1072. (2002).
25. Fetveit ABjorvatn B: Bright-light treatment reduces actigraphic-measured daytime sleep in nursing home patients with dementia: a pilot study. *Am J Geriatr Psychiatry.* 13(5), 420-423. (2005).
26. Dowling GA, Hubbard EM, Mastick J et al.: Effect of morning bright light treatment for rest-activity disruption in institutionalized patients with severe Alzheimer's disease. *Int Psychogeriatr.* 17(2), 221-236. (2005).
27. Ancoli-Israel S, Martin JL, Gehrman P et al.: Effect of light on agitation in institutionalized patients with severe Alzheimer disease. *Am J Geriatr Psychiatry.* 11(2), 194-203. (2003).
28. Ancoli-Israel S, Gehrman P, Martin JL et al.: Increased light exposure consolidates sleep and strengthens circadian rhythms in severe Alzheimer's disease patients. *Behav Sleep Med.* 1(1), 22-36. (2003).
29. Dowling GA, Mastick J, Hubbard EM et al.: Effect of timed bright light treatment for rest-activity disruption in institutionalized patients with Alzheimer's disease. *Int J Geriatr Psychiatry.* 20(8), 738-743. (2005).
30. Artemenko ARLevin Ia I: [The phototherapy of parkinsonism patients]. *Zh Nevropatol Psikhiatr Im S S Korsakova.* 96(3), 63-66. (1996).
31. Reid KJBurgess HJ: Circadian rhythm sleep disorders. *Prim Care* 32(2), 449-473 (2005).

32. Kogan AOGuilford PM: Side effects of short-term 10,000-lux light therapy. *Am J Psychiatry* 155(2), 293-294 (1998).
33. Dhawan V, Healy DG, Pal S et al.: Sleep-related problems of Parkinson's disease. *Age Ageing* 35(3), 220-228 (2006).
34. Adler CH, Caviness JN, Hentz JG et al.: Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. *Mov Disord* 18(3), 287-293 (2003).