Sleep Disturbances in Palliative Care

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Conflict of Interest

• I have no relevant financial conflicts of interest and nothing to disclose for this educational activity
Goals

• Outline different types of sleep disorders and their prevalence in palliative care patients
• Describe the effects of specific chronic medical conditions on sleep
• Explore the sleep disturbances of caregivers
• Introduce treatment options for common sleep disorders
Sleep Disorders

- Insomnia
- Hypersomnia
- Sleep Disordered Breathing
- Restless Legs
- Parasomnias
  - Periodic Limb Movements of Sleep
  - REM Behavioral Disorder
Predictive factors

- Poor Karnofsky score
- Cancer type (Breast, gastrointestinal, head and neck, lung, and prostate)
- Lower level of education
- Younger age
- Hormone therapy, opioids, corticosteroids
- Comorbid anxiety and depression

Effect of Chronic Pain on Sleep

• 50-90% report poor sleep quality¹
• Difficulty falling/staying asleep, lack of restful sleep, daytime somnolence
• Disruption in sleep architecture²
  – Decreased REM and deep sleep
• Sleep deprivation can increase pain³

Effects of Opioids on Sleep

- Can cause sleep disturbance even in absence of pain
- Disruption in sleep architecture
  - Decreased REM sleep
  - Inconsistent effect on deep sleep
- Sleep disordered breathing
  - Increased obstructive and central events
- Poor sleep leads to increased opioid intake the following day

## Effect of Antidepressants on Sleep

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Sleep continuity</th>
<th>SWS</th>
<th>REM latency</th>
<th>REM sleep</th>
<th>Mechanism of action related to effect on sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedative TCA</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>antihistaminergic effect, inhibition of serotonin, and norepinephrine reuptake</td>
</tr>
<tr>
<td>(e.g., amitriptyline, doxepin, trimipramine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>inhibition of serotonin and norepinephrine reuptake</td>
</tr>
<tr>
<td>Activating TCA</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>inhibition of monoamine oxidase enzyme</td>
</tr>
<tr>
<td>(e.g., imipramine, desipramine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>selective inhibition of serotonin reuptake</td>
</tr>
<tr>
<td>MAOI</td>
<td>↓/0</td>
<td>?</td>
<td>↑</td>
<td>↓</td>
<td>inhibition of serotonin and norepinephrine reuptake</td>
</tr>
<tr>
<td>(e.g., tranylcypromine, moclobemide)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>selective inhibition of serotonin reuptake</td>
</tr>
<tr>
<td>SSRI</td>
<td>↓/0</td>
<td>0/↑</td>
<td>↑</td>
<td>↓</td>
<td>inhibition of norepinephrine and dopamine reuptake</td>
</tr>
<tr>
<td>(e.g., fluoxetine, escitalopram, paroxetine, sertraline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>antihistaminergic effect, antagonism at serotonergic 5-HT2A receptors</td>
</tr>
<tr>
<td>SNRI and NRI</td>
<td>↓</td>
<td>0/↑</td>
<td>↑</td>
<td>↓</td>
<td>inhibition of norepinephrine and dopamine reuptake</td>
</tr>
<tr>
<td>(e.g., venlafaxine, duloxetine, reboxetine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>antihistaminergic effect, antagonism at serotonergic 5-HT2A receptors</td>
</tr>
<tr>
<td>Bupropion</td>
<td>0/↓</td>
<td>0/↑</td>
<td>0/↓</td>
<td>0/↑</td>
<td>inhibition of norepinephrine and dopamine reuptake</td>
</tr>
<tr>
<td>Sedative antidepressants</td>
<td>↑</td>
<td>↑</td>
<td>0</td>
<td>0</td>
<td>antihistaminergic effect, antagonism at serotonergic 5-HT2A receptors</td>
</tr>
<tr>
<td>(e.g., mirtazapine, trazodone)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>inhibition of norepinephrine and dopamine reuptake</td>
</tr>
</tbody>
</table>

Cancer Patients

- Sleep disturbance due to
  - Direct effect of neoplasm
  - Cancer surgery
  - Chemotherapy
  - Radiation
  - Pain / other symptoms

Prevalence of Insomnia

- Large observational study of cancer patients in palliative care settings (n=820)
- >60% with major sleep disturbances (insomnia)

**Cancer and Insomnia**

- 823 patients
  - 597 female
  - Mean age 58
  - Prospective study using patient questionnaires

Cancer and Insomnia

Cancer and Insomnia

Sleep Disordered Breathing

• High prevalence of obstructive and central sleep apnea

• Small study of cancer patients receiving palliative care (n=28)
  – 61% with increased obstructive events
  – 32% with increased central events

