A Review of Sleep Disorders in Cancer Patients: Finding the “Dream” Treatment

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Roswell Park Cancer Institute
Oncology Symposium
11/11/17
Objectives

• Evaluate the issues with sleep in oncology patients
• Discuss sleep stages, architecture and neurochemistry
• Discuss positives and negatives of current treatment options
• Evaluate current guidelines as they pertain to treatment of sleep disorders
Sleep Disorders in Cancer Patients

• Sleep disturbances affect over 60% of newly diagnosed or recently treated cancer patients
• Only ~30% of patients offer information about this to their physician
• Sleep Complaints:
  • Latency (40%)
  • Length (63%)
  • Quality (72%)

Sleep Disorders in Cancer Patients

Figure 2. Incidence of Insomnia in Study Sample

Figure 3. Frequency of Insomnia by Demographics

Sleep Disorders in Cancer Patients

Fig 1. Insomnia symptoms in patients after first cycle of chemotherapy (N = 823) versus general population. (*) From multiple epidemiologic studies summarized in Ohayon.¹a

Fig 2. Prevalence of insomnia symptoms by diagnosis at cycle 1.

Three Factor Model of Sleep Disturbances in Cancer Patients

- Predisposing Factors
  - Hyperarousability
  - Gender
  - Age

- Precipitating
  - Cancer Related Treatment
  - Emotional Impact
  - Pain

- Perpetuating
  - Maladaptive Sleep Behaviors
  - Sleep Attitude

Sleep Architecture

Hypnogram

Awakening
REM Sleep
Stage 1
Stage 2
Stage 3
Stage 4

Midnight 0130 0300 0500 0630

Stage 1 (NREM)

- Transitional State
  - “Twilight Phase”
- Sleep Time
  - Per Cycle: 1-7 minutes
  - Total Sleep: 2-5%
- Brain Activity
  - Low-Voltage
  - Mixed-Frequency

Stage 2 (NREM)

• Light Sleep State
  • Decreased Heart Rate/Respiration
  • Decreased Body Temperature
  • Muscle Relaxation

• Sleep Time
  • Per Cycle: 10-25 minutes
  • Total Sleep: 45-55%

• Brain Activity
  • Low-Voltage
  • Mixed-Frequency
  • Sleep Spindles and K-Complexes

Stage 3/4 (NREM)

• Slow-Wave Sleep (Delta)
  • Muscle/Tissue Repair
  • Decreased Cerebral Blood Flow
  • Decreased Metabolism

• Sleep Time
  • Per Cycle: 20-40 minutes
  • Total Sleep: 15%

• Brain Activity
  • High-Voltage
  • Slow-Wave

REM

• “Dream-Sleep”
  • Increased Cerebral Blood Flow
  • Increased Metabolism
  • Decreased Heart Rate/Respiration
  • Paradoxical Sleep

• Sleep Time
  • Per Cycle: 3-10 minutes
  • Total Sleep: 20-25%

• Brain Activity
  • Saw-tooth Wave Forms
  • Theta Activity
Sleep Health

- Shorter Survival
- Increased Pain
- Impaired Memory & Concentration
- Poor Focus and Attention
- Slower Reaction Times
- Greater Utilization of Healthcare $ (More Frequent MVA and Work Place Errors)
- Heightened Inflammation and Risk of Disease

Neurotransmitters of Sleep

**Wakefulness**

**Sedation**

Neurotransmitters of Sleep

Orexin/Hypocretin

Wakefulness

- Monoamines
  - Dopamine
  - Norepinephrine
  - Serotonin
- Acetylcholine
- Histamine

Sedation

- Adenosine
- γ-aminobutyric Acid (GABA)
- Melatonin
- Galanin

Neurotransmitters of Sleep

Monoamines
- Acetylcholine
- Histamine

Adenosine
GABA
Melatonin
Galanin

Orexin/Hypocretin

γ-aminobutyric Acid (GABA)

• Mechanism of Action
  • Inhibitory neurotransmitter of the central nervous system
  • Decreases excitability of neurons

• Role in Sleep
  • Stimulation = Sedation
  • Receptor Manipulation

GABA Agonists

- **Mechanism of Action**
  - Enhancement of the inhibitory effects of GABA on neuronal excitability
  - $\text{BZ}_1$ vs. $\text{BZ}_2$ Receptors

