Tailored lighting intervention to promote entrainment in myeloma transplant patients—A field study

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ABSTRACT

Light is the major synchronizer of circadian rhythms to the local position on Earth. Exposure to light at night and insufficient exposure to light early in the day has been linked with poor sleep and a host of health and behavioral problems. Myeloma patients spend two to three weeks inside their hospital rooms during transplantation, which can lead to circadian disruption due to low light levels typically found indoors. We performed a pilot study to determine whether circadian-effective light could promote entrainment in myeloma patients. We hypothesized that an increase in circadian entrainment would lead to reduced cancer-related fatigue, depression, and sleep problems. Fifty-five participants were randomly assigned to two lighting interventions that used freestanding luminaires to deliver either circadian-effective light (n=27) or circadian-ineffective light (n=28) throughout the hospital room between 7am and 10am during every day of hospitalization. Results showed an increase in nocturnal melatonin levels and an improvement in sleep in those receiving the circadian-effective (active) intervention. The present results suggest that light can be used to help myeloma transplant patients maintain circadian entrainment while hospitalized. Design guidelines and implementation tips to increase circadian stimulus in hospital rooms are also discussed.

Introduction to circadian rhythms

The 24-hour pattern of light and dark that accompanies Earth’s axial rotation regulates the physiology and behavior of almost every living thing on the planet. For humans, light reaching the retinas is the primary exogenous (external) cue that synchronizes or entrains the body’s endogenous (internal) master biological clock and thus our circadian rhythms to the solar day, essentially telling our bodies to do the right thing at the right time. Other secondary exogenous cues include social activity (Salgado-Delgado, Tapia Osorio, Saderi, & Escobar, 2011), meal times (Wehrens et al., 2017), and physical activity (Moreno et al., 2019), among others. Sleeping and waking, feeding and fasting, the regulation of core body temperature, blood pressure, and the secretion of hormones are just a few examples of circadian rhythms. The term “circadian,” coined by biologist Franz Halberg (1959), is a blended word derived from the Latin circa (“about”) and dies (“day”).

Because the human circadian system free-runs at an average period of about 24.2 hours—slightly longer than the solar day—a daily cue of light and dark is required to advance the circadian system by about 10–15 minutes, thereby continually resetting the master biological clock to maintain circadian entrainment (Czeisler et al., 1981).

But what light gives, light can also take away. Exposure to light at the wrong time, or not receiving enough light at the right time, has become increasingly common since the advent of electric lighting over a century ago. Exposure to light at night, and even a complete reversal of the day–night pattern in the case of night-shift workers, are now facts of life in our 24-hour society. But exposure to light at night and insufficient exposure to light early in the day has been linked with poor sleep and a host of health and behavioral problems. Long-term disruption of the daily cycle of light and dark can lead to chronic disruption of the circadian system, which has been associated with metabolic dysregulation (leading to weight gain, obesity, and type 2 diabetes) (Depner, Stothard, & Wright, 2014), certain forms of cancer (Samuelsson, Bovbjerg, Roocklein, & Hall, 2018), depression (Germain & Kupfer, 2008), and other maladies (Abbott, Malikani, & Zee, 2018).

Lighting characteristics affecting the circadian clock

Four characteristics of light and light exposures play crucial roles in the circadian system’s response.

1. The amount or level of light received at the eyes: “Is it bright or dim?”

Early circadian research in animal (Sharma & Daan, 2002; Takahashi, DeCoursey, Bauman, & Menaker, 1984) and human (Boxnin, Duffy, Kronauer, & Czeisler, 1994, 1996) models found that varying light levels at the eyes differentially affect the nighttime suppression of the hormone melatonin (the release of which prepares the body for sleep) and zeitgeber time, either advancing or delaying the timing of the
2. The spectral properties of the light experienced:

Zeitgeber time (a zeitgeber is an environmental cue that suppresses and the greater the advance/delay in circadian system’s 24-hour cycle. The greater “When, and for how long, was I exposed to light?”

