Sleep Medicine 16 (2015) 288–297

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Phase advancing human circadian rhythms with morning bright light, afternoon melatonin, and gradually shifted sleep: can we reduce morning bright-light duration?

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ARTICLE INFO

Article history:
Received 16 June 2014
Received in revised form 4 December 2014
Accepted 5 December 2014
Available online 18 December 2014

Keywords:
Bright light
Melatonin
Circadian rhythms
DLMO
Circadian misalignment
Jet lag

ABSTRACT

Objective: Efficient treatments to phase-advance human circadian rhythms are needed to attenuate circadian misalignment and the associated negative health outcomes that accompany early-morning shift work, early school start times, jet lag, and delayed sleep phase disorder. This study compared three morning bright-light exposure patterns from a single light box (to mimic home treatment) in combination with afternoon melatonin.

Methods: Fifty adults (27 males) aged 25.9 ± 5.1 years participated. Sleep/dark was advanced 1 h/day for three treatment days. Participants took 0.5 mg of melatonin 5 h before the baseline bedtime on treatment day 1, and an hour earlier each treatment day. They were exposed to one of three bright-light (~5000 lux) patterns upon waking each morning: four 30-min exposures separated by 30 min of room light (2-h group), four 15-min exposures separated by 45 min of room light (1-h group), and one 30-min exposure (0.5-h group). Dim-light melatonin onsets (DLMOs) before and after treatment determined the phase advance.

Results: Compared to the 2-h group (phase shift = 2.4 ± 0.8 h), smaller phase-advance shifts were seen in the 1-h (1.7 ± 0.7 h) and 0.5-h (1.8 ± 0.8 h) groups. The 2-h pattern produced the largest phase advance; however, the single 30-min bright-light exposure was as effective as 1 h of bright light spread over 3.25 h, and it produced 75% of the phase shift observed with 2 h of bright light.

Conclusions: A 30-min morning bright-light exposure with afternoon melatonin is an efficient treatment to phase-advance human circadian rhythms.

1. Introduction

Misalignment between the circadian clock and 24-h rhythmic behaviors such as sleep/wake and fasting/feeding ("circadian misalignment") is associated with sleep disruption, excessive sleepiness, and cognitive decrements during wake, and gastrointestinal problems [1–12]. The most recognized cause of circadian misalignment is jet lag after crossing multiple time zones, although night-shift work and early school or work times are other situations in which individuals can experience circadian misalignment. In laboratory studies that experimentally imposed severe acute circadian misalignment, healthy participants showed adverse metabolic responses that are risk factors for cardiovascular disease and type 2 diabetes [1,8,9]. When experienced chronically like in night-shift work, circadian misalignment increases the risk of a number of diseases, including cancer [13–18].

Appropriately timed sleep (dark), light, and exogenous melatonin can phase-shift circadian rhythms, and therefore they can be used to reduce the degree of circadian misalignment and attenuate risks of negative health and daily functioning outcomes [7,11,12]. The direction and magnitude of the shift is predicted by phase response curves (PRCs) [19–29]. Advancing the system (shifting it earlier) is more difficult and typically takes longer than delaying (shifting it later). This may be in part because most humans have an endogenous period that is slightly longer than 24 h [30–34], which favors the ability to delay. Of note, however, mice also have more difficulty advancing despite their average free-running period being <24 h [35]. Our laboratory has focused on testing methods to advance rhythms to attenuate circadian misalignment, which could be utilized by travelers flying east, shift workers who need to wake early for early-morning shifts or who want to take all of their daily sleep

Abbreviations: DLMO, dim-light melatonin onset; PRC, phase response curve; DSPD, delayed sleep phase disorder; SAD, seasonal affective disorder; h, hour; min, minute; BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; SSS, Stanford Sleepiness Scale.

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http://dx.doi.org/10.1016/j.sleep.2014.12.004
1389-9457/

before a night shift, and extreme night owls or patients with delayed sleep phase disorder (DSPD) who struggle to wake up for work or school. Indeed, the most recent American Academy of Sleep Medicine Practice parameters for treatment of circadian rhythm sleep disorders [36] indicated (guideline) timed light exposure and timed melatonin administration for shift work disorder and DSPD. In a gradual sleep/dark shift paradigm, we have examined phase advances in response to afternoon melatonin alone [37], morning bright light alone [38–40], as well as the combination of afternoon melatonin and morning bright light [41] in healthy young adults. The latter combination of afternoon melatonin and morning bright-light exposure produced the largest phase-advance shifts (~2.5 h) over 3 days of treatment.

One of the criticisms of bright-light treatment, however, is that it is time consuming, which could impact compliance to treatment. Little data exist on compliance to the use of bright light (either sunlight or light boxes) for reducing circadian misalignment, although a few reports describing light therapy for seasonal affective disorder (SAD) suggest that compliance rates to using bright-light boxes are mediocre in this particular group of patients. Michalak and colleagues [42] reported that, over a 4-week intervention, mean adherence to the prescribed bright-light treatment was 59%. Others have reported rates of long-term use of prescribed bright-light therapy for SAD ranging between 11% and 42% [43,44]. Therefore, identifying an effective and efficient duration of bright-light treatment that patients can realistically follow is warranted.

