Fatigue in the Setting of Disease

Sleep Disruption

Phyllis C. Zee, MD, PhD
Northwestern University
Feinberg School of Medicine
Disclaimer and Disclosures

Disclaimer
This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

Disclosure
This certifies that I, Phyllis C. Zee, have no financial relationship that is relevant to the subject matter of this presentation.

Consultant and advisory board for companies with products related to sleep therapeutics: Eisai, Jazz, Harmony, Takeda.
CIRCADIAN RHYTHMS

REST (SLEEP)
ACTIVITY (WAKE)

FUEL
METABOLISM
Physiological Determinants of Sleep/Wake Regulation

Circadian and Sleep Homeostatic Processes

Homeostatic sleep drive

Circadian alerting signal

Wake /Sleep Propensity

Melatonin

Recurring Dynamic Cycles of Wake and Sleep

Awake
Stage N1 and REM
Stage N2
Stage N3

Rapid Eye Movement (REM)
Stage NREM (1-3)
Wake

Time of day
Sleep stage
MT
W
REM
1
2
3
18.00 20.00 22.00 24.00 02.00 04.00 06.00 08.00 10.00 12.00 14.00 16.00

Courtesy of R. Ristanovic, MD.
Brain Metabolic Activity in Wake and Sleep

Sleep/Wake Disruption and Fatigue

Insomnia
Prevalence (10-25%)

Sleep Apnea
(6%-20%)

Restless Legs
Prevalence (10%)

Circadian Rhythm Disorder
Prevalence?

Wake Disruption

Sleep Disruption

Circadian Disruption

Metabolism
Brain metabolic activity
Inflammation
Oxidative stress
Autonomic function

Sleepiness ↔ Fatigue

Depression

Genetic vulnerability

Behavioral lifestyle
Psychological well-being
Socio-economic status
Work schedules
Physical activity level
Light exposure

Health
Metabolic
Cardiovascular
Neurologic / Mental

The Alertness-Sleepiness-Fatigue Spectrum

**Sleepiness** - the need for sleep, or propensity to fall asleep

**Fatigue** - the sensation of weariness, tiredness, exhaustion, loss of energy; the desire to rest, lack of motivation...

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Measures of Sleep Quality and Sleepiness

**Subjective**
- Pittsburgh Sleep Quality Index (PSQI)
- PROMIS Sleep Quality/Disturbance
- Epworth Sleepiness Scale (ESS)
- Karolinska Sleepiness Scale (KSS)
- Stanford Sleepiness Scale (SSS)

**Objective**
- Polysomnography
- Actigraphy
- **Multiple Sleep Latency Test (MSLT)**
- Maintenance of wakefulness test
- Wake EEG
- Pupillometry

Sleep Disorders and Fatigue

<table>
<thead>
<tr>
<th>Group studied</th>
<th>Fatigue Severity Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disorders</td>
<td>4.8 (1.4)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>4.8 (1.3)</td>
</tr>
<tr>
<td>Systemic lupus</td>
<td>4.6 (1.5)</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>6.1 (0.8)</td>
</tr>
</tbody>
</table>

Lichstein K et al, Behav Res Ther, 1997

Relationship between sleepiness and fatigue

Table 3. The Pearson correlation between Fatigue Severity Scale (FSS) scores and plausible predictors

<table>
<thead>
<tr>
<th>Predictor</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and anthropometric variables</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.19**</td>
</tr>
<tr>
<td>Age</td>
<td>0.00</td>
</tr>
<tr>
<td>Gender¹</td>
<td>0.29**</td>
</tr>
<tr>
<td>Smoking history²</td>
<td>0.20**</td>
</tr>
<tr>
<td>Sleep and sleepiness</td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency percent</td>
<td>−0.16*</td>
</tr>
<tr>
<td>MSLT</td>
<td>−0.08</td>
</tr>
<tr>
<td>Psychological and sleep pathology</td>
<td></td>
</tr>
<tr>
<td>MMPI-depression</td>
<td>0.44**</td>
</tr>
<tr>
<td>MMPI-average</td>
<td>0.45**</td>
</tr>
<tr>
<td>Myoclonus arousal index</td>
<td>0.06</td>
</tr>
<tr>
<td>Respiratory disturbance index</td>
<td>−0.04</td>
</tr>
<tr>
<td>Oxygen desaturation</td>
<td>−0.16*</td>
</tr>
<tr>
<td>MSLT REM</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01.

¹The coding scheme we used indicates that a positive correlation is associated with being female.

²The coding scheme we used indicates that a positive correlation is associated with smoking more.
Actigraphy Derived Measures of Sleep and Fatigue in Cancer

- All types of invasive cancer N=87 (fatigued 51; non fatigued 36)
- Actigraphy (14 days)
- Sleep Diary (14 days)
- Cancer related fatigue (FACIT-F)
- Insomnia Severity Index (ISI)

Martin, T et al, Curr Oncol, 2021
Subjective sleepiness and Fatigue: Independent/interrelated consequence of sleep disorders?