- **Indication(s)**
  - Short-term treatment of insomnia
  - Clinical trials= 35 days up to 6 months**

- **Medication(s)**
  - Benzodiazepines
    - Estazolam
    - Flurazepam
    - Triazolam
    - Temazepam
  - Z-Drugs
    - Eszopiclone**
    - Zaleplon
    - Zolpidem

GABA Agonists

• Side Effects
  • Amnesia
  • Daytime drowsiness
  • Vertigo
  • Sleep Disturbances
  • Addiction/Abuse Potential

***FALL RISK***

GABA Agonists

1A  | Non-benzodiazepine sedative hypnotic use
---|----------------------------------------

<table>
<thead>
<tr>
<th>Any Falls</th>
<th>Recurrent Falls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>Age + site</td>
<td>Age + site</td>
</tr>
<tr>
<td>Age + education</td>
<td>Age + education</td>
</tr>
<tr>
<td>Age + health status</td>
<td>Age + health status</td>
</tr>
<tr>
<td>Age + IADL impairment</td>
<td>Age + IADL impairment</td>
</tr>
<tr>
<td>Age + chair stand</td>
<td>Age + chair stand</td>
</tr>
<tr>
<td>Age + MMSE score</td>
<td>Age + MMSE score</td>
</tr>
<tr>
<td>Age + GDS score</td>
<td>Age + GDS score</td>
</tr>
<tr>
<td>Age + comorbidity index</td>
<td>Age + comorbidity index</td>
</tr>
<tr>
<td>Age + alcohol use</td>
<td>Age + alcohol use</td>
</tr>
<tr>
<td>Age + BMI</td>
<td>Age + BMI</td>
</tr>
<tr>
<td>Age + PASE score</td>
<td>Age + PASE score</td>
</tr>
<tr>
<td>MV model*</td>
<td>MV model*</td>
</tr>
</tbody>
</table>

Diem et al. J Gerontol Geriatr Res. 2014 Jul 1; 3(3): 158
## GABA Agonists

<table>
<thead>
<tr>
<th>Sleep Stage</th>
<th>Effect on Sleep Architecture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>![arrow down]</td>
</tr>
<tr>
<td>Stage 2</td>
<td>![arrow up]</td>
</tr>
<tr>
<td>Stage 3</td>
<td>![arrow up]</td>
</tr>
<tr>
<td>Stage 4</td>
<td>![arrow up]</td>
</tr>
<tr>
<td>REM</td>
<td>![arrow down]</td>
</tr>
</tbody>
</table>

GABA Agonists

The Disturbing Side Effect Of Ambien. The No. 1 Prescription Sleep Aid

By Allison McCabe
<table>
<thead>
<tr>
<th>Reference</th>
<th>Age, sex, and clinical state</th>
<th>Dose</th>
<th>Description of response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harazin et al. 1999</td>
<td>46, male, shift work related insomnia Negative history for sleepwalking</td>
<td>Zolpidem 10 mg at bedtime</td>
<td>Within 4 days of initiation of zolpidem he would arise at night to prepare a meal and eat it. He had no memory of the events. Medication was discontinued. Unknown whether events recurred off zolpidem.</td>
</tr>
<tr>
<td>Morgenthaler, et al. 2002</td>
<td>Five patients Mean age: 51.4.3 male All 5 patients had restless legs syndrome, 3 had obstructive sleep apnea All 5 patients had a negative history for sleepwalking</td>
<td>Zolpidem 10-20 mg once/d</td>
<td>All exhibited sleepwalking and SRED 4/5 had vague memory of the events. Events ceased in all patients with zolpidem discontinuation</td>
</tr>
<tr>
<td>Sattar et al. 2003</td>
<td>47, male, bipolar disorder Negative history for sleepwalking</td>
<td>Citalopram 40 mg once/d, valproic acid 250 mg twice/d, Zolpidem 5 mg at bedtime</td>
<td>Sleepwalking started when valproic acid was added to citalopram and zolpidem. He had no memory of the events. Events ceased when valproic acid was withdrawn and returned when valproic acid was restarted.</td>
</tr>
<tr>
<td>Sharma et al. 2005</td>
<td>19, male, schizoaffective disorder Negative history for sleepwalking</td>
<td>Zolpidem 10 mg at bedtime</td>
<td>Within a few days of initiation of zolpidem he started to sleepwalk and talk incoherently. He had no memory of the events. Events ceased with zolpidem discontinuation.</td>
</tr>
<tr>
<td>Najjar 2007</td>
<td>46, female, depression, obstructive sleep apnea on continuous positive airway pressure therapy Negative history for sleepwalking or parasomnias</td>
<td>Zolpidem extended-release form 6.25 mg once/d</td>
<td>Sleepwalking and SRED began immediately after initiation of zolpidem use and ceased immediately after it was discontinued.</td>
</tr>
<tr>
<td>Chiang et al. 2008</td>
<td>Two patients: Patient 1: 75, female Patient 2: 70, female Both patients had restless legs syndrome, obstructive sleep apnea, and used continuous positive airway pressure therapy Both patients had a negative history for sleepwalking or SRED</td>
<td>Both patients had sleepwalking and SRED on zolpidem extended release 12.5 mg once/d. Neither patient experienced sleepwalking or SRED on the immediate release form of zolpidem.</td>
<td>Both patients experienced sleepwalking and SRED immediately after initiation of extended release zolpidem use and ceased immediately after it was discontinued</td>
</tr>
<tr>
<td>Sansone et al. 2008</td>
<td>51, female,</td>
<td>Zolpidem 10 mg at bedtime</td>
<td>Arose at night to prepare a meal and eat it. She had no memory of the events. Events stopped with cessation of zolpidem.</td>
</tr>
</tbody>
</table>
Serotonin