• Most subjects with daily use of opioids

COPD and Sleep
COPD and Sleep

- Increased sleep disturbances due to
  - Hypoxia
  - Hypercapnia
  - Dyspnea
  - Chronic cough
  - Anxiety / Depression

Factors Contributing to Hypoxemia during Sleep in COPD

- Increased upper airway resistance
- Reduced tidal volume and minute ventilation
- Hyperinflation, flattening of the diaphragm
- Diminished hypoxic and hypercapnic drive
- Diminished tone and activity of accessory muscles of respiration
- Reduced functional residual capacity (FRC)
COPD and Insomnia

- Cross-sectional study
- 192 pts with COPD
- Questionnaire data in insomnia

Figure 2: Frequency of insomnia according to CAT scores.
Abbreviations: CAT, COPD assessment test; ISI, insomnia severity index.
Sleep Apnea in CHF

• Prevalent
  – 72.8% with moderate to severe
• Predominantly obstructive events
• Frequently asymptomatic
• Sometimes without typical risk factors

Cardiac Event Rates: Cardiac Death and CHF Exacerbation

- Insomnia is an independent predictor of cardiac events in HF pts
- HF pts with insomnia have activated renin-angiotensin-aldosterone system and lower exercise capacity
Chronic Liver Disease and Sleep
Cirrhosis and Sleep

• Sleep Disorders
  – Circadian Rhythm Disorders
  – Restless Legs Syndrome
  – Insomnia
  – Sleep disordered breathing
    • Bidirectional relationship

De Cruz et al. Seminars in Resp and Crit Care Med. 2012;33:26-35.
Cirrhosis and Sleep

- High prevalence of
  - Insomnia
  - Daytime sleepiness
  - Daytime napping
  - Nocturnal awakenings

- Liver transplantation not shown to improve sleep symptoms

Cirrhosis and Sleep Architecture

Alzheimer’s Disease and Sleep
Sleep Disturbances in AD

- Prevalence of 45%\textsuperscript{1}
- Early occurrence in AD
- Correlates with severity of dementia
- Risk factor for early institutionalization\textsuperscript{2}

Sleep Disorders in AD

- Sleep–wake cycle alteration
  - Sundowning
- Sleep Disordered Breathing
  - Increased risk from neurodegeneration

Impairment in memory consolidation

Alzheimer’s Disease

Sleep Disruptions

Degeneration of neural pathways
Somatic/Psychiatric co-morbidities

Parkinson's Disease and Sleep
Parkinson’s Disease

• Sleep disturbances are common (up to 98%)\textsuperscript{1}
• Sleep disturbance contributes to poor patient quality of life\textsuperscript{1}
• Sleep disturbances often worsen with disease progression\textsuperscript{2}

Types of Sleep Disorders

- Insomnia
- REM Behavior Disorder (RBD)  
  – Can be a prodrome
- Obstructive Sleep Apnea (OSA)
- Periodic Limb Movement Disorder (PLMD)
- Restless Legs Syndrome (RLS)
- Nocturia

Kutscher et al. *Curr Treat Options Neurol.* 2014;16(8):304
Sleep Disturbance in Parkinson’s Disease

- Motor Symptoms
- Autonomic Dysfunction
- Circadian Disorder
- Sleep Disorders
- Iatrogenic Insult
- Degeneration of Sleep/Wake Centers

ALS

and

Sleep
Sleep Disorders in ALS

• Sleep Disordered Breathing
  – Weakness of respiratory muscles
  – Decreased central respiratory drive

• Restless Legs
  – Prevalence of 13.8% in cohort of 69 pts

Hypoventilation in ALS

Central Dysregulation

Degeneration

Sleep Disorders in ALS

• Insomnia
  – Anxiety
  – Immobility, cramps
  – Excess saliva, cough\(^1\)

• Circadian Disorders
  – Thalamic and Hypothalamic involvement\(^2\)

Treatment Options to Improve Sleep in ALS

- **Riluzole**
  - Excitatory (Glutamate) regulator
  - Survival benefit
  - Increased sleep duration

- **Non-invasive Ventilation**

- **Secretion management**

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What about the caregiver?
Caregivers of CHF Patients

• Over 90% report sleep disturbances
  – Difficulty with sleep onset
  – Disrupted sleep
  – Daytime sleepiness

• Negative impact on quality of life
• Negative impact on patient outcomes

Caregivers of CHF Patients

- Poor predictors of caregiver well-being
  - Female gender
  - Closer relationship
    - Spouse
  - Younger age
- Patient symptoms / Functional class (NYHA) not predictive of caregiver well-being

Sleep among bereaved caregivers of patients admitted to hospice: a 1-year longitudinal pilot study

