Introduction and Exposure

Studies of Circadian Disruption

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Draft RoC Monograph on Night Shift Work and Light at Night
Peer Review Meeting
5 October 2018
Outline

Modern lighting practices: Characteristics and exposure

- Electric Light at Night (LAN)
- Night Shift Work

Circadian regulation and disruption

Studies of circadian disruption biomarkers

- Electric LAN in humans and animal models
- Night shift work in humans and animal models
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Modern Lighting Practice

Electric light has transformed society

- Enables people to work, sleep, eat, and receive services throughout the 24 hour day
- Two exposure scenarios related to modern lighting practices
  - Electric LAN and Shift Work at Night
- These exposure scenarios can cause circadian disruption and possible health effects
Technology advances have led to a greater proportion of short wavelengths.

- **Incandescent light bulb**, 1890s
- **Fluorescent Light**, mid 1900s
- **Blue and White LED**, late 1900s
Significant number of US residents are exposed to electric light at night

Outdoor light
- > 99% are exposed to sky glow at night

Light before or during sleeping
- Levels vary from 13 to > 400 lux

Self-luminous electronics
- 90% used some form 1 hour before bed time
- Light is closer to the eye
Night shift work is a complex exposure scenario

Extreme LAN
Sleep disruption
Altered meal timing

Vitamin D
Stress and behaviors
Types of night shift work

- Typically working at least 3 hours between midnight and 5 AM
- Types of shifts vary
Types of night shift work

- Typically working at least 3 hours between midnight and 5 AM
- Types of shifts vary

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
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<td>E</td>
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</tbody>
</table>

D = day, E = evening, N = night, R = rest
Night Shift Work

Significant number of US residents frequently work night shifts

- > 10 million adults frequently work nights
- More common among men, minorities, people in lower socioeconomic groups
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<table>
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<tr>
<th>Sector</th>
<th>% Prevalence</th>
<th># of workers</th>
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<td>Transportation</td>
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<td>Healthcare practitioners</td>
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<td>Production &amp; manufacturing</td>
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<td>Healthcare support</td>
<td>10.4</td>
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</table>

US data CDC 2015
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Light:dark cycle is a key environmental cue that synchronizes the circadian system to the 24 hour day

SCN = suprachiasmatic nucleus
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SCN = suprachiasmatic nucleus

Circadian rhythms
Melatonin and clock genes

Produced by the pineal gland and regulated by SCN
Internal synchronizer of circadian rhythms
Other clock gene entrainers include cortisol and other glucocorticoids

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Produced by the pineal gland and regulated by SCN
Internal synchronizer of circadian rhythms
Other clock gene entrainers include cortisol and glucocorticoids

Controls expression of thousands of genes
Generates circadian oscillations in cell-autonomous transcriptional-translational feedback loops
Major genes: CLOCK, BAML1, PER1, PER2, PER3; CRY1 CRY2, REV-ERBA

SCN = suprachiasmatic nucleus
“Internally or externally induced, acute or chronic temporal disorganization including, but not limited to, misalignment of the time structure”
Circadian Disruption Biomarkers

Modern lighting practices
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Environmental disruptors
- LAN
- Night shift work

Circadian disruption
- Melatonin
- Altered clock genes
LAN induces melatonin suppression depending on light characteristics and susceptibility.

**Wavelength**
- Shorter more effective

**Level**
- Dose response

**Duration**
- Depends on other light characteristics

**Timing of light**
- Morning – phase advance
- Early evening – phase delay

**Total Light exposure**
- Insufficient daytime light exposure is also important

**Susceptibility**
- Younger age
- Chronotype
- Clock gene polymorphisms

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Figueiro et al. 2006
LAN induces melatonin suppression depending on light characteristics and susceptibility

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- **Level**: Dose response
- **Duration**: Depends on other light characteristics
- **Timing of light**: Morning – phase advance; Early evening – phase delay
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Figueiro et al. 2006
Electronics with self-luminous displays
- Acutely suppress melatonin onset
- Disrupt sleep
- Blue light greater effect

Light in the sleeping area
- Most observational studies were negative
- Limited methodology: May not have had the ability to detect an effect

Outdoor Light: measured by satellite
- 1 study found a small non-significant inverse relationship between light and 24-hr urinary melatonin
- Light may be too low to suppress melatonin during sleep (closed eyes) and closed curtains
Night shift work suppresses or disrupts melatonin levels

- Few shift workers adapt their rhythms to their sleep schedule
- \(\downarrow\) Night time melatonin levels or average melatonin found in night shift workers compared to day shift workers in almost all studies
- \(\downarrow\) Night time melatonin or average melatonin levels associated with persistent night shift work
- Exposure to LAN among night shift workers may contribute in part to melatonin suppression; however, limited number of studies

![Graph showing melatonin suppression over time]

- Cosinor modeling of melatonin metabolite (aMT6s) production over time
- Day and permanent night shift workers from Spain
- Papantoniou et al. 2014
LAN and shift work are associated with altered clock gene expression

• Strongest evidence is from animal studies
  – Gene expression measured in peripheral tissue, brain tissue, as well as in the master clock
  – Almost all studies found that shift work and LAN altered clock gene expression
  – Findings for specific genes varied and may be dependent on tissue and sample findings

• Human studies provide some support
  – Gene expression measured in blood or surrogate tissue
  – 2 experimental studies of LAN; 3 studies of independent populations of night shift work
  – Findings for specific genes may depend on sample timing and relationship to work schedule
Conclusions

Significant number of US residents
• Are exposed to electric LAN
• Frequently work night shifts

Night shift work is a complex exposure scenario, which includes exposures, such as LAN, that regulate the circadian system

Modern lighting practices are associated with circadian disruption biomarkers
• Melatonin suppression
• Altered clock gene expression
Clarification questions?
Reviewer Questions

Introduction and exposure: Section 1

- Comment on whether the description of the topic is clear and technically accurate and identify any information that should be added or deleted
  - Circadian regulation and disruption
  - Light at night
  - Shift work
  - Transmeridian travel and social jet lag

- Comment on whether the information supports the RoC criteria that
  - Significant number of U.S. residents work night shifts
  - Significant number of U.S. residents are exposed to LAN
Reviewer Questions

Circadian disruption studies: Section 2

• Biomarkers and characteristics of circadian disruption
  – Comment on whether the description of the topic (listed below) is clear and technically accurate and identify any information that should be added or deleted
  – Provide critical comments on NTP assessment

• LAN and circadian disruption biomarkers
  – Comment on whether the description of the topic (listed below) is clear and technically accurate and identify any information that should be added or deleted
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• Shift work and circadian disruption biomarkers
  – Comment on whether the description of the topic (listed below) is clear and technically accurate and identify any information that should be added or deleted
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