• Mechanism of Action
  • Wide family of receptors
    • 5HT_{1-7}
    • Various subtypes
  • Varying effects
    • Emotion
    • Appetite
    • Sleep

• Role in Sleep
  • Regulation of Sleep-Wake Cycle
    • Inhibitory and excitatory effects
    • NREM vs. REM
  • Melatonin production

Serotonergic Medications

- **Mechanism of Action**
  - Antagonism of $5\text{HT}_{2A/C}$ receptors
- **Indication(s)**
  - Off-Label Use
- **Medication(s)**
  - Doxepin
    - Dosing: 3-6 mg**
  - Mirtazapine
    - Dosing: 7.5-15 mg**
  - Trazodone
    - Dosing: 50-100 mg**
  - *Seroquel*
    - Dosing: 25-50 mg QD**

Serotonergic Medications

- Side Effects
  - Somnolence
  - Vertigo
  - Appetite Changes**
  - GI Disturbances
  - Suicidality
  - Serotonin Syndrome

***FALL RISK***

Serotonergic Medications

Table 5. Bivariate and Multivariable Association Between Antidepressant Use and Recurrent Falls Stratified by History of Falls and/or Fracture (After Age 45 Years) at Baseline.

<table>
<thead>
<tr>
<th>Antidepressant Medication Use</th>
<th>History of Falls/Fracture (n = 1092)</th>
<th>No History of Falls/Fracture (n = 1856)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td>Any use</td>
<td>2.02 (1.51-2.69)</td>
<td>1.83 (1.28-2.63)</td>
</tr>
<tr>
<td>Long duration (≥2 years)</td>
<td>1.61 (1.09-2.39)</td>
<td>1.38 (0.82-2.30)</td>
</tr>
<tr>
<td>Short duration</td>
<td>1.85 (1.30-2.64)</td>
<td>1.77 (1.17-2.68)</td>
</tr>
<tr>
<td>SDD ≥2</td>
<td>1.39 (0.81-2.40)</td>
<td>1.06 (0.57-1.97)</td>
</tr>
<tr>
<td>SDD 1-2</td>
<td>1.80 (1.26-2.57)</td>
<td>1.99 (1.31-3.01)</td>
</tr>
<tr>
<td>SDD &lt;1</td>
<td>1.16 (0.41-3.31)</td>
<td>0.75 (0.18-3.05)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specific class use</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>2.12 (1.49-3.02)</td>
<td>1.92 (1.24-2.97)</td>
<td>2.21 (1.40-3.48)</td>
<td>1.11 (0.62-2.01)</td>
</tr>
<tr>
<td>TCA</td>
<td>1.86 (1.11-3.09)</td>
<td>1.47 (0.77-2.82)</td>
<td>1.25 (0.64-2.41)</td>
<td>0.86 (0.35-2.13)</td>
</tr>
<tr>
<td>Others</td>
<td>1.90 (0.90-4.01)</td>
<td>2.22 (0.99-4.94)</td>
<td>1.65 (0.80-3.40)</td>
<td>0.76 (0.27-2.12)</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; SDD, standardized daily dose; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

*Reference group is “No Use.”

