Waking Up to Treatment Guidelines for Shift Work Disorder
Learning Objectives

• Implement guideline-based assessment strategies for patients with suspected shift work disorder

• Educate patients on how to incorporate practical sleep hygiene techniques into their daily lives

• Implement guideline-based treatment strategies for patients with shift work disorder
Pretest Question

Denise is a 32-year-old patient with shift work disorder who reports that she is having difficulty in her job as a pastry chef due to excessive sleepiness during her shift. Which of the following is a potential therapeutic mechanism to promote wakefulness?

1. Inhibit dopamine activity
2. Inhibit histamine activity
3. Inhibit GABA activity
4. All of the above
5. None of the above
Circadian Rhythm

- A self-sustained rhythm of biological process that entrains an organism’s functions to cycles in the environment.
Suprachiasmatic Nucleus (SCN)

Retinohypothalamic Tract
Suprachiasmatic Nucleus (SCN)

Retinohypothalamic Tract

Pineal Gland

melatonin
Zeitgebers

External cues to synchronize circadian rhythms

• Light

• Melatonin

• Eating and drinking patterns

• Social interactions

Molecular Clock Genes

- **CLOCK** (circadian locomotor output cycles kaput)
- **BMAL1** (brain and muscle ARNT-like-1)
- **PER** (period)

- **CRY** (cryptochrome)
- **REV-ERBα**
- **ROR** (retinoic acid-related orphan receptor)

- Code for proteins that act as transcription factors
- Expression waxes/wanes approximately every 24 hours
- Turn on/off expression of other genes including those involved in sleep, metabolism, mood

Circadian Rhythm Disorders

• Problems may arise when there is dyssynchrony between the internal clock and external cues

• Advanced sleep phase rhythm
  – Sleep pattern is earlier than desired (early to bed, early to rise)
  – Associated with polymorphisms in PER gene

• Delayed sleep phase rhythm
  – Sleep pattern is later than desired (late to bed, late to rise)
  – Associated with polymorphisms in PER and CLOCK genes

• Shift workers’ sleep/wake schedules are often out-of-phase with their endogenous circadian rhythms

Shift Work

• Work hours occur between 18:00hrs and 08:00hrs
• 15–25% of all workers in the US perform shift work
• 10–32% of shift workers develop shift work disorder (SWD)
• 9% of shift workers develop severe SWD
  – Unknown what factors differentiate those who develop SWD from those who do not
• Shift workers have a 3-fold risk of occupational accidents compared to day workers
  – Likely due to decreased alertness and cognitive deficits

DIAGNOSING SHIFT WORK DISORDER
Diagnostic Criteria: Circadian Rhythm Disorders

• Persistent or recurring patterns of sleep disturbance primarily attributed to circadian disruption and circadian misalignment

• Circadian-related sleep disruption resulting in insomnia, excessive daytime sleepiness, or both

• Sleep disturbance that is associated with impairment in social, occupational, or other areas of functioning

Diagnostic Criteria: Shift Work Disorder

- In addition to meeting all diagnostic criteria for circadian rhythm disorder
- Insomnia or excessive sleepiness temporarily associated with a recurring work schedule that overlaps with the usual time for sleep
- Symptoms associated with shift work schedule are present for at least 1 month
- Sleep log or actigraphy monitoring (with sleep diaries) for at least 7 days demonstrates disturbed sleep (insomnia) and circadian and sleep-time misalignment
- Sleep disturbance is not due to another current sleep disorder, medical disorder, mental disorder, substance use disorder, or medication use

Supportive Criteria for Shift Work Disorder

• Early morning shifts may be associated with difficulty initiating sleep and awakening

• Permanent evening shifts may be associated with difficulty initiating sleep

• Excessive sleepiness usually occurs during the work shift (mainly night), often accompanied by a need to nap and impaired mental stability

• Reduced alertness, not only during the work shift, may be associated with reduced performance capacity and consequences for safety

• Major portions of free time may have to be used for recovery of sleep with adverse social consequences

• Increased irritability may be present

Supportive Criteria for Shift Work Disorder

• Irregular sleep/wake schedule that varies by more than 2–4 hours between work days and days off

• Insomnia or hypersomnia on either side of the scheduled sleep period
  – Delayed sleep phase syndrome
    • Insomnia at the desired bedtime and hypersomnia at the desired work time
  – Advanced sleep phase syndrome
    • Hypersomnia at bedtime and insomnia prior to the desired wake time

