Effects of artificial dawn on subjective ratings of sleep inertia and dim light melatonin onset

Gimenez, Marina C.; Hessels, Martijn; van de Werken, Maan; de Vries, Bonnie; Beersma, Domien G. M.; Gordijn, Marijke C. M.

Published in:
Chronobiology International

DOI:
10.3109/07420528.2010.496912

Publication date:
2010

Chronobiology International, 27(6): 1219–1241, (2010)

ISSN 0742-0528 print/1525-6073 online
DOI: 10.3109/07420528.2010.496912

informa
healthcare

EFFECTS OF ARTIFICIAL DAWN ON SUBJECTIVE RATINGS OF SLEEP INERTIA AND DIM LIGHT MELATONIN ONSET

Marina C. Giménez,[1] Martijn Hessels,[2] Maan van de Werken,[1] Bonnie de Vries,[1] Domien G. M. Beersma,[1] and Marijke C. M. Gordijn[1]

[1]*Department of Chronobiology, Center for Life Sciences, University of Groningen, Groningen, The Netherlands*
[2]*Medical Design Engineering, Amsterdam, The Netherlands*

The timing of work and social requirements has a negative impact on performance and well-being of a significant proportion of the population in our modern society due to a phenomenon known as social jetlag. During workdays, in the early morning, late chronotypes, in particular, suffer from a combination of a nonoptimal circadian phase and sleep deprivation. Sleep inertia, a transient period of lowered arousal after awakening, therefore, becomes more severe. In the present home study, the authors tested whether the use of an alarm clock with artificial dawn could reduce complaints of sleep inertia in people having difficulties in waking up early. The authors also examined whether these improvements were accompanied by a shift in the melatonin rhythm. Two studies were performed: Study 1: three conditions (0, 50, and 250 lux) and Study 2: two conditions (0 lux and self-selected dawn-light intensity). Each condition lasted 2 weeks. In both studies, the use of the artificial dawn resulted in a significant reduction of sleep inertia complaints. However, no significant shift in the onset of melatonin was observed after 2 weeks of using the artificial dawn of 250 lux or 50 lux compared to the control condition. A multilevel analysis revealed that only the presence of the artificial dawn, rather than shift in the dim light melatonin onset or timing of sleep offset, is related to the observed reduction of sleep inertia complaints. Mechanisms other than shift of circadian rhythms are needed to explain the positive results on sleep inertia of waking up with a dawn signal. (Author correspondence: m.c.gimenez@rug.nl)

Keywords Artificial dawn; Chronotype; Dim light melatonin onset; Sleep inertia; Human; Well-being

Submitted January 18, 2010; Returned for revision February 3, 2010; Accepted April 6, 2010
Address correspondence to Marina C. Giménez, Research Unit of Chronobiology, University of Groningen, Kerklaan 30, 9751 NN Haren, The Netherlands. Tel: +31 50 363 4184; Fax: +31 50 363 2148; E-mail: m.c.gimenez@rug.nl

INTRODUCTION

The 24-h sleep-wake cycle is controlled by both circadian and homeostatic processes (Borbély, 1982; Daan et al., 1984). However, large individual differences are found between human subjects in their preferred (Tonetti et al., 2008) or actual (Horne & Östberg, 1976; Roenneberg et al., 2003) sleep timing. These differences are referred to as chronotypes. Chronotypes can be classified as early, intermediate, and late types. Extreme early types are characterized by going to bed and waking up early, especially during free days (22:00–06:00 h), whereas late types do the opposite (04:00–12:00 h), based on Dutch general population data (Zavada et al., 2005). Nowadays, work and social requirements impose difficulties, especially for subjects in both extreme ends of the distribution. This misalignment between internal and external timing is known as social jetlag. The amount of social jetlag correlates significantly with mental distress, and unhealthy behaviors, such as the tendency to smoke and to consume alcohol (Wittmann et al., 2006).

Early and late types not only sleep earlier and later, respectively, than intermediate types, but they also exhibit shifted rhythms in physiological and psychological parameters (Baehr et al., 2000; Duffy et al., 1999; Kerkhof & Van Dongen, 1996) as well as in alertness and mood (Kerkhof, 1998; Kerkhof & Van Dongen, 1996). Subjective alertness and calculation performance have been shown to cycle in a circadian manner (Johnson et al., 1992; Monk et al., 1985). As a possible consequence of the differences in phase, performance in the early hours is especially impaired in late chronotypes, whereas the opposite occurs in early types. Impaired performance, confusion, and sleepiness in the early morning after waking up are states that are experienced by most people to some extent. This transient period after sleep is known as "sleep inertia" (Åkerstedt & Folkard, 1997; Dinges, 1990; Tassi & Muzet, 2000). Depending on sleep timing and sleep phase upon awakening, sleep inertia may differ (see review of Tassi & Muzet, 2000). However, it seems that the main factor influencing sleep inertia is the preceding amount of sleep (Achermann et al., 1995; Jewett et al., 1999). Sleep-inertia severity is increased under sleep-deprivation conditions (Balkin & Badia, 1988; Dinges et al., 1985). Subjects getting up early on workdays at their nonoptimal circadian phase and after being sleep deprived during previous working days may suffer from a combination of detrimental factors causing severe sleep inertia.

Lack of morning light during winter days may also worsen sleep-inertia complaints due to the absence of the phase-advancing stimulus of morning light (Beersma & Daan, 1993; Gordijn et al., 1999; Honma & Honma, 1988; Khalsa et al., 2003; Minors et al., 1991) and the lack of its acute alerting effect (Cajochen et al., 2000; Campbell et al., 1995; Rüger

et al., 2003, 2006). Because of the impact that sleep inertia may have in our society when high performance and alertness are required in the early morning, diminishing complaints of sleep inertia is of great interest.

The two studies described here investigate whether it is possible, in a natural home setup, to reduce sleep-inertia complaints in persons who have difficulties waking up early by means of an artificial dawn during the dark winter months. Based on the hypothesis that a late circadian phase is one of the factors causing these difficulties in waking up in the morning by later types, it is also tested whether improvements are accompanied by a shift in the melatonin and/or the sleep-wake rhythm.

METHODS

Subjects

Subjects, who were recruited by advertisement at the University of Groningen and public places, had to have a regular life style consisting of at least 4 days/wk when they had to rise earlier than on free days. They completed the Munich Chronotype Questionnaire (MCTQ; Roenneberg et al., 2003) as part of the selection process. From this questionnaire, data were obtained on sleep habits on work and free days. Other main selection criteria, also obtained from this questionnaire, were self-reported need for ≥60 min after awakening to feel fully alert in the morning and not to nap. After a general health screening by means of questionnaires, 92 subjects (51 and 41 subjects for Studies 1 and 2, respectively) who did not suffer from winter depression (Beck Depression Inventory–II, Dutch version [BDI-II-NL] ≤8; Beck et al., 1996) enrolled in this home study. Subjects suffering from somatic and/or sleep disorders, or who used sleep medication or other drugs, were excluded

The study protocol was approved by the Medical Ethics Committee of the University Medical Center of Groningen, The Netherlands, and conformed to international ethical standards (Portaluppi et al., 2008). All subjects signed a written informed consent form prior to their participation.

Study 1

Thirty-six subjects participated in the months of November–December 2006 (sunrise range: 07:32–08:49 h., sunset range: 16:25–17:02 h). The remaining 15 subjects participated in the months of January–February 2007 (sunrise range: 07:25–08:48 h, sunset range: 16:26–18:09 h). Although the number of subjects who dropped out was low (n = 3), several subjects failed to follow the protocol, e.g., not all the questionnaires were completed for all conditions. Thus, complete data sets for all measured variables were obtained only from 23 subjects.

Study 2

Forty-one subjects participated in the months of January–February 2007 (sunrise range: 07:25–08:48 h, sunset range: 16:26–18:09 h). Due to violation of the protocol complete data sets were obtained only from 23 subjects.

