Light Treatment: Where Have We Come From and Where Can We Go?

Helen J. Burgess, Ph.D.
Professor, Department of Psychiatry
Sleep and Circadian Research Laboratory
University of Michigan, Ann Arbor
Conflict of Interest Disclosure

1. I do not have any relationships with any entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients, OR

2. I have the following relationships with entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

<table>
<thead>
<tr>
<th>Type of Potential Conflict</th>
<th>Details of Potential Conflict</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td></td>
</tr>
<tr>
<td>Consultant</td>
<td>Natrol, LLC – exogenous melatonin manufacturer</td>
</tr>
<tr>
<td>Speakers’ Bureaus</td>
<td></td>
</tr>
<tr>
<td>Financial support</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

3. The material presented in this lecture has no relationship with any of these potential conflicts, OR

4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

1.
2.
3.
Outline

- Human circadian system
  - measuring the clock
  - phase shifting the clock

- Circadian misalignment
  - night work
  - social jet lag

- Light Treatment
  - chronic pain:
    - fibromyalgia
    - low back pain
  - post-traumatic stress
Outline

• **Human circadian system**
  • measuring the clock
  • phase shifting the clock

• Circadian misalignment
  • night work
  • social jet lag

• Light Treatment
  • chronic pain:
    • fibromyalgia
    • low back pain
  • post-traumatic stress
The Central Circadian System

Period ~24.2 h

Emens & Burgess, *Sleep Med Clin* 2015
>70% humans have an endogenous circadian period >24 h

→ Most of us have a natural tendency to drift later (phase delay)

→ Most of us need to shift earlier (phase advance) to stay in sync with the external 24 h day
The Central Circadian System

Emens & Burgess, *Sleep Med Clin* 2015
The Dim Light Melatonin Onset (DLMO)

- Gold standard circadian phase marker in humans
- Melatonin must be measured in dim light (~6h before sleep onset)
- Time when melatonin levels rise above a threshold
- Often occurs about 2-3 h before habitual lights off
- Key to diagnosis of circadian rhythm disorders vs. insomnia
- Key to optimal treatment of circadian rhythm disorders

![Graph showing melatonin levels over time](image-url)
Outline

• Human circadian system
  • measuring the clock
  • phase shifting the clock

• Circadian misalignment
  • night work
  • social jet lag

• Light Treatment
  • chronic pain:
    • fibromyalgia
    • low back pain
  • post-traumatic stress
Circadian Misalignment

Scheer et al. *PNAS* 2009

→ Evidence to support an intrinsic adverse effect of circadian misalignment on glucose metabolism, independent of sleep

Leproult et al. *Diabetes* 2014
Social Jet Lag

Social jet lag = Δ midsleep

Wittmann et al. *Chronobiol Int* 2006
Social Jet Lag & Health

Social Jetlag = ▲ sleep midpoint work days vs. days off

Social jet lag ≥ 2 hours:

- ↑ depression
- ↑ alcohol, nicotine, caffeine
- ↑ BMI if already overweight
- ↑ resting heart rate (5 bpm in healthy people)
- ↑ HbA1c
- ↑ C-reactive protein
- ↓ HDL
- ↑ triglycerides

Wittman et al. *Chronobiol Int* 2006
Levandovski et al. *Chronobiol Int* 2011
Roenneberg et al. *Curr Biol* 2012
Rutters et al. *J Biol Rhythms* 2014
Parsons et al. *Int J Obesity* 2015
Wong et al. *JCEM* 2015
Outline

• Human circadian system
  • measuring the clock
  • phase shifting the clock

• Circadian misalignment
  • night work
  • social jet lag

• Light Treatment
  • chronic pain:
    • fibromyalgia
    • low back pain
  • post-traumatic stress
The Central Circadian System

- Light
- Exogenous Melatonin
- Endocrine Systems (Endogenous melatonin, Cortisol, etc.)
- Behavioral Systems (Sleep, Wake, Mood, etc.)
- Inflammatory Systems
- Peripheral Circadian Clocks

Emens & Burgess, *Sleep Med Clin* 2015
5.2. Social factors’ as zeitgebers

The concept that ‘social factors’ are the most important zeitgeber in man has already been mentioned when Wever’s account of rhythms in the blind were considered; such a view has been enthusiastically championed by Aschoff and Wever (Aschoff, 1979; Wever, 1979a).


Rütger Wever
passed away August 13, 2010 (87 years).
Light Suppresses Melatonin Secretion in Humans

Abstract. Bright artificial light suppressed nocturnal secretion of melatonin in six normal human subjects. Room light of less intensity, which is sufficient to suppress melatonin secretion in other mammals, failed to do so in humans. In contrast to the results of previous experiments in which ordinary room light was used, these findings establish that the human response to light is qualitatively similar to that of other mammals.