Most Common Symptoms of Shift Work Disorder

- Insufficient sleep
  - Average sleep duration 5.5 hrs
- Tendency to doze off at work
- Overall unsatisfactory quality of sleep
- Reduced sense of well-being
- Decreased physical and mental well-being
- 53.2% of patients with SWD report insomnia
  - Difficulties falling asleep, staying asleep, and waking up too early
- 35.6% of patients with SWD report excessive sleepiness
  - Multiple sleep latency in SWD is 2 min (vs. 10–20 min in controls)
- 23.4% of patients with SWD report both insomnia and excessive sleepiness

Tools for Assessing Shift Work Disorder (see appendix)

- Sleep/wake diary
- Morningness-Eveningness Questionnaire (MEQ)
- Epworth Sleepiness Scale (ESS)
- Multiple Sleep Latency Test (MSLT)
- Melatonin levels
- Actigraphy
  - Measures gross motor activity to detect rest/activity cycles
- Polysomnography to rule out other sleep disorders

Taking A Sleep History

• Work schedule
• Sleep/wake schedule
  – Work days, days off, vacation days
• Quality of sleep and quality of wakefulness
• Snoring and witnessed apneas
• Abnormal nocturnal behaviors
• Sleep paralysis and cataplexy
• Use of drugs/medications to help with sleep or alertness
• Quality of sleeping environment and waking environment
• General medical and psychiatric history
CAUSES AND CONSEQUENCES OF SHIFT WORK DISORDER
Desynchronization of the Molecular Clock

Shift work

Mutated Clock genes

Impaired Neurotransmission

prefrontal cortex

NE DA

brainstem neurotransmitter centers

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Common Comorbid Conditions in Shift Workers

- Prevalence of sleep apnea is increased
- Prevalence of ulcers is increased
  - Day shift workers: 6%
  - Rotating shift workers: 12.5%
  - Night shift workers: 15.4%
- Prevalence of bowel disorders is increased
  - Day shift workers: 20%
  - Rotating shift workers: 38%
- Prevalence of mood disorders is increased

Cardiometabolic Consequences

• Compared to day workers, night shift workers have:
  – Higher BMI
  – Elevated cholesterol
  – Elevated triglycerides
  – Greater risk of hypertension

• Risk of developing cardiovascular disease may be increased by as much as 40% in shift workers

Cardiometabolic Consequences

• Many hormones involved in metabolism (e.g., ghrelin, leptin) exhibit circadian oscillation
  – The expression of these hormones is regulated by molecular clock genes/transcription factors
  – Many of these hormones also regulate the expression of molecular clock genes/transcription factors

• CLOCK polymorphisms are associated with an increased risk for obesity and metabolic syndrome

• BMAL1 polymorphisms are associated with susceptibility to hypertension and type 2 diabetes

• Chronic misalignment of feeding cycles and sleep cycles results in metabolic disorders and DNA damage

Cancer

• Shift workers have a higher incidence of breast, colon, and prostate cancers

• Several cell cycle genes (e.g., MYC, WEE1) are regulated by molecular clock genes/transcription factors

• PER interacts with proteins involved in the DNA damage response

• PER expression is deregulated in breast cancer cells

• DNA damage can also act as a zeitgeber (reset the molecular clock)

• Circadian rhythm/cell cycle synchronization may prevent DNA replication during times of high exposure to damaging UV rays or by-products of intense metabolism

“Shift work that involves circadian disruption is probably carcinogenic to humans”

-The World Health Organization

-International Agency for Research on Cancer

TREATING SHIFT WORK DISORDER: Adapting Circadian Rhythms
Optimizing Sleep Hygiene

- Dark sunglasses and a dark quiet room for sleeping to minimize exposure to bright light
- The bedroom should be kept cool as it is important to try and retrain the core body temperature to the shifted time
- No stimulants in the second half of a shift
- Strategic use of caffeine early in the shift may be helpful
- Planned napping
- Decrease extended work hour shifts
- Clockwise progression of rotating shifts is best