Experimental Design

Instructions to subjects were given personally during a session when the experimental setup and methods of data collection were explained. After giving consent, subjects received an artificial dawn wake-up light with an incandescent 100-W E27 Philips Softtone softwhite 230-V T55 lamp (see Figure 1A for spectral composition) (Philips Wake-up Light; Philips Consumer Lifestyle, Drachten, The Netherlands) to be used at home. The increase in light intensity follows an exponential function where the ratio of the step to the absolute intensity is constant. The very beginning of the curve follows a linear function starting with 0 lux. Light intensity increases every 10 ms. The smallest step size is in the order of 0.01 lux, whereas the largest is in the order of 2.5 lux (Figure 1B). The experiment was conducted during the wintertime to avoid large differences in exposure to external natural light after waking up between conditions. Two different studies served to test the effects of this home-light system in subjects with difficulties in waking in the morning.

Study 1

The aim of Study I was to assess whether changes in sleep-inertia complaints depend on light intensity. Secondly, it was tested if those changes were accompanied by a phase advance of the biological clock estimated by the dim light melatonin onset (DLMO).

In a home study, a modified wake-up light (modified Philips Wake-up Light; Philips Consumer Lifestyle) was used by the subjects for 42 days (6 wks). In a within-subject design, the maximum intensity of light reached during the 30-min dawn signal was varied every 2 wks between 0 lux (control, no dawn signal), 50 lux (medium), or 250 lux (high). The order of the conditions was randomized between subjects. At the subject's defined time, this maximum intensity was reached, and an audible alarm sounded. To avoid differences in light exposure after waking up between conditions within subjects, the wake-up light was modified so that light was turned off automatically when the audible alarm sounded. The snooze function was disabled.

Each condition lasted exactly 14 days. Within this period, subjects were free to either use or not use the artificial dawn, depending on

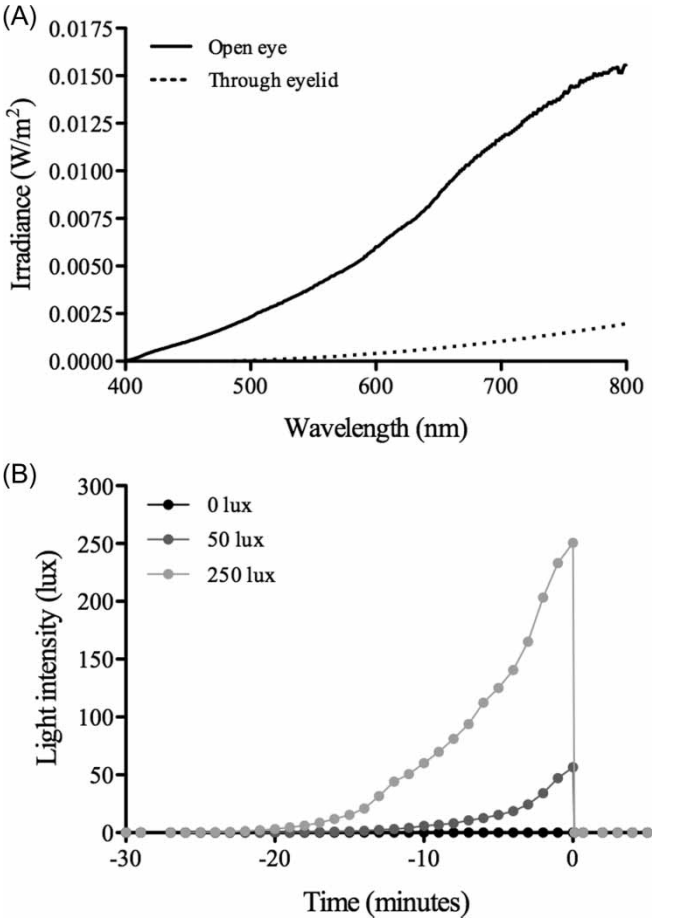

FIGURE 1 Wake-up light characteristics. (A) Irradiance (W/m^2) as a function of wavelength (nm) of the wake-up light set at 250 lux and recorded at 40 cm distance (straight line). Irradiance after the filtering effects of the eyelid (dashed line) derived from Moseley et al. (1988). (B) Light intensity as a function of time during the 30 min before the alarm (alarm time = 0), for the modified wake-up light where the light turns off at the time of the alarm. Dark grey circles: 250 lux; light grey triangles: 50 lux; black circles: 0 lux.

whether they did or did not need an alarm clock. However, subjects were instructed to start and end this 14-day period during a working week, so assessment of the effects of the use of the artificial dawn took place during a span of structured social routine. On average (± SD) the artificial dawn was used 11.8 ± 1.7 days.

Study 2

Study 2 was conducted to investigate the range of light intensities preferred by people and whether those intensities, in comparison to an

alarm wake-up only (no dawn signal), led to a decrease of sleep-inertia complaints. A nonmodified artificial dawn wake-up light with the snooze function available (Philips Wake-up Light; Philips Consumer Lifestyle) was used for 28 days (4 wks). Subjects were asked to select the intensity with which they felt most comfortable, ranging from 20 up to 400 lux. They were asked to determine their preferred intensity within the first 3 days and to retain it for the rest of the experimental condition. In a randomized order, subjects used for 2 wks either the self-selected intensity (dawn condition) or the 0 lux intensity (control condition, no dawn). As in Study 1, subjects were free to use or not use the artificial dawn, depending on their own needs, but were instructed to start and end the 14-day period during a span of structured social routine. On average (±SD) the artificial dawn was used 11.5 ± 2 days.

Measurements

Sleep-Inertia Duration and Severity, Well-Being, and Sleep Parameters

Sleep inertia was characterized by means of subjective ratings, both prospectively and retrospectively. Sleep-inertia duration was defined as the amount of time required per subject to feel fully awake. An evaluation form was developed for the purpose of assessing general well-being. Several parameters, i.e., wake-up quality, easy rising, energetic feeling, mood after waking up, social interactions, concentration, and productivity, relevant to describe general well-being and often used in chronobiological studies, were assessed (Norden & Avery, 1993). For each parameter a 1 to 10 rating was obtained, 1 being very bad and 10 being excellent. Sleep-inertia duration and general well-being were assessed retrospectively at the end of every 2-wk period.

The Karolinska Sleepiness Scale (KSS), an often-used questionnaire that has been validated against electroencephalographic (EEG) parameters (Åkerstedt & Gillberg, 1990; Kaida et al., 2006), was completed daily 5 and 30 min after rising. The KSS ranges from 1 to 9; the higher the reported value the greater the sleepiness. These values were used as a prospective measurement of sleep-inertia severity, i.e., how sleepy the person felt within the first 30 min when the feelings of sleep inertia are common (Tassi & Muzet, 2000). The Groningen Sleep Quality Scale (GSQS; Leppämäki et al., 2003) was also completed daily 30 min after awakening. The GSQS ranges from 0 to 14; the higher the value, the poorer the sleep quality.

Sleep timing, i.e., bedtime, sleep onset, alarm time, sleep offset, and get-up time, was recorded daily. This allowed us to check for a regular sleep-wake schedule and to record the timing of the artificial dawn. For

the present study, sleep offset is of particular interest due to its sensitivity to the phase-advancing effects of morning light (Gordijn et al., 1999).

The sleep diaries, including both prospective and retrospective measurements, were returned to the investigators at the end of every 2-wk condition. In this way, subjects did not have access to their estimations made in previous conditions.

Melatonin

In Study 1, subjects collected saliva samples at home at the end of every 2-wk condition to assess whether changes in sleep-inertia complaints were accompanied by a shift of the dim light melatonin onset (DLMO). Saliva samples were collected hourly starting 5 h before subject's habitual bedtime and continued for 1 h after it. In total, saliva samples were collected at seven timepoints per experimental condition. Subjects were carefully instructed about the requirements of collecting saliva. No chocolate, bananas, artificially colored sweets, coffee, or black tea were allowed during measurements. Eating and drinking were restricted to 15 min after the collection of saliva, and 45 min before each sample subjects were instructed to rinse their mouths with water. Brushing teeth with toothpaste was not allowed. Subjects were also asked to expose themselves to as little light as possible by keeping the curtains closed, using only small light bulbs, and wearing sunglasses inside, commencing 1 h before the first sample was taken. Watching TV was allowed at a distance of $\geq$2 m. Postural changes were not allowed during the 10-min period before and during saliva collection.