*Controlling for variables forced into the model (ie, site, drugs that increase the risk of falls, self-reported depression, depressive symptoms per Center for Epidemiologic Studies Depression Scale–10, bodily pain, sleep problems, and anxiety symptoms) and those from forward selection procedures (ie, age, pulmonary disease, arthritis, urinary problems, cerebrovascular disease, diabetes, vision problems, hospitalization in previous 12 months, and private physician).

*Each antidepressant subclass was run as a separate model and controlled for antidepressant subclass use other than the subclass being evaluated.

*Others: trazodone, bupropion, venlafaxine, mirtazapine, phenelzine.
# Serotonergic Medications

<table>
<thead>
<tr>
<th>Sleep Stage</th>
<th>Effect on Sleep Architecture</th>
</tr>
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<tbody>
<tr>
<td>Stage 1</td>
<td>![downward arrow]</td>
</tr>
<tr>
<td>Stage 2</td>
<td>![circle]</td>
</tr>
<tr>
<td>Stage 3</td>
<td>![circle]</td>
</tr>
<tr>
<td>Stage 4</td>
<td>![circle]</td>
</tr>
<tr>
<td>REM</td>
<td>![upward arrow]</td>
</tr>
</tbody>
</table>

Histamine

• Mechanism of Action
  • Four Subtype Receptors
    • $H_1$: Sleep-Wake, Body Homeostasis
    • $H_2$: Gastric Acid Secretion
    • $H_3$: Histamine Regulation, Appetite
    • $H_4$: Immune Response

• Role in Sleep
  • Regulation of Sleep-Wake Cycle
    • Inhibitory effects of lead to sedation
    • Increase in NREM
    • Decrease REM

Anti-Histamines

• Mechanism of Action
  • Inverse agonists that stabilize the inactive conformation of $H_1$ receptors interfering with histamine
  • Poor receptor selectivity

• Indication(s)
  • OTC Temporary Sleep Aid
  • Off-Label Use

• Medication(s)
  • Diphenhydramine
  • Doxylamine
  • Hydroxyzine
  • Seroquel
    • Dosing: 25-50 mg QD**
Anti-Histamines

• Side Effects
  • Anticholinergic Properties
    • TSLUD
  • Daytime drowsiness
  • Vertigo
  • Sleep Disturbances
  • Dependence/Tolerance???

***FALL RISK***

## Anti-Histamines

<table>
<thead>
<tr>
<th>Sleep Stage</th>
<th>Effect on Sleep Architecture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>![Down Arrow]</td>
</tr>
<tr>
<td>Stage 2</td>
<td>![Up Arrow]</td>
</tr>
<tr>
<td>Stage 3</td>
<td>![Stop Symbol]</td>
</tr>
<tr>
<td>Stage 4</td>
<td>![Stop Symbol]</td>
</tr>
<tr>
<td>REM</td>
<td>![Down Arrow]</td>
</tr>
</tbody>
</table>

Melatonin

• **Mechanism of Action**
  • Secreted from the pineal gland and is the main regulator of sleep/darkness

• **Role in Sleep**
  • Regulation of Circadian Rhythms
  • Sleep-Wake Syndromes

Melatonin Receptor Agonists

- **Mechanism of Action**
  - Selective Melatonin Type-1 and Type-2 receptor agonist

- **Indication**
  - Insomnia
  - Circadian Rhythm Disorders

- **Medication(s)**
  - Ramelteon
  - Tasimelteon
  - Melatonin**

- **Side Effects**
  - Dizziness
  - Somnolence

## Melatonin Receptor Agonists

<table>
<thead>
<tr>
<th>Sleep Stage</th>
<th>Effect on Sleep Architecture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>![Arrow Down]</td>
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<tr>
<td>Stage 2</td>
<td>![Circle]</td>
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<tr>
<td>Stage 3</td>
<td>![Circle]</td>
</tr>
<tr>
<td>Stage 4</td>
<td>![Circle]</td>
</tr>
<tr>
<td>REM</td>
<td>![Arrow Up]</td>
</tr>
</tbody>
</table>