Sleep/Wake Hygiene

**Sleep Time**
- No stimulants before bed
- Dark room
- Sunglasses
- Cool environment
- No disturbances

**Wake Time**
- Activity
- Bright Light
Bright Light Therapy

• Exposure to light alters circadian rhythms and suppresses melatonin release

• 10,000 lux (bright light) for 30 min/day

• Must be timed with patient’s circadian phase of melatonin secretion
  – Administer light 7.5–9.5 hrs after evening melatonin secretion
  – Determined using the Morningness-Eveningness Questionnaire

• Dawn simulation therapy
  – Slow incremental light signal at the end of the sleep cycle

• Side effects (headaches, eyestrain, nausea, agitation) are rare

Dallaspezia S, Benedetti F. Expert Rev Neurother 2011;11(7):961-70;
BLT Effects

- Shift workers can be completely re-entrained with bright light intermittently for 20 minutes during the night.
- Performance, alertness, and mood during night shift improve.

Melatonin Levels in Shift Workers

Stahl SM, Diagnosis and Treatment of Sleep/Wake Disorders, 2007.
Melatonin

- Melatonin receptor levels are high during the evening and low during the night.
- Melatonin administered in the evening advances the circadian rhythm to allow a person to sleep earlier.
- Melatonin given early in the morning can cause a phase delay, so that a person will not feel sleepy until later.
- It is better to use melatonin for shift work disorder during the night, at around the normal circadian low of 03:00.
  - Administer 3 hours before dim-light melatonin onset.
- The melatonin agonist ramelteon is not FDA approved for the treatment of SWD, but is indicated for insomnia characterized by difficulty of sleep onset.

TREATING SHIFT WORK DISORDER: Sleeping When You Need To
Benzodiazepine Hypnotics

• Bind with equal affinity to $\alpha_1$, $\alpha_2$, $\alpha_3$, and $\alpha_5$ subunits of the GABA-A receptor
  – Alpha subunit expression differs throughout the brain
  – The selectivity of a hypnotic for different $\alpha$ subunits will induce effects in addition to sedation (e.g., anxiolytic, anti-pain, tolerance)

• Higher risk of tolerance and withdrawal effects compared to non-benzodiazepine hypnotics
  
  • Estazolam
  • Flurazepam
  • Quazepam
  • Temazepam
  • Triazolam

*FDA-approved for the treatment of insomnia*
Non-benzodiazepine Hypnotics

• Bind selectively to 1 or 2 $\alpha$ subunits of the GABA-A receptor
  – The selectivity of a hypnotic for different $\alpha$ subunits will induce effects in addition to sedation (e.g., $\alpha_2$ and $\alpha_3$ subunits may have anxiolytic, antidepressant, and anti-pain effects)

• Eszopiclone
  – Selective for $\alpha_2$ and $\alpha_3$ subunits
  – The only hypnotic approved for use over 35 days

• Zaleplon
  – Selective for $\alpha_1$ subunits
  – Can be used for awakening during the night without residual daytime effects

• Zolpidem
  – Selective for $\alpha_1$ subunits
  – Sublingual form approved for middle of the night awakening

FDA-approved for the treatment of insomnia
# Mechanism of Trazodone and Doxepin as Hypnotics

<table>
<thead>
<tr>
<th></th>
<th>Antidepressant dose</th>
<th>Hypnotic dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trazodone</strong></td>
<td><img src="https://via.placeholder.com/150" alt="Diagram of Trazodone" /></td>
<td><img src="https://via.placeholder.com/150" alt="Diagram of Trazodone" /></td>
</tr>
<tr>
<td><strong>Doxepin</strong></td>
<td><img src="https://via.placeholder.com/150" alt="Diagram of Doxepin" /></td>
<td><img src="https://via.placeholder.com/150" alt="Diagram of Doxepin" /></td>
</tr>
</tbody>
</table>

- **Trazodone**
  - Antidepressant dose: (150-600 mg)
  - Hypnotic dose: (25-150 mg)

- **Doxepin**
  - Antidepressant dose: (150-600 mg)
  - Hypnotic dose: (1-6 mg)

*FDA-approved for the treatment of insomnia*

TREATING SHIFT WORK DISORDER: Staying Awake When You Need To
Modafinil and Armodafinil

• Used to reduce excessive sleepiness in patients with narcolepsy, obstructive sleep apnea, shift work disorder

• **Immediately reduces daytime sleepiness and improves cognitive performance**

• Optimization can take several days

• Activates brain areas involved in controlling wakefulness (hypothalamus)

• Side effects include headache, nausea, dizziness, and insomnia

Modafinil’s MOA: Alpha-Adrenergic Stimulation via DAT Inhibition?