Saliva was collected using Sarstedt Salivettes with a cotton swab (Sarstedt B.V., Etten-Leur, The Netherlands). Samples were stored at 4°C until sent to our lab (the period between collection and arrival in the lab was $\leq$1 wk). Once the samples arrived, they were stored at $-$20°C. Melatonin concentration was assessed by radioimmunoassay (RIA) (RK-DSM; Bühlmann Laboratories AG, Siemens Medical Solutions Diagnostics, Breda, The Netherlands). All samples from one individual were analyzed within the same series.

Data Analysis

Sleep-Inertia Duration and Severity, Well-Being, and Sleep Parameters

Depending on their obligations, subjects were free to choose when to use the artificial dawn alarm clock. The analysis of the subjective ratings was conducted only for those days when subjects used the alarm clock. In order to avoid possible bias, data analysis was conducted on those subjects

who completed all of the three conditions for all the measured variables (n = 23). To check for robustness of the data, it was assessed whether the general pattern for each particular parameter remained if data of all available subjects were included.

Melatonin

The limit of detection for the RIA was 0.3 pg/mL, with an intraassay variation of 6.7% at a low melatonin concentration (mean = 1.5 pg/mL, n = 30) and 6.5% at a high melatonin concentration (mean = 15 pg/mL, n = 30). Interassay variation was 12.2% at low melatonin concentration (mean = 2.1 pg/mL, n = 15) and 19.7% at high melatonin concentration (mean = 17.5 pg/mL, n = 16).

The DLMO was used as a phase marker. To avoid differences in the DLMO between subjects due to variation in total amount of melatonin production, melatonin levels were normalized within subjects to the maximum value attained during any condition. DLMO was defined as the clock time when the melatonin values crossed a threshold of 15% of the maximum concentration. This value was chosen on the basis of a frequency analysis of percentage melatonin. It was the timepoint when changes in melatonin concentration became apparent (after 15% melatonin concentrations only increased up to their maximum and then started to decrease). DLMO was determined by linear interpolation between the last sample with a lower concentration and the first sample with a higher concentration than the threshold value.

Statistics

The use of the artificial dawn was expected to reduce sleep-inertia duration and severity in comparison with the non–dawn simulation condition (0 lux), as well as to improve well-being and sleep quality. Nonparametric tests were conducted due to the non-normal distribution of the sleep-inertia variables. In Study 1, one-tailed Friedman tests were conducted to assess the main effects of condition, the main effects of time, and the interaction between both. In order to have an approach conceptually similar to a repeated-measures analysis of variance (ANOVA) (a test generally used to deal with this type of design), data were treated as follows. Data were averaged over conditions to investigate the main effect of time, and data were averaged over time to investigate the main effect of condition. After finding a significant main effect, comparisons between conditions were performed. In Study 2, a one-tailed Wilcoxon test was conducted. All tests were performed with $\alpha = .05$

The use of the artificial dawn was expected to advance the DLMO and/or sleep offset. A repeated-measures ANOVA was used to test for

significant differences in DLMO and sleep timing between conditions in Study 1. The effects of the use of the artificial dawn in Study 2 as well as sleep timing were tested by means of a paired *t* test.

To determine the role of DLMO and sleep offset as an alternative or additionally to the main effects of light on sleep-inertia duration, a multilevel analysis was conducted by means of MLwiN software (Centre of Multilevel Modeling, Institute of Education, London, UK). The following model equation was used:

$$\text{Sleep-inertia duration} = \beta_{0ij} + \beta_{1ij} \times \text{condition} + \beta_{2ij} \times \text{DLMO} + \beta_{3ij} \times \text{sleep offset}$$

where β_0 represents the model intercept, β_1 the main effect of condition, β_2 the effect of DLMO (only tested in Study 1), and β_3 the effect of the timing of sleep offset. βs correspond to the slope of the correlations between the y and x variables. The model takes into account the hierarchy of the protocol consisting of i = conditions nested in j = subjects. The regression coefficients were tested with a *z*-test.

RESULTS

Subjects

The average mid-sleep time on free days (MSF) has been used to define chronotype (Roenneberg et al., 2003). The MSF observed among the 46 subjects (21 males/25 females, average age ± SD: 30 ± 11 yrs) who completed all conditions was on average (±SD) 04:56 h ± 49 min and 05:04 h ± 1:06 h for Study 1 and Study 2, respectively. Mid-sleep on workdays (MSW) was on average (±SD) 03:15 h ± 41 min and 03:38 h ± 48 min for Study 1 and Study 2, respectively. Social jetlag, defined as the difference between mid-sleep on free and workdays, was on average (±SD) 1:40 h ± 56 min (Study 1) and 1:26 h ± 39 min (Study 2), being relatively long. On average (±SD), subjects awoke 2:09 h ± 50 min later on free days.

Sleep-Inertia Duration and Severity, Well-Being, and Sleep Parameters

Study 1

Sleep-inertia duration was estimated retrospectively as the amount of time needed to feel fully awake. Overall, a significant effect of condition was found (n = 23, $\chi^2 = 6.844$, $p < .05$). Further analysis revealed a significant reduction of sleep-inertia duration of 19.7 min between the control

and 250-lux conditions (n = 23, $z = -2.311$, $p < .01$), and a smaller, but significant, reduction of 8.9 min between the 250-lux and 50-lux conditions (n = 23, $z = -2.030$, $p < .05$). A 10.8-min difference, although not statistically significant, was found between the 50-lux and control conditions (n = 23, $z = -0.769$, $p = .22$) (Figure 2A). When considering the maximum number of subjects, the significant effect of condition remained (n = 33, $\chi^2 = 7.600$, $p < .05$). Although differences in sleep-

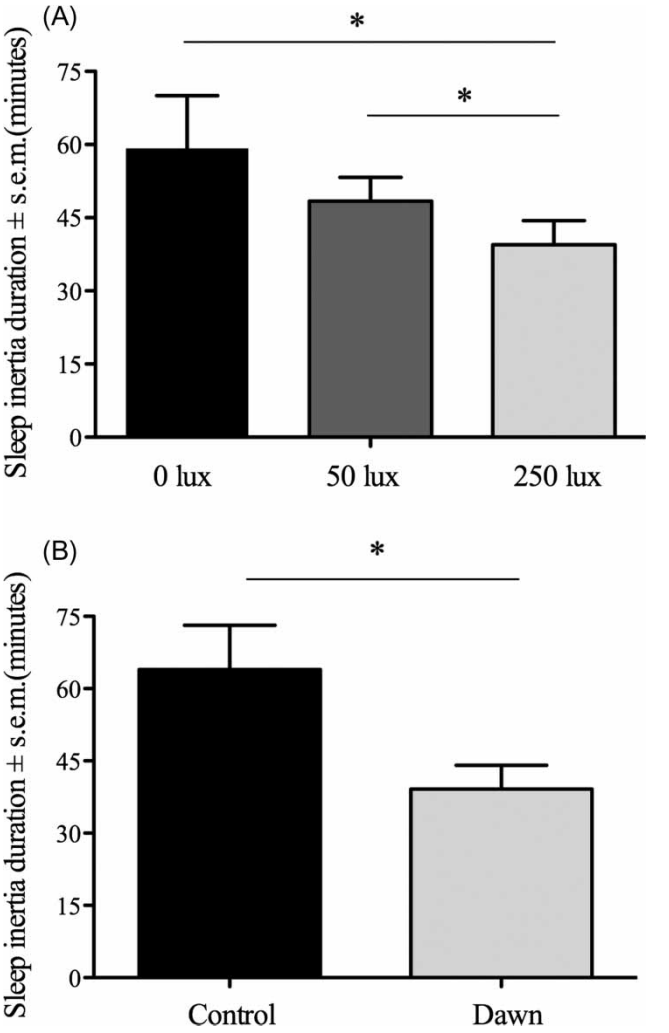

FIGURE 2 Sleep-inertia duration. Mean ± SEM values of subjective sleep-inertia duration measured as the amount of minutes needed to feel fully awake after waking up. A significant effect of the artificial dawn was found in both studies. Study I (A): significant 19.7-min and 8.9-min decreases were found between the 250 lux and the 0 lux (control) conditions, and between the 250-lux and 50-lux conditions, respectively. Study II (B): a significant 24.8-min decrease was found between the artificial dawn (self-selected intensities) and 0-lux (control) conditions.

inertia duration became a bit shorter (15.8 min, 8.8 min, and 7.1 min between 250 and 0 lux, 250 and 50 lux, and 50 and 0 lux, respectively), the statistical significances between conditions remained the same ($z = -2.612$, -2.228, and -0.628, $p < .005$, $p < .05$, and $p = .26$ for the differences between 250 and 0 lux, 250 and 50 lux, and 50 and 0 lux, respectively).