Hypocretin/Orexin

• Mechanism of Action
  • Peptide associated with arousal stability

• Role in Sleep
  • Conductor of neuromodulation network
  • Coordinator of sleep-wake cycles

Herring et al. Neurology 2012; 79:2265
Orexin Receptor Agonist

- **Mechanism of Action**
  - Selective antagonism of ORX1 and ORX2 receptors
- **Indication**
  - Insomnia
  - Narcolepsy
- **Medication(s)**
  - Suvorexant
- **Side Effects**
  - Somnolence

Herring et al. Neurology 2012; 79:2265
### Orexin Receptor Agonist

<table>
<thead>
<tr>
<th>Sleep Stage</th>
<th>Effect on Sleep Architecture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>✖</td>
</tr>
<tr>
<td>Stage 2</td>
<td>✖</td>
</tr>
<tr>
<td>Stage 3</td>
<td>✖</td>
</tr>
<tr>
<td>Stage 4</td>
<td>✖</td>
</tr>
<tr>
<td>REM</td>
<td>✅</td>
</tr>
</tbody>
</table>

Herring et al. Neurology 2012; 79:2265
Dopamine

• Mechanism of Action
  • Movement Control
  • Reward System
  • Sleep-wake Cycles

• Role in Sleep
  • REM modulation
  • Movement Disorders

Khanday et al. Dopamine in REM Sleep Regulation. 2016 Springer, Cham
Dopamine Agonists

- **Mechanism of Action**
  - Affinity for D2 receptors associated with rhythmic movement in caudate nucleus

- **Indication**
  - Restless Leg Syndrome

- **Medications**
  - Ropinrole

- **Side Effects**
  - Orthostatic Hypotension
  - Vertigo
  - Somnolence

Khanday et al. Dopamine in REM Sleep Regulation. 2016 Springer, Cham
Alternative Therapies

• L-Tryptophan
  • Precursor to serotonin
  • No improvement in sleep latency

• Valerian Root
  • Inhibits GABA uptake, adenosine/serotonin agonist
  • Minimal sleep latency effects
  • CYP 450, P-GP interactions

• Medicinal Marijuana
  • Mild Stimulant
  • Dose Variability
  • REM Suppression

Sleep Hygiene

GENERAL TIPS FOR HAVING HEALTHY SLEEP HYGIENE

- Go to bed and wake up at the same time every day (even on the weekends!)
- Avoid caffeine consumption (e.g., coffee, soft drinks, chocolate) starting in the late afternoon
- Expose yourself to bright light in the morning – sunlight helps the biological clock to reset itself each day
- Make sure your bedroom is conducive to sleep – it should be dark, quiet, comfortable, and cool
- Sleep on a comfortable mattress and pillow
- Don’t go to bed feeling hungry, but also don’t eat a heavy meal right before bed
- Develop a relaxing routine before bedtime – ideas include bathing, music, and reading
- Reserve your bedroom for sleeping only – keep cell phones, computers, televisions and video games out of your bedroom
- Exercise regularly during the day
- Don’t have pets in your bedroom

Sleep Disorders (DSM-V Categories)

• Sleep-Wake Disorders
  • Disrupted sleep
  • Altered daytime function

• Circadian Rhythm Disorders
  • Altered internal clock

• Parasomnias
  • Abnormal movements/behaviors
Circadian Rhythm Disorders

- Non 24-hour Disorder
- Shift Worker Disorders
  - Jet-Lag
  - Overnight Schedules
- Sleep Phase Disorders
  - Advanced
  - Delayed

Parasomnias

- Chemical Induced Disorders
- NREM/REM Sleep Arousal Disorders
  - Sleepwalking
  - Sleep Terror
  - Sleep Paralysis
- Restless Leg Syndrome
- Unspecified Sleep Disorders

Sleep-Wake Disorders

- Hypersomnolence Disorders
  - Idiopathic
- Insomnia
  - Transient
  - Acute
  - Chronic
- Narcolepsy
  - Orexin Deficiency
  - Secondary to another medical condition
- Sleep-Related Breathing Disorders
  - Obstructive Sleep Apnea