When appropriately specified according to these four characteristics, light exposures can be tailored to remedy symptoms of seasonal affective disorder (Goldstein et al., 2005), increase sleep efficiency in older adults (including those with Alzheimer’s disease) (Fēvēt, Skīrve, & Bjoırvān, 2003; Figueiro et al., 2014; Van Someren, Ressler, Mirmiran, & Swaab, 1997); promote circadian rhythmicity in premature infants (Rihee, 2003); increase alertness at all times of day and night (Badia, Myers, Boecker, Cullpepper, & Harsh, 1991; Cajochen et al., 2005; Cajochen, Zeitzer, Czeisler, & Dijk, 2000); and improve alertness and selected measures of performance (Sahin & Figueiro, 2013; Sahin, Wood, Plitnick, & Figueiro, 2014).

Light and myeloma transplant patients

Multiple myeloma (MM) patients undergoing autologous stem cell transplantation (ASCT) experience clinically significant negative sequelae that affect prognosis and survival as well as quality of life. These sequelae include increases in production of inflammatory cytokines, higher rates of neutropenic fever, and higher symptom burden (e.g., depression, pain). These symptoms are associated with circadian rhythm disruption (CRD), a disruption in naturally occurring 24-hour cycles of hormone secretion, temperature, and rest-activity. CRD increases production of pro-inflammatory cytokines, causing a cascade of negative side effects, including higher symptom burden and increased risk of neutropenic fever. CRD has been associated with decreased prognosis and survival.

To address these concerns, we performed a pilot research study to determine whether circadian-effective light could promote entrainment (as measured by an increase in nighttime melatonin levels) in MM patients. For the purpose of this contribution, we limited our focus on the range of negative sequelae experienced by patients undergoing ASCT, and we hypothesized that an increase in circadian entrainment would lead to reductions in cancer-related fatigue, depression, and sleep problems among MM patients, both during and after ASCT hospitalization.

Methods and materials

Tailored lighting intervention

Fifty-five participants were randomly assigned to two lighting interventions delivering either circadian-effective light (n=27) or circadian-ineffective light (n=28) throughout the participants’ rooms from 7–10am daily during hospitalization. The circadian-effective light stimulus was specified following the Rea et al. model (Rea, Figueiro, Bullough, & Bierman, 2005). Following the model, the measured spectral irradiance at the cornea is first converted into circadian light (CL), which reflects the spectral sensitivity of the circadian system. CL is then transformed into a circadian stimulus (CS) value, which reflects the absolute sensitivity of the circadian system. Thus, CS is a measure of the effectiveness of the retinal light for stimulating the human circadian system, as measured by acute melatonin suppression, from threshold (CS = 0.1, or 10% melatonin suppression) to saturation (CS = 0.7, or 70% melatonin suppression). It is important to note that, strictly speaking, CL and CS characterize the spectral and absolute sensitivities of light-induced nocturnal melatonin suppression as regulated by the master biological clock. It is assumed, however, that CL and CS characterize the spectral and absolute sensitivities of the entire human circadian system because the biological clock plays a key role in regulating a wide variety of daily bodily functions, such as hormone production and sleep. For the purpose of the present study, it was assumed that the spectral and absolute sensitivities of nocturnal melatonin suppression are similar to those controlling light-induced changes of circadian timing and circadian entrainment.

Acuity Brands developed an experimental freestanding luminaire that used 3000 K, ambient “warm white” light to deliver either a CS of 0.3 for the circadian-effective (“active”) bright white light (BWL) intervention (approximately 1000 lux at the participants’ eye level) or a CS of 0.1 for the comparison (“inactive”) dim white light (DWL) intervention (approximately 50 lux at the participant’s eye level). A warm light source was chosen for both interventions to make the space appear less institutional and more residential.

The experimental luminaire used to deliver the BWL (active) and DWL (inactive) interventions in participants’ rooms.
Because it was not confirmed by the present study, providing ambient circadian-effective light in hospital rooms has been shown to reduce symptoms resulting from disruption of the circadian system that are commonly experienced by hospitalized and survivor cancer patients, including cancer-related fatigue (Ancoli-Israel et al., 2012; Johnson et al., 2018; Redd et al., 2014) and depression (Dessautels, Savard, Ivers, Savard, & Caplette-Gingras, 2018; Sun et al., 2014). Previous studies have also shown that bright white light delivered by light box (Litebook) reduced cancer-related fatigue and improved sleep efficiency among cancer survivors following completion of their treatment and release from the hospital (Wu et al., 2018).