Sleepiness scores obtained 5 and 30 min after waking up by means of the KSS were used as an estimation of sleep-inertia severity (Table 1). A significant main effect of time was found. Sleepiness was reduced 30 min compared to 5 min after waking up for all conditions considered together ($n = 23$, $z = -4.197$, $p < .001$). This change over time represents the expected reduction of sleep inertia in the period shortly after waking up. A significant effect of condition was also found ($n = 23$, $\chi^2 = 10.783$, $p < .001$). Further comparisons between conditions showed a significant reduction in sleep-inertia severity by the 50-lux condition compared to the control condition ($n = 23$, $z = -2.220$, $p < .05$) and compared to the 250-lux condition ($n = 23$, $\chi = -1.780$, $p < .05$). No differences were found between the 250-lux and control conditions. There was no significant interaction between condition and time ($n = 23$, $\chi^2 = 2.264$, $p = .32$). The significant main effects of time and condition remained for the maximum number of subjects that completed the questionnaires ($n = 42$, $z = -5.646$, $\chi^2 = 8.491$, $p < .001$, $p < .005$ for time and condition, respectively). Again, only the 50-lux condition was significantly different from the control condition ($n = 42$, $z = -1.888$, $p < .05$).

From the variables selected to assess general subjective well-being, waking-up quality, easy rising, energetic feelings, mood, social interactions, and productivity were significantly improved in the artificial dawn condition compared to the control condition ($n = 23$, χ^2 for all variables between 6.677 and 12.030; both 50 and 250 lux, $p < .05$). No significant differences were observed between the two light intensities (Figure 3A). When considering the maximum number of subjects, the parameters social interactions, concentration, and productivity were no

TABLE 1 Summary data on sleep-inertia severity

Assessment/Condition	0 lux	50 lux	250 lux	*Average per timepoint*
5 min after rising	7.07 ± 0.26	6.83 ± 0.23	6.92 ± 0.23	*6.94 ± 0.21*[a]
30 min after rising	5.36 ± 0.28	4.97 ± 0.21	5.19 ± 0.22	*5.17 ± 0.22*[b]
Average per condition	*6.22 ± 0.26**	*5.89 ± 0.12*[§]	*6.06 ± 0.21**	

Note. Data are the average ± SEM sleepiness ratings as obtained by the Karolinska Sleepiness Scale (KSS).

[a,b]Significantly different from each other ($p < .001$).

*,[§]Significantly different from each other ($p < .001$).

No significant interaction was found between condition and time ($p = .32$).

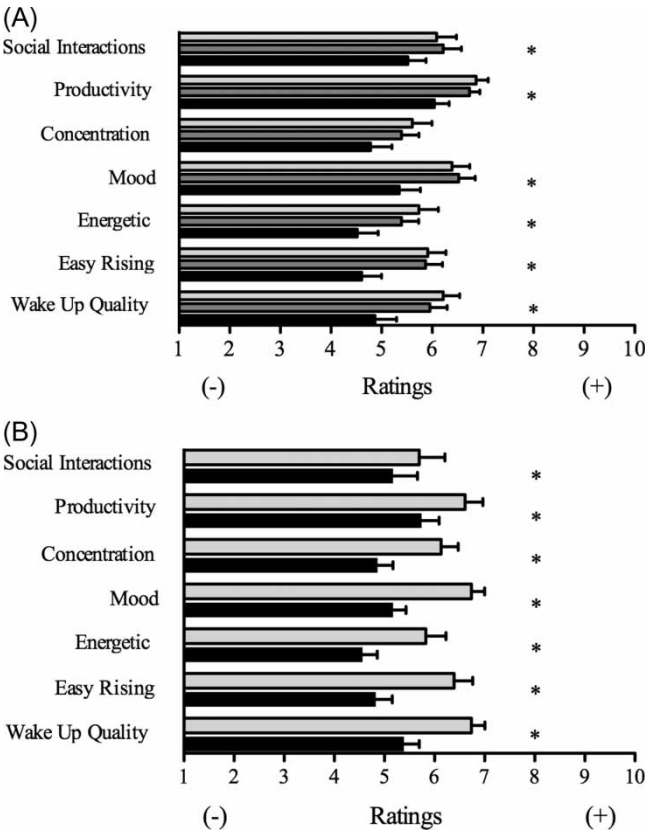

FIGURE 3 General well being. Mean ± SEM values for subjective ratings on different parameters to assess general well-being after waking up. A significant improvement in waking up quality, easy rising, energy, and mood was found in Study I by the use of the artificial dawn at any light condition. Black, dark grey, and light grey columns represent the control, 50-lux, and 250-lux conditions, respectively. (A). A further improvement in social interactions, concentration, and productivity was found in Study II when the artificial dawn (self-selected intensities, light grey columns) condition is compare to the 0 lux (control, black columns) condition (B).

longer significantly different when the artificial dawn condition was compared to the control (n = 33, χ^2 between 3.022 and 3.639; $p = .16$, $p = .10$, and $p = .11$, respectively). The pattern remained the same for the other variables.

Sleep quality (GSQS) was relatively good in all conditions (n = 23, average ± SEM: 3.4 ± 0.2, 3.6 ± 0.3, and 3.2 ± 0.3 for the 0-, 50-, and 250-lux conditions, respectively). No significant effects resulted from the use of the artificial dawn alarm clock at any of the intensities compared to the control condition (n = 23, $\chi^2 = 1.826$, $p = .2$). No significant differences were observed when considering the maximum number of subjects (n = 42, average ± SEM: 3.4 ± 0.3, 3.5 ± 0.2, and 3.4 ± 0.2 for the 0-, 50-, and 250-lux conditions, respectively).

Bedtime and sleep offset did not differ significantly between conditions (average ± SD: bedtime: 0 lux = 22:44 h ± 46 min, 50 lux = 23:11 h ± 56 min, 250 lux = 23:13 h ± 52 min; sleep offset: 0 lux = 07:09 h ± 42 min, 50 lux = 07:22 h ± 58 min, 250 lux = 07:04 h ± 43 min; $F = 2.512$, $p = .105$). Exposure to the artificial dawn always occurred during the dark span before sunrise, and its timing was not significantly different between conditions. The artificial dawn signal started on average (±SD) at 06:41 h ± 44 min for 0 lux, 06:30 h ± 49 min for 50 lux, and 06:41 h ± 45 min for 250 lux ($F = 0.502$, $p = .613$)

The multilevel analysis confirmed the significant main effect of condition on the reduction of sleep-inertia duration (β1 estimate: −0.08 ± 0.04 min/lux, $p < .05$). In addition, sleep offset was negatively and significantly related to sleep-inertia duration (β3 estimate: −10.57 ± 5.33 min/h, $p < .05$), indicating that the later people awoke the less they suffered from sleep inertia. The multilevel analysis revealed no effect of DLMO on the observed sleep-inertia duration (β2 estimate: 6.03 ± 4.68 min/h, $p = .2$).