American Academy of Sleep Medicine Guidelines: Circadian Rhythm Sleep-Wake Disorders

Table 5—Overview of AASM recommendation status for Intrinsic CRSD treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ASWPD</th>
<th>DSWPD</th>
<th>N24SWD</th>
<th>ISWRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribed sleep-wake scheduling</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
</tr>
<tr>
<td>Timed physical activity/exercise</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
</tr>
<tr>
<td>Strategic avoidance of light</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
</tr>
<tr>
<td>Light therapy</td>
<td>5.1.4a WEAK FOR (adults)</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>5.4.4a WEAK FOR (elderly with dementia)</td>
</tr>
<tr>
<td>Sleep-promoting medications</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>5.4.5a STRONG AGAINST (elderly with dementia)</td>
</tr>
<tr>
<td>Timed oral administration of melatonin or agonists</td>
<td>No Recommendation</td>
<td>5.2.6.1a WEAK FOR (adults with and without depression)</td>
<td>5.3.6.1a WEAK FOR (blind adults)</td>
<td>5.4.6.1a WEAK AGAINST (elderly with dementia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.2.6.2.1a WEAK FOR (children/adolescents without comorbidities)</td>
<td>5.4.6.2a WEAK FOR (children/adolescents with neurologic disorders)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.2.6.2.2a WEAK FOR (children/adolescents with psychiatric comorbidities)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wakefulness-promoting medications</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
</tr>
<tr>
<td>Other somatic interventions</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
</tr>
<tr>
<td>Combination treatments</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>No Recommendation</td>
<td>5.4.9.1a WEAK AGAINST (combination treatment of light and melatonin for demented, elderly patients)</td>
</tr>
</tbody>
</table>

American Academy of Sleep Medicine Guidelines: Circadian Rhythm Sleep-Wake Disorders

### Figure 2
Meta-analysis of data for PSG determined TST in response to melatonin treatment of adult patients with DSWPD and comorbid depression.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Melatonin Tx Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kayumov, 2001</td>
<td>404.3</td>
<td>60.4</td>
<td>20</td>
<td>382</td>
<td>55.55</td>
<td>20</td>
<td>36.2%</td>
<td>22.30 [-13.66, 58.26]</td>
<td></td>
</tr>
<tr>
<td>Rahman, 2010</td>
<td>436</td>
<td>17.8</td>
<td>8</td>
<td>383.7</td>
<td>19.7</td>
<td>8</td>
<td>63.8%</td>
<td>52.30 [33.90, 70.70]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>28</strong></td>
<td></td>
<td><strong>28</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>41.44 [13.19, 69.70]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 237.59; Chi² = 2.12, df = 1 (P = 0.15); I² = 53%
Test for overall effect: Z = 2.87 (P = 0.004)

### Figure 3
Meta-analysis of data for PSG determined ISL in response to melatonin treatment of adult patients with DSWPD and comorbid depression.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Melatonin Tx Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kayumov, 2001</td>
<td>20.2</td>
<td>17.7</td>
<td>20</td>
<td>58.9</td>
<td>30.3</td>
<td>20</td>
<td>34.8%</td>
<td>-38.70 [-54.08, -23.32]</td>
<td></td>
</tr>
<tr>
<td>Rahman, 2010</td>
<td>15.3</td>
<td>5.4</td>
<td>8</td>
<td>61.4</td>
<td>15.3</td>
<td>8</td>
<td>65.2%</td>
<td>-46.10 [-57.34, -34.86]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>28</strong></td>
<td></td>
<td><strong>28</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>-43.52 [-52.60, -34.45]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 9.40 (P < 0.00001)

American Academy of Sleep Medicine Guidelines: Circadian Rhythm Sleep-Wake Disorders

**Figure 6**—Meta-analysis of evidence for entrainment as a result of melatonin treatment of blind adult patients with N24SWD.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Melatonin</th>
<th>Control</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hack, 2003</td>
<td>6/9</td>
<td>0/9</td>
<td>35.29 [1.55, 804.41]</td>
</tr>
<tr>
<td>Lockley, 2000</td>
<td>1/3</td>
<td>0/3</td>
<td>4.20 [0.12, 151.97]</td>
</tr>
<tr>
<td>Sack, 2000</td>
<td>5/6</td>
<td>0/6</td>
<td>47.67 [1.60, 1422.69]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>18/18</td>
<td>100.0%</td>
<td>21.18 [3.22, 139.17]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 1.10$, df = 2 (P = 0.58); $I^2 = 0\%$