These results should be interpreted in the context of a few important study limitations. Perhaps most importantly, the study is preliminary and was conducted with a small sample size. In our preliminary data, we observed a marginally significant (p = 0.059) lighting intervention x assessment time interaction for melatonin. The effect size for this interaction is f^2 = 0.009, which is midway between a “small” and “moderate” effect size using the Cohen (1988) characterization. Moreover, since the results do not include post-hospitalization assessments, it is not yet known whether circadian-effective light delivered during hospitalization affects cancer treatment symptoms during the post-transplant period. Larger clinical trials measuring immune function biomarkers should be performed to extend these preliminary results.

While we are still learning about the benefits of lighting design for the circadian system, the present research and the work of others in the field clearly show that avoiding disturbance from light at night and creating a robust light-dark pattern can stimulate the circadian system, promote daytime alertness, and yield benefits for health and well-being. Despite the study’s limitations, our findings nonetheless demonstrate that this easy-to-deliver, low-cost intervention improves sleep and circadian entrainment among MM bone marrow transplant patients during hospitalization.

### Implementation tips
A patient’s stay in the hospital can range from a day to a few months. No matter the duration, lighting in a patient’s room can positively impact the patient’s psychological and physiological recovery. In addition to providing good visibility, low glare, and good color rendering, lighting for patient rooms should be designed to promote circadian entrainment by delivering high CS during the day and low CS in the evening to increase patients’ sleep times and improve their sleep quality.

### Circadian-effective lighting for designers and manufacturers
Circadian-effective lighting to promote circadian entrainment requires designers to create a CS schedule that, at a minimum, delivers a pattern of bright light during the day and dim light in the evening. Although not necessarily required, the CS schedule can mimic the spectral properties and illuminance levels that are provided by the daily solar cycle. As indicated in the UL Design Guidelines (Underwriters Laboratories Inc., 2019), the circadian-effective lighting design process includes six essential steps:

1. **Step 1:** Establish a circadian-effective lighting design criterion (e.g., CS > 0.3)
2. **Step 2:** Select a luminaire type (e.g., direct/indirect).
3. **Step 3:** Select a light source type (e.g., 3000 K LED).
Step 4: Perform photometrically realistic software (e.g., AGi32) calculations for the building space.

Step 5: Calculate CS from the vertical illuminance (measured at the eye) and the light source’s spectral power distribution (SPD).

Step 6: Determine whether the lighting system meets the circadian-effective lighting design criterion, repeat steps 2–6 if necessary.

The space’s occupants are the most important considerations in circadian-effective lighting design and the establishment of a design criterion CS for step 1. One important thing to consider is the occupants’ ages. Age-related changes to the eye can render CS prescriptions for elementary school students inappropriate for office workers or seniors in elderly care environments. It is also very important to take into account where, when, and how the occupants use the space. Because hospital beds can be angled to position patients upright (viewing the wall and windows) or fully reclined (viewing the ceiling), room lighting should accommodate both patient orientations. It is thus very important that lighting systems can provide appropriate CS levels without glare of direct views of luminaires in both positions. When specifying CS for patient rooms, it is recommended that illuminance be measured at the patients’ eyes while sitting up at a 45° tilt and while laying down looking straight up at the ceiling (Figure 5).

Establishing these parameters helps designers determine appropriate CS exposures and the timing of exposure. Finally, when you reach step 6, it is important to avoid viewing the design process as a hard-and-fast series of steps that inevitably lead to the desired outcome. Successful designs actually grow from a dynamic interchange between architects, lighting designers, and manufacturers, all of whom fit together as important pieces of the puzzle. And like all designs, several iterations may be required, with input from all of these actors, to achieve optimal CS performance. If your design does not meet the criterion CS, try altering one of the components from the diagram in Figure 6. Keep in mind that the design must meet all visual criteria established by organizations such as the Illuminating Engineering Society.

Putting it all together

The varied intricacy and difficulty of visual tasks performed in patient rooms also call for varying lighting specifications. Generally, the higher the light level, the faster the visual system can convert optical stimuli into usable information (Chan et al., 2012). For tasks involving objects that are very small or have low contrast with their environment, high horizontal illuminance (measured on the workplane) levels (> 1000 lux) are required. For tasks involving larger objects or those that have suitable contrast with the environment, where increased light levels provide diminishing returns, low-level ambient lighting (100–200 lux) is acceptable (Chan et al., 2012).