Study 2

In this study subjects, chose their own individually preferred light intensity. The chosen light intensities ranged between 120 and 400 lux. On average, when considering the advised 40 cm distance to the artificial dawn alarm clock, the chosen light intensity was 264.7 ± 85.8 lux. The median light intensity was 280 lux.

Sleep-inertia duration, measured as the time needed to feel fully awake, was significantly decreased by 24.8 min in the dawn compared to the control condition (Figure 2B; n = 23, $z = -2.827$, $p < .001$). The effects on sleep-inertia duration remained when considering the maximum number of subjects available for this analysis (n = 25, $z = -3.138$, $p < .001$) and amounted to a difference of 25.8 min.

Sleep-inertia severity was estimated by means of the KSS at 5 and 30 min after waking up (Table 2). A significant main effect of time was found. Sleepiness was lower after 30 min compared to 5 min after waking up (n = 23, $z = -4.199$, $p < .001$). The use of the artificial dawn at a self-selected intensity significantly reduced the complaints of sleep-inertia severity (n = 23, $z = -2.566$, $p < .005$). There was no significant interaction between condition and time (n = 23, $z = -1.620$, $p = .1$). The overall effects of time and condition were still present when considering the maximum number of subjects (n = 26, $z = -4.459$ and -3.055, $p < .001$ and $p < .001$ for time and condition, respectively).

Figure 3B shows the subjective measurements of well-being. Use of the artificial dawn lead to an improvement of all variables (n = 23, z values between −2.194 and −3.265, all $p < .05$) except "social

TABLE 2 Summary data on sleep-inertia severity

Assessment Condition	0 lux	Artificial dawn	*Average per timepoint*
5 min after rising	6.85 ± 0.18	6.43 ± 0.25	*6.64 ± 0.12*[a]
30 min after rising	5.26 ± 0.23	4.69 ± 0.23	*4.98 ± 0.21*[b]
Average per condition	*6.05 ± 0.18*[*]	*5.56 ± 0.22*[§]	

Note. Data are the average sleepiness ratings as obtained by the Karolinska Sleepiness Scale (KSS) ± SEM.

[a,b]Significantly different from each other ($p < .001$).

[*,§]Significantly different from each other ($p < .001$).

No significant interaction was found between condition and time ($p = .1$).

interactions" (n = 25, $z = -1.414$, $p = .08$). The results remained the same when calculated over the maximum number of subjects.

In Study 2, sleep quality was also relatively good in both conditions (mean ± SEM: 3.6 ± 0.3 and 3.1± 0.3 for the control and artificial dawn conditions, respectively). Sleep quality did not significantly improve with the use of the artificial dawn ($z = -1.543$, $p = .06$). When considering the maximum number of subjects, the observed tendency becomes significant. The use of the artificial dawn improved, although to a small extent, the quality of sleep (n = 26, average ± SEM: 3.7 ± 0.3 and 3.1 ± 0.3 in the experimental and control conditions, respectively, $z = -1.844$, $p < .05$).

Bedtime did not differ significantly between conditions (average ± SD: 0 lux = 23:13 ± 1:19 h versus artificial dawn = 23:37 h ± 57 min). Sleep offset was earlier in the artificial dawn condition (average ± SD: artificial dawn = 07:22 h ± 55 min versus control = 07:32 h ± 1:07 h, $p < .05$). Exposure to the artificial dawn occurred always during the dark before sunrise, and the timing did not differ significantly between conditions. The artificial dawn signal started on average (± SD) at: 06:59 h ± 51 min (0 lux) and 06:47 h ± 41 min (artificial dawn).

Multilevel analysis confirmed the significant main effect of condition on sleep-inertia duration. Use of the artificial dawn reduced sleep-inertia duration (β1 estimate: −24.74 ± 10.25 min/lux, $p < .05$). Although sleep offset was earlier in the artificial dawn condition, when added to the model the timing of sleep offset did not contribute significantly to the observed sleep-inertia duration (β2 estimate: 0.5 ± 5.38 min/h, $p = .93$).

Melatonin

Saliva samples were received from 41 subjects. However, nine subjects either did not produce complete data sets (n = 5) or the expected pattern in melatonin levels was not found (n = 4), suggesting these subjects did not follow the protocol. The curves were either completely flat with mostly zeros, started at high levels and became lower with time (opposite

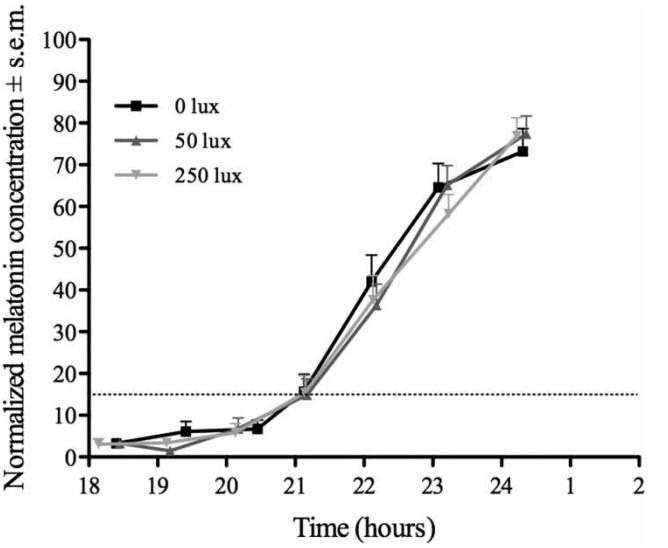

FIGURE 4 Melatonin profiles. Average melatonin profiles ± SEM for the three conditions. DLMO ± SD measured at 15% level (dotted line) showed no significant differences between conditions. Average DLMO (± SD) was 21:23 h ± 58 min for the control condition, 21:25 h ± 52 min for the 50-lux condition, and 21:23 h ± 57 min for the 250-lux condition.

direction), or fluctuated rather randomly crossing the DLMO criterion value repeatedly. Only those 23 subjects who completed the subjective ratings on sleep inertia and well-being were included in the analysis. Figure 4 shows the average normalized melatonin curves for the three conditions. The average DLMO did not differ significantly between the three conditions (average DLMO ± SD: 0 lux = 21:23 h ± 58 min; 50 lux = 21:25 h ± 52 min; 250 lux = 21:23 h ± 57 min; $F = 0.039$, $p = .49$). Time-of-year (first period in November/December, second period in January/February) when the samples were collected had no significant effect on the DLMO (between-subject comparison: $F = 0.083$, $p = .77$) or on the effect of the artificial dawn on the DLMO ($F = 0.387$, $p = .68$).

DISCUSSION

By definition, sleep inertia is a severe subjective feeling of sleepiness and grogginess upon awakening (Tassi & Muzet, 2000); therefore, human subjects are the best models to investigate how these symptoms can be affected. In the present home study, we assessed the effects of the artificial dawn on sleep inertia in healthy subjects. Home studies may have disadvantages because of the absence of direct control over conditions and measurements. However, it constitutes a natural setup to assess the potential effects of this artificial dawn system in the way it will ultimately be used. Being a light device available on the market, studying

its effects is of great relevance. In addition, the results of the present two studies provide insight on the awakening process.

For this purpose, subjects who suffered from sleep inertia were selected. The average MSF of the participating subjects was ~29 min later than the average found for an age-matched group of the Dutch population (Zavada et al., 2005). This can easily be understood by the fact that the later the chronotype, the more difficult it becomes to wake up early during workdays (Roenneberg et al., 2003). By waking up after being sleep deprived due to previous working days and after a relatively short sleep, late chronotypes are particularly prone to severe symptoms of sleep inertia during the early hours of the day. Therefore, although we did not choose for late chronotypes, due to our selection criteria, i.e., ≥60 min needed to feel fully awake, later chronotypes are overrepresented in our sample.