Many studies of phase shifting designed for practical purposes used long durations (≥3 h) of continuous bright-light exposures [38,45–54]; however, intermittent bright-light exposure is likely more feasible and it mimics real-life treatment patterns compared to continuous light exposure [55,56]. For this reason, we often utilize intermittent bright light in our studies [57–59]. Furthermore, previous studies from our laboratory [38] and others [60,61] showed that intermittent bright-light patterns can be almost as effective as continuous exposure producing about 60–90% of the phase shift obtained with continuous exposure. These data may suggest that the total time that the light is on may not be as important as the amount of time light exposure spans the appropriate portion of the PRC to light. Alternatively, or in addition, the beginning of a bright-light exposure may be the most effective in eliciting a phase-resetting response due to light adaptation [62].

While using a sleep schedule that was advanced by 1 h/day for 3 days, we previously tested the combination of intermittent morning bright light and afternoon melatonin [41] to produce a phase advance while maintaining circadian alignment. The purpose of the current study was to identify whether there was a more efficient bright-light treatment that could be implemented in combination with 0.5 mg of exogenous melatonin to phase-advance rhythms. The light pattern in the previous study [41] was intermittent such that the bright-light box was turned on four times for 30 min with 30 min of normal room lighting in between. Therefore, the total bright-light exposure was 2 h, but the total treatment time was spread over 3.5 h. Using this "2-h" group as a comparison group, the aims of this study were to examine whether phase-advance shifts were smaller when total bright-light treatment duration was shortened using the following strategies: (1) reducing the duration of the intermittent bright-light exposures from 30 to 15 min ("1-h" group) and (2) reducing the number of bright-light exposures from four to one 30-min exposure ("0.5 h" group). Two additional groups of participants completed the study, and they were compared to the historical comparison group.

2. Methods

2.1. Participants

Data from 50 participants (27 males) aged 18–40 years (mean = 25.9 ± 5.1 years) were included in this analysis. The 2-h group included 16 participants (10 males), the 1-h group included 17 participants (nine males), and the 0.5-h group included 17 participants (eight males). Age, sex distribution, morningness/eveningness, and body mass index (BMI) did not differ among the three bright-light groups. Morningness-eveningness was measured using the Horne-Östberg questionnaire [63]; 32 participants were intermediate types, 10 were moderate morning types, six were moderate evening types, one was a definite morning type, and one was a definite evening type (mean = 52.2, SD = 8.6). BMI was <30 kg/m^2 (mean ± SD = 23.4 ± 2.8), and they weighed between 47 and 96 kg (mean ± SD = 68.5 ± 10.5 kg). The majority of participants (66%) reported their race as White/Caucasian (12% Black/African American, 10% Asian, 6% more than one race, and 6% other); race distribution did not differ among groups. Inclusion/exclusion criteria and procedures for all groups were similar, and they are described together below.

All participants were free of medical and psychiatric disorders, as assessed by in-person interviews, the Minnesota Multiphasic Personality Inventory-2 (MMPI-2), and part of a health questionnaire [64]. Participants reported not taking any prescription medications, except for five women who were taking oral contraceptives. Participants reported no more than moderate alcohol (≤2 drinks per day) and caffeine (<500 mg per day) intake, and they were nonsmokers. The inclusion criteria included habitual sleep duration between 6.5 and 9 h per night, habitual bedtimes between 23:00 and 02:00, and habitual wake times between 07:00 and 10:00. Participants reported no sleep problems over the proximal month of enrollment as assessed by a Pittsburgh Sleep Quality Index (PSQI) [65] score of ≤5, and no problems with excessive daytime sleepiness as assessed by an Epworth Sleepiness Scale [66] score of <10. Participants reported not working night shifts during the 2 months before the start of the study or crossing >3 time zones in the month before beginning the study.

The Rush University Medical Center Institutional Review Board approved the study protocols, and, therefore, the study was performed in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki. Each participant gave written informed consent.

2.2. Procedures

2.2.1. Experimental protocol

Participants completed the 14-day protocol illustrated in Fig. 1. Each participant was given a fixed sleep schedule to follow at home during baseline days (1–6 and 8–11) and were provided 8 h of time in bed. The sleep schedule assigned to each participant was based on their reported average bedtime and wake time before starting the study. Assigned baseline bedtimes ranged from 23:00 to 02:00 (mean = 00:10, SD = 56 min), and thus wake time ranged from 07:00 to 10:00 (mean = 08:10, SD = 56 min). Each baseline morning, participants were required to go outside for at least 10 min during the second hour after waking for daylight exposure. The fixed sleep schedule and morning light was designed to stabilize the circadian phase and ensure that participants were not sleep deprived before the phase-advancing treatment in the laboratory. Participants slept at home on days 1–6 and 8–11; on the other days, they slept in private temperature-controlled bedrooms in the laboratory. Participants lived in the laboratory from days 12 through 15. Wake times in the laboratory were gradually advanced by 1 h/day over the three treatment days (days 12, 13, and 14). Bedtimes were also advanced by 1 h/day, except in the 2-h group. Participants in the 2-h group were put to bed at their baseline bedtime on the first treatment day instead of 1 h earlier. Then their bedtime shifted by 2 h relative to baseline on the second treatment day (day 13), and by 3 h relative to baseline on the third treatment day (day 14). On the second and third treatment days, the sleep schedule among the three