Al Lewy, M.D., Ph.D.
Modern humans spend ~90% of their time indoors
Primary Circadian Photoreceptor (ipRGCs)
90% Americans report using technological device in hour before bedtime (National Sleep Foundation, 2011)
High sensitivity and interindividual variability in the response of the human circadian system to evening light

Andrew J. K. Phillips, Parisa Vidafar, Angus C. Burns, Elise M. McGlashan, Clare Anderson, Shantha M. W. Rajaratnam, Steven W. Lockley, and Sean W. Cain

Fig. 2. Comparison of two individuals with high and low light sensitivity. (Left) Highlights two individual dose–response curves: an individual with high sensitivity (blue) and an individual with low sensitivity (red) and includes individual-level curves for all other participants (gray). Individual data points are shown (crosses). Right show the two individuals’ respective melatonin concentrations across time under the <1-lux (dim control; Top), 10-lux (Middle), and 100-lux (Bottom) conditions, where their differences in responsiveness manifest. The x-axis values are hours relative to habitual bedtime (0).

n=55 healthy subject
18-30 years
10-2,000 lux for 5 hours
Mean ED$_{50}$ = 26 lux
Range 6-350 lux
Light Phase Response Curve

Many subjects receive light at different times relative to DLMO

Symbol for DLMO

Delay (move later)

Advance (move earlier)

NIGHT

MORNING

Reduced sensitivity

~ 3500 lux for 2 h
Primary Circadian Photoreceptor (ipRGCs)

~480 nm

cones + rods

LeGates et al.
Nature Rev Neurosci 2014
Bright light exposure during acute tryptophan depletion prevents a lowering of mood in mildly seasonal women.

Abstract
We investigated the influence of bright light exposure on the mood-lowering effect of acute tryptophan depletion (ATD). Mildly seasonal healthy young women without a personal or family history of psychiatric disorders remained in either dim or bright light during two test days. Tryptophan-deficient and nutritionally balanced amino acid mixtures were administered in counterbalanced order. Mood state was assessed using the Profile of Mood States (POMS) and Visual Analogue Scales (VAS). In dim light, ATD decreased POMS scores across most subscales, indicating a worsening of mood. In bright light, mood was unaffected by ATD. Thus, bright light blocked the worsening of mood caused by ATD. This was also observed on the positive mood VAS. These results indicate a direct, immediate interaction between bright light and serotonin function. Bright light might help protect against ATD-induced mood change by increasing serotonin above the threshold level below which there is a lowering of mood.

Bright light may increase serotonin levels in the brain
Pain - Fibromyalgia

- antidepressants, antiepileptics: small Tx effects, side effects
- CBT – somewhat effective
- exercise – requires high patient motivation
- light treatment – minimal side effects, available, affordable

Morning Light Treatment

Circadian

Sleep

Mood

Pain

Fibromyalgia syndrome and chronotype: late chronotypes are more affected.

Kantermann T, Theadom A, Roenneberg T, Cropley M.

Burgess, Park, Ong, Shakoor, Williams & Burns, *Pain Medicine*, 2017
Pain - Fibromyalgia

- n=10 women previously diagnosed with fibromyalgia (22-59 years)

- 2010 ACR criteria, including normal blood test results
  - normal CBC, and normal ESR or CRP [medical record verified]
  - symptoms present ≥ 3 months
  - pain sufficiently widespread and severe

Burgess, Park, Ong, Shakoor, Williams & Burns, *Pain Medicine*, 2017
Pain - Fibromyalgia

**n=4**

Placebo to light box?

**n=6**

Assessed baseline and post treatment: DLMO
FIQ
Heat pain threshold
Heat pain tolerance

Burgess, Park, Ong, Shakoor, Williams & Burns, *Pain Medicine*, 2017
Home light box treatment

Subject burden:
• sitting in front of light box for 1 hour a day
• rearrangement of living room space, extension cords, impact on family

Burgess, Park, Ong, Shakoor, Williams & Burns, *Pain Medicine*, 2017
Pain - Fibromyalgia

- Function and pain sensitivity improved after morning and evening light
- Larger effects after morning light
- Clinically meaningful improvement in function after morning light

Burgess, Park, Ong, Shakoor, Williams & Burns, *Pain Medicine*, 2017

Equal treatment expectations

85% compliance

24% improvement from baseline ≈ CBT
~1/2 exercise training

Clinically meaningful improvement
≥14% improvement from baseline

Bennett *J Rheumatol* 2009
Circadian phase advancing (shifting earlier) associated with improvements in function and pain sensitivity

Burgess, Park, Ong, Shakoor, Williams & Burns, *Pain Medicine*, 2017

Suggests morning light treatment should be further investigated as a potential adjunctive treatment for chronic pain

- Circadian phase advancing (shifting earlier) associated with improvements in function and pain sensitivity