In the present study, as expected, sleep inertia was shown to decrease with time (Achermann et al., 1995; Jewett et al., 1999; Wertz et al., 2006). Moreover, also in accordance with previous studies in people suffering from winter depression (Avery et al., 2002) and subsyndromal winter depression (Norden & Avery, 1993), exposure to a 30-min artificial dawn signal before the alarm sounded led to lower subjective ratings of sleep inertia and to improvement of general well-being. Interestingly, self-selected intensities in combination with lights-on at the time the alarm went off (Study 2) led to an even larger decrease of sleep-inertia complaints. Light intensity, however, cannot explain the strengthening of the results. In Study 2, the chosen intensity (264.7 lux on average) was rather similar to the high light intensity used in Study 1 (250 lux). Persistence of light after the alarm went off, on the other hand, could explain this finding. Light is known to have direct activating and alerting effects both at night and during the daytime (Cajochen, 2007; Cajochen et al., 2000; Campbell et al., 1995; Phipps-Nelson et al., 2003; Rüger et al., 2006). Waking up in a dark in contrast to an illuminated room might increase subjective ratings of sleep inertia.

All retrospective and longitudinal measurements of sleep inertia showed an improvement in the artificial dawn condition. The congruency between these analyses is generally interpreted as supporting evidence of the findings. A dose-response relationship for the different light intensities, however, was only visible for the sleep-inertia duration measurements. Although measured on a daily basis, this suggests that the KSS might have not been sensitive enough to detect dose-dependent changes in sleep-inertia severity. The KSS is limited to a restricted range of values (Åkerstedt & Gillberg, 1990). In measuring sleep-inertia duration, on the other hand, there is more freedom to select for the number of minutes needed to feel fully awake, which could allow for more sensitive measurements. Similarly, no significant differences were detected between the

50- and 250-lux conditions in the assessment of well-being. These results, together with the larger effect found in the second study in which subjects were asked to find their preferred intensities, seem to indicate that the mere presence of light does lead to beneficial results. Preferred intensities were ~250 lux, and although this intensity might not be necessarily needed to reduce the symptoms, the duration of sleep inertia after waking up was shortened with higher intensities.

Most studies conducted with dawn simulators were developed as an alternative to bright-light treatment for seasonal affective disorders (SADs). Interestingly, it has been shown that a simulated dawn was more effective than a square-wave, bright-light stimulus (light-on/lights-off) in treating SAD patients (Avery et al., 2001; Terman & Terman, 2006). This suggests that light exposure before consciously waking up exerts some effect that cannot be achieved even with exposure to bright light after awakening. The mechanism by which artificial dawn signals might work could be related to the gradual increase of light intensity, allowing for a gradual wake up in contrast to lights-on/lights-off. It has been shown that an abrupt wake up can negatively influence sleep inertia (Dinges, 1990; Dinges et al., 1985). Although we did not test the effects of lights-on/lights-off, most participating subjects experienced the artificial dawn during the winter mornings in a positive way. When subjects were asked for an internal evaluation to compare the use of the artificial dawn alarm clock with their normal alarm clock, by means of a 1 to 5 scale (1 = worse and 5 = better), 27% chose 5, 45% chose 4, 19% chose 3 (no difference), 6% chose 2, and 3% chose 1. Because the major part of the exposure to the natural dawn signal occurs while sleeping, with eyelids closed (Beersma et al., 1999), an alternative (or complementary) mechanism by which dawn signals could exert an effect is due to the transmittance characteristics of the eyelids; only light of longer wavelengths is transmitted (Ando & Kripke, 1996; Moseley et al., 1988). During the past decade a new photoreceptor key in nonvisual responses called the intrinsically photosensitive retinal ganglion cells (ipRGCs) was discovered (Berson et al., 2002; Hattar et al., 2002). Interestingly melanopsin, the photopigment found in the ipRGCs, shows two states: the 11-*cis*-retinal state (rhodopsin, R state) and the all-*trans*-retinal state (metarhodopsin, M state). Under broadband natural or artificial light exposure, these two states exist in equilibrium. However, under monochromatic light exposure, it was shown that whereas especially short wavelengths initiated the phototransduction cascade (from R to M), long wavelengths could restore responsiveness by regeneration of the M to the R states (Melyan et al., 2005; Mure et al., 2009). The light intensities used in Mure et al.'s study to drive the M state back to the R state were quite high. Exposure to long wavelengths during dawn after a full night of darkness, however, could shift the equilibrium of the M and R states to a higher sensitivity

for short wavelengths after waking up or even before, during the regular arousals that occur during sleep (Gordijn et al., 1999). More studies on how different mono- and polychromatic light sources can modulate melanopsin-dependent nonvisual responses are needed.

A limitation of our study is the lack of performance measurements during the sleep-inertia period. In a laboratory study by our group using the same device during 1 day, similar improvements of sleepiness, but no clear effects on a simple reaction time or addition task, were found (Van de Werken et al., 2010). In future field studies, it would be interesting to test whether other measures of sleep inertia, for instance more complex reaction-time performance, grip strength, or cognitive functioning, are improved with the long-term use of the artificial dawn. We cannot exclude a placebo effect of the use of the artificial dawn to explain the improvements in subjective ratings (Eastman, 1990). In studies using light, subjects are always aware of the treatment. However, neither the existence of dose-response effects nor extra measurements can ever rule out the possibility of a placebo effect underlying the observed differences.

We hypothesized that the possible improvements in subjective ratings of sleep inertia could have been due to a shift towards a more optimal phase of the circadian system. Although exposure to the artificial dawn occurred during the advance portion of the phase response curve (PRC), ~9:22 h after the DLMO (Khalsa et al., 2003), no significant differences were found in the DLMO between conditions. One could argue that this lack of detection is due to the resolution of our saliva sampling frequency (one sample/h). However, because we were not able to detect even a trend, this is unlikely to be the case. An alternative possibility is that exposure to evening light prohibited a phase advance. Although season was not a factor, there was no difference in effects on the DLMO between the darker first period and the maybe somewhat more evening light-containing second period, exposure to artificial light in the evening could, indeed, have prevented a phase advance to occur. Nevertheless, the main question whether a phase shift accompanies an improvement of sleep inertia can still be answered with "no," irrespective of the reason that no phase advance was observed. Earlier studies found a shift in the DLMO after exposure to an artificial dawn signal (Danilenko et al., 2000; Terman et al., 1989). The discrepancy with these studies can be easily explained by the differences in the experimental setup, in the light intensities used, and/or in the duration of the artificial dawn signal. In our study, light was not only in the low range of intensities (Zeitzer et al., 2005), but it was also shifted to the long wavelength range of the visible spectrum. It has been extensively shown that the circadian system is more sensitive to short wavelengths (Brainard et al., 2001; Cajochen et al., 2005; Lockley et al., 2003; Revell et al., 2005, 2006; Thapan et al., 2001). Higher intensities of long wavelengths of light could have shifted the

DLMO (Hanifin et al. 2006; Zeitzer et al. 1997), but they may also lead to undesired earlier wakefulness. The present study shows that an improvement in sleep inertia is possible without a shift of the onset of the melatonin rhythm. This leads to the conclusion that shifts in the underlying rhythms are not a prerequisite to obtain an improvement in waking up by an artificial dawn signal. A possible shift in the offset of the melatonin rhythm or suppression in the early morning was not measured. It could be hypothesized that morning light induces a larger phase advance in the offset than in the onset of the melatonin rhythm (Illnerová & Sumová, 1997; Warman et al., 2003; Wehr et al., 2001). This effect, however, is thought to be transient and only present during the first days after morning light. In the present study, the artificial dawn effects on DLMO were assessed after 2 wks. A shift in morning decline is not expected in the absence of a shift in the onset. Furthermore, a possible suppression of melatonin by the artificial dawn signal was not expected. The dawn signal occurred during the last 30 min of sleep before waking up, more than 9 h after the DLMO, when the synthesis of melatonin is most likely already turned off (Lewy et al., 1999). The possible effects of the unmodified wake-up light (Study 2) on melatonin profile and suppression were not tested. Interestingly, it was found that the timing of sleep offset was earlier. The earlier sleep offset occurred after the alarm went off. Exposure to light prior to the alarm, therefore, was not longer in Study 2 compared to Study 1. By means of a multilevel analysis, the effects of DLMO and sleep offset on sleep-inertia duration were tested as an alternative or additional effect to the effects of the artificial dawn treatment. Although the DLMO asserts no significant effect on the reduction of sleep inertia, sleep offset related negatively. This indicates that the later the sleep offset, the lower the suffering from sleep inertia. This is understandable in view of our relatively late chronotypes, who will suffer less from sleep inertia the later they wake up. The use of the artificial dawn, however, did not affect the timing of sleep offset. In Study 2, although sleep offset was earlier, the multilevel analysis revealed no effect of it on the duration of sleep inertia.