Modafinil May Also Affect Histaminic and Orexinergic Neurotransmission

Armodafinil

Modafinil vs. Armodafinil

- Both promote wakefulness through activation of hypothalamus, prefrontal cortex, and anterior cingulate cortex

- Modafinil contains both R (long-acting) and S (short-acting) isomers

- Armodafinil consists of the R isomer only
  - Less plasma drug variability than modafinil
  - May be more effective in promoting wakefulness toward the end of an 8-hr shift in patients with SWD

Off-Label Treatments for Excessive Sleepiness

• Stimulants
  – Low dose (5–10 mg) of methamphetamine
    • Potential for abuse
    • Adverse effects at higher doses (10–20 mg) are not uncommon
  – Caffeine
    • 300 mg has been shown to increase performance and alertness in shift workers
  – Energy drinks: no evidence supports their use

• Avoid stimulants during the second half of the work shift

• A person who relies on stimulants may experience insomnia and subsequent excessive sleepiness on the next shift

Summary

• Shift work disorder is due to circadian rhythm misalignment and may have severe consequences on both physical and mental health

• There are several assessment tools that can aid in the diagnosis of shift work disorder

• Treatments for shift work disorder include pharmacological and non-pharmacological strategies to synchronize the circadian rhythm with external cues, to reduce insomnia, and to alleviate excessive sleepiness

• A combination of treatment measures may be more effective than the sum of individual treatments
APPENDIX
Polysomnography

- Eye movements
- Muscle activity
- Brain activity
- Muscle activity
- Respiration
- Heart activity
- Oxygen level
Multiple Sleep Latency Testing

**Method**

Nocturnal polysomnogram

5 daytime nap opportunities

- Quiet, dark room
- 2-hour intervals

Score time to sleep onset

Max time: 20 min

Wake patient 15 min from sleep onset

<table>
<thead>
<tr>
<th>Degree of sleepiness</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean sleep latency (min)</td>
<td><img src="#" alt="Graph" /></td>
<td><img src="#" alt="Graph" /></td>
<td><img src="#" alt="Graph" /></td>
<td><img src="#" alt="Graph" /></td>
</tr>
</tbody>
</table>
Actigraphy
## Sleep/Wake Diary

<table>
<thead>
<tr>
<th></th>
<th>First day</th>
<th>Second day</th>
<th>Third day</th>
<th>Fourth day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete in morning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bedtime (date/time)</td>
<td>10:45 p.m. (4/10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise time (date/time)</td>
<td>7:00 a.m. (4/11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated time to fall asleep</td>
<td>30 minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated number of awakenings and total time awake</td>
<td>5 times 2 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated amount of sleep obtained</td>
<td>4 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Complete at bedtime</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naps (number, time, and duration)</td>
<td>1 at 3:30 p.m. 45 minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic drinks (number and time)</td>
<td>1 drink at 8:00 p.m. 2 drinks at 9:00 p.m.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>List stresses of the day</td>
<td>Flat tire</td>
<td>Argued with son</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate how you felt today</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 = Very tired/sleepy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 = Somewhat tired/sleepy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 = Fairly alert</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 = Wide awake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability level</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 = None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 = Some</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 = Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 = Fairly high</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 = High</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Epworth Sleepiness Scale

<table>
<thead>
<tr>
<th>Situation</th>
<th>would never doze (0)</th>
<th>slight chance of dozing (1)</th>
<th>moderate chance of dozing (2)</th>
<th>high chance of dozing (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sitting and reading</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>2. Watching TV</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>3. Sitting, inactive in a public place (e.g., a theatre or a meeting)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>4. As a passenger in a car for an hour without a break</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>5. Lying down to rest in the afternoon when circumstances permit</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>6. Sitting and taking to someone</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>7. Sitting quietly after a lunch without alcohol</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>8. In a car, while stopped for a few minutes in traffic</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

**Calculate Total Score**

**Interpretation:**

- **Score**
  - 0-9 Normal (a low score does not exclude significant daytime sleepiness)
  - 10-11 Borderline
  - 12-24 Abnormal
Morningness-Eveningness Questionnaire (MEQ)

- An automated version of the MEQ is available at:

  http://www.cet.org/eng/Tools_ENG.html