Burgess, Park, Ong, Shakoor, Williams & Burns, *Pain Medicine*, 2017
FibroLight Study

• R21 NINR
  • final sample of 60 people with fibromyalgia
  • 4 week morning bright vs. dim [placebo] light treatment

To enhance effects on sleep and mood
Pain – chronic low back pain in Veterans

- **Protocol:** single arm (no placebo) open label trial

<table>
<thead>
<tr>
<th>Day</th>
<th>Lab Visit #1</th>
<th>Lab Visit #2</th>
<th>Lab Visit #3</th>
<th>Lab Visit #4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Sleep at Home on usual schedule

+ 30 day follow up

Burgess & Burns, multi PI R34
Pain – chronic low back pain in Veterans

- Protocol: single arm (no placebo) open label trial (n=37)
  - 10 females, 27 males; age 25-68 years

- Inclusion/exclusion criteria:
  - self-report of chronic low back pain of ≥ 4/10, ≥ 6 months
    - confirmed with previous report of back pain in medical record
  - no other significant chronic disease
    - medication controlled diabetes and hypertension ok
  - no other significant chronic pain condition
  - no psychosis, bipolar depression, suicidal ideation
  - no high risk for sleep apnea, restless leg disorder, SAD
  - no eye disease, no photosensitizing medications
  - no previous experience with light treatment
  - no daily medications that suppress melatonin (NSAIDs, beta-blockers)

5 veterans failed drug and alcohol testing, 7 more dropped out baseline → 25 veterans started light treatment, 1 dropped after 6 days for vacation
Pain – chronic low back pain in Veterans

Semi-parametric generalized estimating equation regression model

Pain Threshold (deg. C)

Baseline 6 Days 13 Days

40 41 42 43 44 45

p=0.005
reduced pain sensitivity

Pain Tolerance (deg. C)

First feels painful

Burgess & Burns, multi PI R34
Pain – chronic low back pain in Veterans

Burgess & Burns, multi PI R34
Pain – chronic low back pain in Veterans

- More depression (CES-D)
- More anxiety (STAI)
- Worse PTSD symptoms (PCL-5)

Comparison at baseline, 6 days, and 13 days, with significance level p=0.0495.
Pain – chronic low back pain in Veterans

Reduction in pain possibly driven by improvements in sleep quality and circadian phase advance

\[ \Delta \text{Pain interference} \quad \text{and} \quad \Delta \text{ISI} \quad r=0.46, \quad p=0.03 \]

\[ \Delta \text{Pain interference} \quad \text{and} \quad \Delta \text{DLMO} \quad r=0.55, \quad p=0.02 \]

Suggests morning light treatment should be further investigated as a potential adjunctive treatment for chronic pain

\[ \text{Dim Light Melatonin Onset} \]

\[ p<0.0001 \]
Wearable light treatment - Re-timer

Figure 2. Spectral power distribution of the bright vs. credible dim (placebo) Re-Timer®.

Figure 3. Sample data from the Re-timer® light treatment.
Top: Green light indicates the bright Re-timer® is on. Bottom: Activity indicates Re-timer® is worn.
Post-traumatic Stress Disorder

- Pilot study:
  - n=15 probable PTSD (Criterion A trauma + PCL-5 >33)
  - bright (n=9) vs. dim [placebo] (n=6) Re-timer for 4 weeks

Clinical trial NCT00701064

Zalta…& Burgess
Depression and Anxiety
2019

Alyson Zalta, PhD

- Worse PTSD symptoms
  - p=0.0495
  - d=0.95

- Clinical trial NCT00701064

- Bright vs. Dim
  - d=0.85
Post-traumatic Stress Disorder

Emotional faces task in fMRI

K. Luan Phan, MD

Israel Liberzon, MD
n=30 healthy males
3 weeks of 30 mins of morning light, 100-10,000 lux
Amygdala reactivity in response to fearful faces, pre- to post- treatment
Post-traumatic Stress Disorder

R61/R33 grant proposal – transdiagnostic:
- criterion A trauma in past 5 years + DASS >22
- 3 groups of 4 weeks of morning light with Re-timer:
  - 15 mins or 30 mins or 1 hour (~n=15 per group)
- Target engagement:
  - dose response relationship b/n light “dose” and reduction in amygdala reactivity d≥0.5
Acknowledgements

Faculty
Todd Arnedt, Ph.D.
Deirdre Conroy, Ph.D.
Leslie Swanson, Ph.D.

Clinical Coordinator
Ann Mooney, M.S.W.

Research Assistants
Emily Spence, B.A.
Katelyn Wilensky, B.S.
Nema Kebbeh, B.A.
Trevor de Sibour, B.S.

Lab Manager
Muneer Rizvydeen, B.A.

Registered Sleep Technician
Kelley Dubuc, RPSGT

Biostatistician
Myra Kim, PhD