Taken all together, only the artificial dawn treatment is responsible for the reduction of sleep-inertia complaints. The activating effects of light have been shown to be present both during the night and daytime, indicating that melatonin suppression may not necessarily be a prerequisit to assert the effect (Cajochen et al., 2000; Campbell et al., 1995; Phipps-Nelson et al., 2003; Rüger et al., 2003, 2006). We hypothesize that this is the most likely mechanism by which complaints are reduced. In a recent review, Vandewalle and co-authors (2009) concluded that several brain structures, especially the thalamus, might play a key role in the light-induced changes in alertness and cognitive functioning. It would be interesting to measure the effects of an artificial dawn on brain

activity shortly after waking up. A wide range of physiological changes accompanies the waking-up process in the morning, such as heat dissipation (Kräuchi et al., 2004), awakening cortisol response (Edwards et al., 2001), and changes in EEG spectrum (Tassi et al., 2006). The immediate effects of artificial dawn on these aspects were tested in the study of Van de Werken and co-authors (2010) under laboratory-controlled conditions. A faster decline in distal skin temperature after waking up and an increase in the number of arousals during the last 30 min of sleep have been shown to be related to a reduction in sleep inertia. These mechanisms, rather than a shift of circadian rhythms, may explain the positive effects of a dawn signal on sleep inertia.

CONCLUSION

Both studies clearly show that artificial dawn during the last 30 min of sleep exerts beneficial effects on subjective ratings of sleep inertia. However, as tested in the present study, no significant shifts in DLMO were observed. The artificial dawn signal, although not capable of having circadian effects, is hypothesized to assert an effect on physiological processes at waking up by activating/alerting the system.

ACKNOWLEDGMENTS

Our work was supported by Philips Consumer Lifestyle, Drachten, The Netherlands, and by the 6th European Framework EUCLOCK (018741).

Declaration of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

Achermann P, Werth E, Dijk DJ, Borbely AA. (1995). Time course of sleep inertia after nighttime and daytime sleep episodes. *Arch. Ital. Biol.* 134:109–119.

Åkerstedt T, Folkard S. (1997). The three-process model of alertness and its extension to performance, sleep latency, and sleep length. *Chronobiol. Int.* 14:115–123.

Åkerstedt T, Gillberg M. (1990). Subjective and objective sleepiness in the active individual. *Int. J. Neurosci.* 52:29–37.

Ando K, Kripke DF. (1996). Light attenuation by the human eyelid. *Biol. Psychiatry* 39:22–25.

Avery DH, Eder DN, Bolte MA, Hellekson CJ, Dunner DL, Vitiello MV, Prinz PN. (2001). Dawn simulation and bright light in the treatment of SAD: a controlled study. *Biol. Psychiatry* 50:205–216.

Avery DH, Kouri ME, Monaghan K, Bolte MA, Hellekson C, Eder D. (2002). Is dawn simulation effective in ameliorating the difficulty awakening in seasonal affective disorder associated with hypersomnia? *J. Affect. Disord.* 69:231–236.

Baehr EK, Revelle W, Eastman CI. (2000). Individual differences in the phase and amplitude of the human circadian temperature rhythm: with an emphasis on morningness-eveningness. *J. Sleep Res.* 9:117–127.

Balkin TJ, Badia P. (1988). Relationship between sleep inertia and sleepiness: cumulative effects of four nights of sleep disruption/restriction on performance following abrupt nocturnal awakenings. *Biol. Psychol.* 27:245–258.

Beck AT, Steer RA, Brown GK. (1996). *Manual for the Beck Depression Inventory–II.* San Antonio, TX: The Psychological Corporation. Nederlandse vertaling en bewerking: van der Does, A. J. W. Lisse: Swets Test Publishers.

Beersma DG, Daan S. (1993). Strong or weak phase resetting by light pulses in humans? *J. Biol. Rhythms* 8:340–347.

Beersma DGM, Spoelstra K, Daan S. (1999). Accuracy of human circadian entrainment under natural light conditions: model simulations. *J. Biol. Rhythms* 14:525–532.

Berson DM, Dunn FA, Takao M. (2002). Phototransduction by retinal ganglion cells that set the circadian clock. *Science* 295:1070–1073.

Borbély AA. (1982). A two process model of sleep regulation. *Hum. Neurobiol.* 1:195–204.

Brainard GC, Hanifin JP, Greeson JM, Byrne B, Glickman G, Gerner E, Rollag MD. (2001). Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J. Neurosci.* 21:6405–6412.

Cajochen C. (2007). Alerting effects of light. *Sleep Med. Rev.* 11:453–464.

Cajochen C, Zeitzer JM, Czeisler CA, Dijk DJ. (2000). Dose-response relationship for light intensity and ocular and electroencephalographic correlates of human alertness. *Behav. Brain Res.* 115:75–83.

Cajochen C, Münch M, Kobialka S, Kräuchi K, Steiner R, Oelhafen P, Orgül S, Wirz-Justice A. (2005). High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. *J. Clin. Endocrinol. Metab.* 90:1311–1316.

Campbell SS, Dijk DJ, Boulos Z, Eastman CI, Lewy AJ, Terman M. (1995). Light treatment for sleep disorders: consensus report. III. Alerting and activating effects. *J. Biol. Rhythms* 10:129–132.

Daan S, Beersma DG, Borbély AA. (1984). Timing of human sleep: recovery process gated by a circadian pacemaker. *Am. J. Physiol.* 246:R161–R183.

Danilenko KV, Wirz-Justice A, Kräuchi K, Cajochen C, Weber JM, Fairhurst S, Terman M, (2000). Phase advance after one or three simulated dawns in humans. *Chronobiol. Int.* 17:659–668.

Dinges D. (1990). Are you awake? Cognitive performance and reverie during the hypnopompic state. In Bootzin R, Kihlstrom J, Schacter D (eds.). *Sleep and cognition.* Washington, DC: American Psychological Association, pp. 159–175.

Dinges D, Orne M, Orne E. (1985). Assessing performance upon abrupt awakening from naps during quasi-continuous operations. *Behav. Res. Meth. Instrum. Comput.* 17:37–45.

Duffy JF, Dijk DJ, Hall EF, Czeisler CA. (1999). Relationship of endogenous circadian melatonin and temperature rhythms to self-reported preference for morning or evening activity in young and older people. *J. Invest. Med.* 47:141–150.

Eastman CI. (1990). What the placebo literature can tell us about light therapy for SAD. *Psychopharmacol. Bull.* 26:495–504.

Edwards S, Evans P, Hucklebridge F, Clow A. (2001). Association between time of awakening and diurnal cortisol secretory activity. *Psychoneuroendocrinology* 26:613–622.

Gordijn MC, Beersma DG, Korte HJ, van den Hoofdakker RH. (1999). Effects of light exposure and sleep displacement on dim light melatonin onset. *J. Sleep Res.* 8:163–174.

Gordijn M, Tamanini F, Janssen R, Zavada A, Govaerts LC, Beersma, DGM, Daan S, Van der Horst BT. (2006). Circadian periodicity of melatonin rhythm and cellular per2 oscillations in early and late human chronotypes. *J. Sleep Res.* 15:53.

Hanifin JP, Stewart KT, Smith P, Tanner R, Rollag M, Brainard GC. (2006). High-intensity red light suppresses melatonin. *Chronobiol. Int.* 23:251–268.