Anners Lerdal,1,2 Kari Slåtten,3 Elisabeth Saghaug,2 Ellen Karine Grov,4,5 Are Peder Normann,2 Kathryn A Lee,6 Bjørn Bjørvatn,7,8 Caryl L Gay2,6
Age

![Graph showing the nightly sleep duration (hours) for caregivers of different age groups (≤65 and ≥65) over time (Hospice, 6-month and 12-month follow-up).]
Relationship
A quick word about treatment...
Sleep Apnea

- Weight loss
- PAP therapy
- Dental devices
- Positional therapy
- Nasal preclusion
Insomnia

- Cognitive Behavioral Therapy for Insomnia (CBT-I)
- Pharmacologic therapy
## Cognitive Behavioral Treatments

<table>
<thead>
<tr>
<th>Technique</th>
<th>Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep hygiene</td>
<td>Promote habits that help sleep; provide rationale for subsequent instructions.</td>
</tr>
<tr>
<td>Stimulus control</td>
<td>Strengthen bed &amp; bedroom as sleep stimulus</td>
</tr>
<tr>
<td>Sleep restriction</td>
<td>Restrict time in bed to improve sleep depth &amp; consolidation</td>
</tr>
<tr>
<td>Relaxation training</td>
<td>Reduce arousal &amp; decrease anxiety</td>
</tr>
<tr>
<td>Cognitive therapy</td>
<td>Address thoughts and beliefs that interfere with sleep.</td>
</tr>
</tbody>
</table>

AMERICAN ACADEMY OF SLEEP MEDICINE
CBT-I in Cancer

Insomnia Severity

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savard et al. 2005 [29]</td>
<td>0.74 (0.28, 1.20)</td>
<td>12.50</td>
</tr>
<tr>
<td>Epstein &amp; Dirksen 2007 [40]</td>
<td>0.56 (0.09, 1.03)</td>
<td>11.66</td>
</tr>
<tr>
<td>Fiorentino et al. 2009 [45]</td>
<td>0.63 (-0.35, 1.61)</td>
<td>2.71</td>
</tr>
<tr>
<td>Ritterband et al. 2012 [43]</td>
<td>1.37 (0.54, 2.20)</td>
<td>3.78</td>
</tr>
<tr>
<td>Garland et al. 2014 [46]</td>
<td>0.90 (0.50, 1.29)</td>
<td>16.66</td>
</tr>
<tr>
<td>Savard et al. 2014a [44]</td>
<td>0.97 (0.63, 1.31)</td>
<td>22.02</td>
</tr>
<tr>
<td>Savard et al. 2014b [44]</td>
<td>0.61 (0.26, 0.96)</td>
<td>20.84</td>
</tr>
<tr>
<td>Matthews et al. 2014 [42]</td>
<td>0.49 (-0.02, 1.01)</td>
<td>9.83</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.486)</td>
<td>0.76 (0.60, 0.93)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

CBT-I in Cancer

Sleep Efficiency

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savard et al. 2005</td>
<td>0.74 (0.28, 1.19)</td>
<td>10.65</td>
</tr>
<tr>
<td>Epstein &amp; Dirksen</td>
<td>0.60 (0.12, 1.07)</td>
<td>9.87</td>
</tr>
<tr>
<td>Espie et al. 2008</td>
<td>0.61 (0.22, 1.01)</td>
<td>14.31</td>
</tr>
<tr>
<td>Ritterband et al.</td>
<td>0.49 (-0.29, 1.27)</td>
<td>3.62</td>
</tr>
<tr>
<td>Garland et al. 2014</td>
<td>0.72 (0.34, 1.11)</td>
<td>14.64</td>
</tr>
<tr>
<td>Savard et al. 2014a</td>
<td>0.49 (0.16, 0.82)</td>
<td>20.31</td>
</tr>
<tr>
<td>Savard et al. 2014b</td>
<td>0.31 (-0.04, 0.66)</td>
<td>18.05</td>
</tr>
<tr>
<td>Matthews et al. 2014</td>
<td>0.28 (-0.23, 0.79)</td>
<td>8.54</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.729)</td>
<td>0.53 (0.38, 0.68)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Medications

- Effective short term
- Lose effectiveness over long term
- Side effects
- Dependence
Summary

• Patients with chronic illnesses are at increased risk for various sleep disorders including Insomnia, Sleep Disordered Breathing, Circardian Disorders, Restless Legs, and parasomnias

• Chronic pain and medications can exacerbate these problems
Summary

- Caregivers of patients in palliative care are also at increased risk for insomnia and disrupted sleep.
- Female gender, closer relationship, and younger age are poor predictive factors.
- Variety of treatment options available for sleep disorders in palliative care patients.
Thank you

“Take this. It’ll help you sleep.”