Test for overall effect: $Z = 3.18$ (P = 0.001)

Insomnia (DSM-V Criteria)

• Dissatisfaction with sleep quantity or quality associated with ≥ 1 of the following:
  • Sleep Initiation
  • Sleep Latency
  • Sleep Maintenance

• Clinically Significant
  • Distress
  • Impairment in daily function
  • Behavioral changes

Insomnia Variability

- **Transient**
  - Symptoms for \( \leq 1 \) week

- **Acute**
  - Symptoms for \( >1 \) week up to 3 months*

- **Chronic**
  - Symptoms for \( \geq 3 \) months*

*Disturbances occurring \( \geq 3 \) nights per week

## Recommended for Treating Sleep Onset Insomnia

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Sleep latency: Mean reduction was 14 min greater, compared to placebo (95% CI: 3 to 24 min reduction); Quality of sleep*: Moderate-to-Large improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 2, “Harms”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eszopiclone</td>
<td>This recommendation is based on trials of 2 mg and 3 mg doses of eszopiclone.</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>Sleep latency: Mean reduction was 9 min greater, compared to placebo (95% CI: 6 to 12 min reduction); Quality of sleep*: No improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 7, “Harms”</td>
</tr>
<tr>
<td></td>
<td>This recommendation is based on trials of 8 mg doses of ramelteon.</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Sleep latency: Mean reduction was 37 min greater, compared to placebo (95% CI: 21 to 53 min reduction); Quality of sleep*: Small improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 6, “Harms”</td>
</tr>
<tr>
<td></td>
<td>This recommendation is based on trials of 15 mg doses of temazepam.</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Sleep latency*: Mean reduction was 9 min greater, compared to placebo (95% CI: 4 to 22 min reduction); Quality of sleep*: Moderate improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 5, “Harms”</td>
</tr>
<tr>
<td></td>
<td>This recommendation is based on trials of 0.25 mg doses of triazolam.</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Sleep latency: Mean reduction was 10 min greater, compared to placebo (95% CI: 0 to 19 min reduction); Quality of sleep*: No improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 3, “Harms”</td>
</tr>
<tr>
<td></td>
<td>This recommendation is based on trials of 5 mg and 10 mg doses of zaleplon.</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Sleep latency: Mean reduction was 5–12 min greater, compared to placebo (95% CI: 0 to 19 min reduction); Quality of sleep*: Moderate improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 4, “Harms”</td>
</tr>
<tr>
<td></td>
<td>This recommendation is based on trials of 10 mg doses of zolpidem.</td>
</tr>
</tbody>
</table>
### American Academy of Sleep Medicine Guidelines: Chronic Insomnia in Adults

**Recommended for Treating Sleep Maintenance Insomnia**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total sleep time: Mean improvement</th>
<th>Wake after sleep onset:</th>
<th>Quality of sleep*</th>
<th>Side effects:</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin</td>
<td>26–32 min longer, compared to placebo (95% CI: 18 to 40 min improvement)</td>
<td>Mean reduction was 22–23 min greater, compared to placebo (95% CI: 14 to 30 min reduction)</td>
<td>Small-to-moderate* improvement in quality of sleep, compared to placebo</td>
<td>See Recommendation 8, &quot;Harms&quot;</td>
<td>Sateia et al. Jour. Clin. Sleep Med. 2017;13 (2):307-348</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>28–57 min longer, compared to placebo (95% CI: 18 to 76 min improvement)</td>
<td>Mean reduction was 10–14 min greater, compared to placebo (95% CI: 2 to 18 min reduction)</td>
<td>Moderate-to-Large* improvement in quality of sleep, compared to placebo</td>
<td>See Recommendation 2, &quot;Harms&quot;</td>
<td></td>
</tr>
<tr>
<td>Temazepam</td>
<td>99 min longer, compared to placebo (95% CI: 63 to 135 min improvement)</td>
<td>Not reported</td>
<td>Small* improvement in quality of sleep, compared to placebo</td>
<td>See Recommendation 6, &quot;Harms&quot;</td>
<td></td>
</tr>
<tr>
<td>Suvorexant</td>
<td>10 min longer, compared to placebo (95% CI: 2 to 19 min improvement)</td>
<td>Mean reduction was 16–28 min greater, compared to placebo (95% CI: 7 to 43 min reduction)</td>
<td>Not reported</td>
<td>See Recommendation 1, &quot;Harms&quot;</td>
<td></td>
</tr>
<tr>
<td>Zolpidem</td>
<td>29 min longer, compared to placebo (95% CI: 11 to 47 min improvement)</td>
<td>Mean reduction was 25 min greater, compared to placebo (95% CI: 18 to 33 min reduction)</td>
<td>Moderate* improvement in quality of sleep, compared to placebo</td>
<td>See Recommendation 4, &quot;Harms&quot;</td>
<td></td>
</tr>
</tbody>
</table>
American Academy of Sleep Medicine Guidelines: Chronic Insomnia in Adults