Hattar S, Liao HW, Takao M, Berson DM, Yau KW. (2002). Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science* 295:1065–1070.

Homma K, Homma S. (1988). A human phase response curve for bright light pulses. *Jpn. J. Psychiatry Neurol.* 42:167–168.

Horne JA, Östberg O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int. J. Chronobiol.* 4:97–110.

Illnerová H, Sumová A. (1997). Photic entrainment of the mammalian rhythm in melatonin production. *J. Biol. Rhythms* 12:547–555.

Jewett ME, Wyatt JK, Ritz-De Cecco A, Khalsa SB, Dijk DJ, Czeisler CA. (1999). Time course of sleep inertia dissipation in human performance and alertness. *J. Sleep Res.* 8:1–8.

Johnson MP, Duffy JF, Dijk DJ, Ronda JM, Dyal CM, Czeisler CA. (1992). Short-term memory, alertness and performance: a reappraisal of their relationship to body temperature. *J. Sleep Res.* 1:24–29.

Kaida K, Takahashi M, Akerstedt T, Nakata A, Otsuka Y, Haratani T, Fukasawa K. (2006). Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clin. Neurophysiol.* 117:1574–1581.

Kerkhof GA. (1998). The 24-hour variation of mood differs between morning- and evening-type individuals. *Percept. Mot. Skills* 86:264–266.

Kerkhof GA, Van Dongen HP. (1996). Morning-type and evening-type individuals differ in the phase position of their endogenous circadian oscillator. *Neurosci. Lett.* 218:153–156.

Khalsa SBS, Jewett ME, Cajochen C, Czeisler CA. (2003). A phase response curve to single bright light pulses in human subjects. *J. Physiol.* 549:945–952.

Kräuchi K, Cajochen C, Wirz-Justice A. (2004). Waking up properly: is there a role of thermoregulation in sleep inertia? *J. Sleep Res.* 13:121–127.

Leppämäki S, Meesters Y, Haukka J, Lönnqvist J, Partonen T. (2003). Effect of simulated dawn on quality of sleep—a community-based trial. *BMC Psychiatry* 3:14.

Lewy AJ, Cutler NL, Sack RL. (1999). The endogenous melatonin profile as a marker for circadian phase position. *J. Biol. Rhythms* 14:227–236.

Lockley SW, Brainard GC, Czeisler CA. (2003). High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. *J. Clin. Endocrinol. Metab.* 88:4502–4505.

Melyan Z, Tarttelin EE, Bellingham J, Lucas RJ, Hankins MW. (2005). Addition of human melanopsin renders mammalian cells photoresponsive. *Nature* 433:741–745.

Minors DS, Waterhouse JM, Wirz-Justice A. (1991). A human phase-response curve to light. *Neurosci. Lett.* 133:36–40.

Monk TH, Fookson JE, Moline ML, Pollak CP. (1985). Diurnal variation in mood and performance in a time-isolated environment. *Chronobiol. Int.* 2:185–193.

Moseley MJ, Bayliss SC, Fielder AR. (1988). Light transmission through the human eyelid: in vivo measurement. *Ophtalmic. Physiol. Opt.* 8:229–230.

Mure LS, Cornut P-L, Rieux C, Drouyer E, Denis P, Gronfier C, Cooper HM. (2009). Melanopsin bistability: a fly's eye technology in the human retina. *PLoS ONE* 4:pe5991.

Norden MJ, Avery DH. (1993). A controlled study of dawn simulation in subsyndromal winter depression. *Acta Psychiatr. Scand.* 88:67–71.

Phipps-Nelson J, Redman JR, Dijk D-J, Rajaratnam SMW. (2003). Daytime exposure to bright light, as compared to dim light, decreases sleepiness and improves psychomotor vigilance performance. *Sleep* 26:695–700.

Portaluppi F, Touitou Y, Smolensky MH. (2008). Ethical and methodological standards for laboratory and medical biological rhythm research. *Chronobiol. Int.* 25:999–1016.

Revell VL, Arendt J, Terman M, Skene DJ. (2005). Short-wavelength sensitivity of the human circadian system to phase-advancing light. *J. Biol. Rhythms* 20:270–272.

Revell VL, Arendt J, Fogg LF, Skene DJ. (2006). Alerting effects of light are sensitive to very short wavelengths. *Neurosci. Lett.* 399:96–100.

Roenneberg T, Wirz-Justice A, Merrow M. (2003). Life between clocks: daily temporal patterns of human chronotypes. *J. Biol. Rhythms* 18:80–90.

Rüger M, Gordijn MCM, Beersma DGM, de Vries B, Daan S. (2003). Acute and phase-shifting effects of ocular and extraocular light in human circadian physiology. *J. Biol. Rhythms* 18:409–419.

Rüger M, Gordijn MCM, Beersma DGM, de Vries B, Daan S. (2005). Nasal versus temporal illumination of the human retina: effects on core body temperature, melatonin, and circadian phase. *J. Biol. Rhythms* 20:60–70.

Rüger M, Gordijn MCM, Beersma DGM, de Vries B, Daan S. (2006). Time-of-day-dependent effects of bright light exposure on human psychophysiology: comparison of daytime and nighttime exposure. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 290:R1413–R1420.

Tassi P, Muzet A. (2000). Sleep inertia. *Sleep Med. Rev.* 4:341–353.

Terman M, Terman JS. (2006). Controlled trial of naturalistic dawn simulation and negative air ionization for seasonal affective disorder. *Am. J. Psychiatry* 163:2126–2133.

Tassi P, Bonnefond A, Engasser O, Hoeft A, Eschenlauer R, Muzet A. (2006). EEG spectral power and cognitive performance during sleep inertia: the effect of normal sleep duration and partial sleep deprivation. *Physiol. Behav.* 87:177–184.

Terman M, Schlager D, Fairhurst S, Perlman B. (1989). Dawn and dusk simulation as a therapeutic intervention. *Biol. Psychiatry* 25:966–970.

Thapan K, Arendt J, Skene DJ. (2001). An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans. *J. Physiol.* 535:261–267.

Tonetti L, Fabbri M, Natale V. (2008). Sex difference in sleep-time preference and sleep need: a cross-sectional survey among Italian pre-adolescents, adolescents, and adults. *Chronobiol. Int.* 25:745–759.

Vandewalle G, Maquet P, aDijk DJ. (2009). Light as a modulator of cognitive brain function. *Trends Cogn. Sci.* 13:429–438.

Van de Werken M, Giménez MC, de Vries B, Beersma DGM, Van Someren EJW, Gordijn MC. Effects of artificial dawn on sleep inertia, skin temperature, and awakening cortisol response. *J. Sleep Res.* 2010. Retrieved April 2010 online.

Warman VL, Dijk DJ, Warman GR, Arendt J, Skene DJ. (2003). Phase advancing human circadian rhythms with short wavelength light. *Neurosci. Lett.* 342:37–40.

Wehr TA, Aeschbach D, Duncan WC. (2001). Evidence for a biological dawn and dusk in the human circadian timing system. *J. Physiol.* 535:937–951.

Wertz AT, Ronda JM, Czeisler CA, Wright KP. (2006). Effects of sleep inertia on cognition. *JAMA* 295:163–164.

Wittmann M, Dinich J, Merrow M, Roenneberg T. (2006). Social jetlag: misalignment of biological and social time. *Chronobiol. Int.* 23:497–509.

Zavada A, Gordijn MCM, Beersma DGM, Daan S. Roenneberg T. (2005). Comparison of the Munich Chronotype Questionnaire with the Horne-Ostberg's Morningness-Eveningness Score. *Chronobiol. Int.* 22:267–278.

Zeitzer JM, Kronauer RE Czeisler CA. (1997). Photopic transduction implicated in human circadian entrainment. *Neurosci. Lett.* 232:135–138.

Zeitzer JM, Khalsa SBS, Boivin DB, Duffy JF, Shanahan TL, Kronauer RE, Czeisler CA. (2005). Temporal dynamics of late-night photic stimulation of the human circadian timing system. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 289:R839–R844.