Hossain JL et al, Journal Sleep Res, 2005

<table>
<thead>
<tr>
<th></th>
<th>High fatig/low sleepiness</th>
<th>High fatig/low sleepiness</th>
<th>Low fatig/low sleepiness</th>
<th>Low fatig/high sleepiness</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45.0 ± 15.0</td>
<td>43.0 ± 14.0</td>
<td>48.2 ± 16.8</td>
<td>50.2 ± 13.6</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>28.1 ± 6.7</td>
<td>31.5 ± 11.7</td>
<td>27.6 ± 7.6</td>
<td>30.7 ± 6.7</td>
<td>F(3,279) = 3.0, P &lt; 0.03</td>
</tr>
<tr>
<td>ESS Score</td>
<td>6.9 ± 3.8</td>
<td>17.2 ± 2.7</td>
<td>5.4 ± 2.8</td>
<td>14.5 ± 2.9</td>
<td>F(3,279) = 138.5, P &lt; 0.0001</td>
</tr>
<tr>
<td>FSS Score</td>
<td>5.1 ± 0.9</td>
<td>5.4 ± 1.0</td>
<td>2.1 ± 0.7</td>
<td>1.9 ± 0.6</td>
<td>F(3,279) = 143.0, P &lt; 0.0001</td>
</tr>
<tr>
<td>CES-D Score</td>
<td>21.7 ± 11.0</td>
<td>23.0 ± 11.9</td>
<td>13.2 ± 10.6</td>
<td>19.4 ± 11.2</td>
<td>F(3,279) = 6.86, P &lt; 0.001*</td>
</tr>
<tr>
<td>THAT Score</td>
<td>26.3 ± 8.0</td>
<td>23.12 ± 6.8</td>
<td>32.7 ± 9.5</td>
<td>25.0 ± 12.0</td>
<td>F(3,279) = 10.35, P &lt; 0.001*</td>
</tr>
<tr>
<td>IIRS Score</td>
<td>42.1 ± 16.6</td>
<td>49.9 ± 17.3</td>
<td>23.9 ± 10.5</td>
<td>30.4 ± 15.0</td>
<td>F(3,279) = 21.0, P &lt; 0.0001*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>FSS Score</th>
<th>ESS Score</th>
<th>THAT Score</th>
<th>CES-D Score</th>
<th>IIRS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive sleep apnea (n = 93)</td>
<td>4.4 ± 1.6</td>
<td>9.8 ± 5.6</td>
<td>28.6 ± 8.8</td>
<td>18.9 ± 12.5</td>
<td>39.2 ± 20.8</td>
</tr>
<tr>
<td>Periodic leg movements (n = 33)</td>
<td>4.6 ± 1.4</td>
<td>7.2 ± 7.3</td>
<td>27.0 ± 7.8</td>
<td>20.6 ± 12.5</td>
<td>39.9 ± 15.1</td>
</tr>
<tr>
<td>Restless legs syndrome (n = 12)</td>
<td>5.1 ± 1.0</td>
<td>11.9 ± 7.3</td>
<td>24.3 ± 6.3</td>
<td>18.4 ± 11.7</td>
<td>39.1 ± 17.3</td>
</tr>
<tr>
<td>Insomnia (n = 33)</td>
<td>4.4 ± 1.5</td>
<td>7.6 ± 5.2</td>
<td>28.0 ± 9.1</td>
<td>16.8 ± 8.5</td>
<td>39.4 ± 16.8</td>
</tr>
<tr>
<td>Depression (n = 58)</td>
<td>4.7 ± 1.4</td>
<td>7.7 ± 4.6</td>
<td>24.0 ± 8.5</td>
<td>27.0 ± 10.5</td>
<td>43.9 ± 17.4</td>
</tr>
<tr>
<td>Narcolepsy (n = 9)</td>
<td>4.8 ± 1.2</td>
<td>16.2 ± 5.5</td>
<td>21.5 ± 6.2</td>
<td>15.8 ± 7.3</td>
<td>39.4 ± 14.6</td>
</tr>
<tr>
<td>Parasomnia (n = 11)</td>
<td>5.2 ± 1.2</td>
<td>9.3 ± 6.2</td>
<td>21.5 ± 7.1</td>
<td>29.4 ± 5.6</td>
<td>44.3 ± 18.2</td>
</tr>
<tr>
<td>Delayed sleep phase syndrome (n = 15)</td>
<td>4.6 ± 1.6</td>
<td>7.0 ± 5.6</td>
<td>25.4 ± 7.8</td>
<td>19.0 ± 9.9</td>
<td>35.3 ± 16.9</td>
</tr>
</tbody>
</table>

Hossain JL et al, Journal Sleep Res, 2005
Insomnia

“My creativity diminishes, my irritability increases, my disposition suffers, my outlook is gloomier, my muscles feel weaker, my energy is kaput some days. Some days I’m too tired to accomplish anything but still unable to nap or sleep. It’s an odd sensation. I feel as if I’ve been deprived of sleep and am exhausted but at the same time, as if I had drunk 5 cups of coffee and were overstimulated.”
Brain Metabolic Activity in Wake and Sleep

**Healthy Sleep**

Structures that did not show decreased metabolic rate from waking to sleep


**Insomnia**

Relative metabolism while awake was higher in healthy subjects compared to insomnia

Nofzinger EA et al, Am J Psychiatry, 2004
Interventions for Chronic Insomnia in Older Adults

- Age 55 and older with diagnosis of insomnia
- No primary sleep pathology other than insomnia
- No cognitive impairment (MMSE < 25)
Reid, KR et al, Sleep Med 2010; baron K et al, JCSM, 2013
Light Therapy, Sleep Disturbance and Fatigue

Hastings MH, Maywood ES, Brancaccio M, Nat Rev, 2018
Light Therapy and Fatigue in Cancer Survivors with Sleep Disturbance

Fatigue and sleep disruption-disorder

• Majority of research on fatigue and sleep disturbance are in the context of other medical, neurological and psychiatric disorders in which both are common

• Sleep medicine: If not excessive sleepiness-then fatigue

• Limited objective clinical and research measures/biomarkers

• Differentiating sleepiness and fatigue objectively makes a difference in management approaches