- **Strength of Recommendations:** WEAK
  - Head to Head Studies
- **Limited information on adverse effects**
  - Limited evaluation
- **Co-morbid conditions not evaluated**
  - Anxiety/Depression
  - Psychosis
- **American Geriatric Society BEER’s Criteria**
  - Recommendation to avoid use
    - First-Generation Antihistamines
    - Anti-Psychotics
    - Benzodiazepines
  - Recommendation to caution and avoid chronic use
    - Z-Drugs

Clinical Analysis: Efficacy

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Sleep Latency (Avg. Decrease in Minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>9-37</td>
</tr>
<tr>
<td>Z-Drugs</td>
<td>5-14</td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>8-10</td>
</tr>
<tr>
<td>Orexin Agonists</td>
<td>2-10</td>
</tr>
<tr>
<td>Anti-psychotics</td>
<td>9</td>
</tr>
<tr>
<td>Melatonin</td>
<td>9</td>
</tr>
<tr>
<td>Melatonin Agonists</td>
<td>9</td>
</tr>
<tr>
<td>Anti-histamines</td>
<td>8</td>
</tr>
</tbody>
</table>

Clinical Analysis: Efficacy

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Total Sleep Time (Avg. Increase in Minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>99</td>
</tr>
<tr>
<td>Z-Drugs</td>
<td>29-57</td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>26-32</td>
</tr>
<tr>
<td>Anti-psychotics</td>
<td>24</td>
</tr>
<tr>
<td>Melatonin</td>
<td>13</td>
</tr>
<tr>
<td>Anti-histamines</td>
<td>12</td>
</tr>
<tr>
<td>Melatonin Agonists</td>
<td>2-12</td>
</tr>
<tr>
<td>Orexin Agonists</td>
<td>10</td>
</tr>
</tbody>
</table>

## Clinical Analysis: Sleep Quality

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Quality of Sleep</th>
<th>Sleep Architecture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-depressants</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Melatonin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Melatonin Agonists</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anti-psychotics</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Z-Drugs</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Orexin Agonists</td>
<td>N/A</td>
<td>+</td>
</tr>
<tr>
<td>Anti-histamines</td>
<td>N/A</td>
<td>-</td>
</tr>
</tbody>
</table>

## Clinical Analysis: Safety

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Addiction/Abuse Potential</th>
<th>Beer’s Criteria</th>
<th>Daytime Sedation</th>
<th>Fall Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Melatonin Agonists</td>
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<tr>
<td>Orexin Agonists</td>
<td>+</td>
<td>-</td>
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<td>--</td>
</tr>
<tr>
<td>Anti-depressants</td>
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<td>Anti-psychotics</td>
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<tr>
<td>Anti-histamines</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Benzodiazepines</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Z-Drugs</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Discussion

• Evaluate your patient
  • Circadian Rhythm vs. Insomnia
  • Transient vs. Chronic
  • Risk Factors

• Concerns of current guidelines
  • Elderly Patients
  • Length of treatment

• Understand your treatment options
  • Safety vs. Efficacy
A Review of Sleep Disorders in Cancer Patients:
Finding the “Dream” Treatment

Jordan Pleskow, PharmD
Roswell Park Cancer Institute
Oncology Symposium
11/11/17