Glares caused by electric lighting, daylight, reflective surfaces, and other sources can be avoided by selecting the appropriate luminaries and making interior design changes within the space. Indirect light sources can be

• Vertical illuminance levels, or light at the occupants’ eyes.
• The light source’s intensity distribution, whether from a single luminaire or multiple luminaires, will determine how the light is distributed into the room and ultimately to the eye and work plane.
• Duration of exposure plays an important role in how the circadian system responds to a given light source. It should be noted that CS > 0.3 is based on a 1-hour exposure.

Once the fundamentals of occupant(s) and lighting characteristics are taken into account, the lighting design can be extended to incorporate information about the room to accomplish the aims of step 4. Lighting design software and manufacturers’ published photometric data files (IES, or * ies) are especially valuable tools for step 5, as they permit simulated predictions of luminaire performance. CS delivery, lighting power density (LPD), and energy usage values for the same amount of photopic (lux) light at the eye.

As shown in Figure 6, several major lighting characteristics that are encompassed by design steps 2 and 3 contribute to how well the system can deliver the criterion CS:

1. The light source’s spectral power distribution (SPD), which represents the radiant power emitted by a light source as a function of wavelength, is crucial for circadian lighting design.
2. Higher short-wavelength content generally delivers greater CS values for the same amount of photopic (lux) light at the eye.
3. Vertical illuminance levels, or light at the occupants’ eyes.
4. The light source’s intensity distribution, whether from a single luminaire or multiple luminaires, will determine how the light is distributed into the room and ultimately to the eye and work plane.
5. Duration of exposure plays an important role in how the circadian system responds to a given light source. It should be noted that CS > 0.3 is based on a 1-hour exposure.

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used to avoid glare while still meeting visual and circadian requirements, and other sources of glare can be reduced or eliminated by selecting nonreflective finishes for surfaces, altering window locations, and using window blinds. Finally, color rendering is another important consideration for luminaire selection, as accurate color perception is crucial for caregivers’ patient diagnoses.

Patient room lighting that provides a robust 24-hour light-dark pattern can have profound positive effects on patient recovery. Lighting for patient rooms should be designed to promote circadian entrainment, providing high CS during the day and low CS in the evening, in order to increase patients’ sleep times and improve their sleep quality. Nighttime lighting should be conducive to patient sleep while also accommodating visiting families and permitting caregivers to perform their tasks. Circadian lighting schemes have been shown to be effective for improving sleep in hospital ICU patients (Engwall et al., 2015).

Due to the nature of the population, their temporary removal from the familiar surroundings of home, and the dynamic nature of the hospital environment, circadian rhythm disruption is not uncommon among hospital patients. The patient’s health conditions (e.g., psychiatric and neurodegenerative diseases) can also lead to circadian rhythm disruption, as can critical illness generally (Oldham, 2016). Environmental influences such as ambient lighting in patient rooms can also disrupt the circadian system. A study conducted in three intensive care units found that patients typically sleep for only about 6 hours over a given 24-hour period, with only half of that sleep time occurring at night (Gabor et al., 2003). Improving and increasing nighttime sleep by promoting entrainment of a patient’s circadian rhythm to a robust light-dark cycle can lead to improved health outcomes (Engwall et al., 2015).

The recommended lighting pattern (Table 1 and Figure 7) for patients over the course of the day begins with a CS of 0.3 in the morning for at least 3 hours, drops to a CS of 0.2 for the midafternoon, and then drops once again to a CS of 0.1 in the late afternoon through the evening until bedtime. After bedtime, room lighting should be turned off, and nightlights should be added to permit safe navigation. This schedule can be accomplished using lighting designs that employ either static or tunable CCT systems.

<table>
<thead>
<tr>
<th>Time of day</th>
<th>CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>7–10am</td>
<td>0.3</td>
</tr>
<tr>
<td>10–11am</td>
<td>0.3 → 0.2</td>
</tr>
<tr>
<td>11am–4pm</td>
<td>0.2</td>
</tr>
<tr>
<td>4–5pm</td>
<td>0.2 → 0.1</td>
</tr>
<tr>
<td>5pm-end of day</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Table 1: Recommended lighting pattern for hospital patient rooms to promote circadian entrainment.

Figure 7: Simulations of hospital room lighting delivering high CS in the morning (left), medium CS in the afternoon (middle), and low CS in the evening (right).

References
Figueiro, M. G. (2017). Disruption of circadian rhythms by light during day and night. Current Sleep Medicine Reports, 3(2), 76-84. doi:10.1007/s40675-017-0069-0


