Chronic Pain and Impairment of Sleep: A Case-based Approach
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Disclosure Statement
I, Sarah Melton, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation AND DO anticipate discussing the unapproved/investigative use of a commercial product/device during this activity or presentation (i.e., medications used off-label for insomnia)

Learning Objectives
1. Evaluate sleep complaints in patients with chronic pain
2. Describe the effects of chronic pain on sleep architecture
3. Discuss the consequences of sleep disturbances in patients with chronic pain
4. Formulate a treatment plan including behavioral and pharmacologic approaches to improve sleep in patients with co-existing chronic pain
Which of the following best describes you?
1. Physician
2. Nurse practitioner
3. Physician assistant
4. Pharmacist
5. Nurse
6. Other

What percentage of your patients with chronic pain complain of sleep dysfunction?
1. 10%
2. 25%
3. 50%
4. 90%

A 57-year-old male presents with chronic pain treated with opioids, an antidepressant, and physical therapy. He complains of daytime fatigue and very poor sleep quality. His pain level is a 7/10 today and states he only slept 2 hours the night before. Which of the following would you address first?
1. Pain
2. Sleep
Sleep and Pain

- National Sleep Foundation
  - Pain is the leading cause of insomnia
  - 20% of Americans say pain interrupts their sleep a few nights a week
- Clinically significant insomnia is reported by 53% of chronic pain patients
- Receiving either less than 6 hours of sleep or more than 9 hours of sleep is associated with increase in next-day pain frequency
- Sleeping in excess of 11 hours 137% increase in pain

http://www.sleepfoundation.org/article/ask-the-expert/pain-and-sleep

Which of the following is the most commonly reported pain-related sleep complaint?

1. Delay in sleep onset
2. Frequent nocturnal awakening
3. Poor sleep quality
4. Daytime fatigue

What is Sleep Dysfunction?

• Any reduction in sleep efficiency or architecture
  – Delay in sleep onset
  – Frequent sleep awakening
  – Poor sleep quality
  – Low restorative effectiveness

Terminology

• Sleep onset latency
  – Time to fall asleep
  – Normal is less than 20 minutes
• Sleep efficiency
  – Number of minutes of sleep/number of minutes in bed
  – Normal is 85-90% or greater
• Wake after sleep onset
  – Amount of time spent awake after sleep has been initiated and before final awakening
Pain and Sleep

- Sleep disturbances
  - Modify the sensitivity to nociceptive stimuli
  - Contributes to lowering pain threshold
- Rebound sleep after sleep deprivation
  - Produces an analgesic effect
- Intimate relationship between pain and sleep loss

Interactions Between Pain and Sleep Disturbances
Case I

A 48-year-old coal miner presents with complaints of insomnia. It takes him over an hour to go to sleep and he wakes up frequently during the night secondary to his back pain. Current pain level today is 6/10. Current medications include hydrocodone/acetaminophen 7.5/325 mg po every 12 hours and cyclobenzaprine 10 mg BID prn muscle spasms.

How do you assess his sleep complaints?

Assessment of Sleep
Subjective Assessments

• Self-report sleep diary
  – Kept daily to document key components
    • Time retiring to bed
    • Time awakening
    • How long to go to sleep
    • Total number of hours slept
    • Medications taken
    • Caffeine intake
    • Subjective quality of sleep

Self-Report Questionnaires

• Insomnia Severity Index
  – Self-administered; 7 questions
  – Designed to assess the nature, severity, and impact of insomnia and monitor treatment response in adults

• Stanford Sleepiness Scale
  – Self-administered; 8-item
  – Used following sleep deprivation
  – Every 15 minutes to evaluate subjective alertness

• Epworth Sleepiness Scale
  – Self-administered, 8-item
  – Subjective sleepiness during preceding month

• Pittsburg Sleep Quality Index
  – Input from patient and sleep partner
  – Sleep habits over the past month
Objective Assessment
Polysonmography

- Electroencephalogram
- Electrooculogram
- Electromyogram
- Respiratory variables
- Snoring
- Fixed or portable

Discussion

- What is the most challenging situation you encounter in practice when treating a patient with chronic pain and sleep dysfunction?

Sleep Studies in Painful Conditions

<table>
<thead>
<tr>
<th>Painful Condition</th>
<th>Design</th>
<th>Polysomnographic Findings</th>
<th>Author, year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibromyalgia</td>
<td>Parallel groups, 20 patients vs. 10 healthy controls</td>
<td>Fragmented sleep with increased arousals, low sleep efficiency</td>
<td>Jennum et al.</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Parallel groups, 12 patients vs. 15 healthy controls</td>
<td>Decreased REM sleep, increased stage 1 sleep</td>
<td>Anck et al.</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Parallel groups, 19 patients vs. 10 healthy controls</td>
<td>Fragmented sleep with increased arousals, increased REM sleep efficiency, increased periodic leg movements, increased NREM alpha-EEG activity, no correlation between disease activity and sleep disturbances</td>
<td>Hirsch et al.</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Parallel groups, 41 patients vs. 10 healthy controls</td>
<td>Increased periodic leg movements, Increased NREM alpha-EEG activity</td>
<td>Drewes et al.</td>
</tr>
</tbody>
</table>
Sleep Architecture Changes in Patients with Chronic Pain

1. Lower sleep efficiency
2. Longer percentage of sleep in stage 1; less in stages 3 and 4
3. Numerous sleep stage shifts (3 and 4 toward stages 2 or 1)
4. Fragmentation of sleep continuity assessed by an increase in number of microarousals, awakenings, respiratory disturbances, and movement intrusions
5. Absence of reduction in heart rate variability in sleep, suggesting cardiac sympathetic overactivation during sleep
6. Alpha EEG intrusions in stages 3 and 4 sleep with or without elevated arousal (cyclic alternating pattern)


When encountering a patient with moderate chronic pain and sleep dysfunction, which of the following type of medication are you most likely to try first?

1. Opioid
2. Muscle relaxant
3. Benzodiazepine
4. Sedative like zolpidem
5. Antidepressant
6. Anticonvulsant like gabapentin

Sleep Disturbances from Analgesics

- Acetaminophen
  - No alteration of sleep architecture
- Aspirin and NSAIDS
  - Increase sleep latency
  - Increase awakenings
  - Decreased slow wave sleep
- Opioids
  - Decrease slow wave sleep
  - Decrease REM sleep
  - Increase nocturnal wake time
  - Induces/worsens sleep apnea
- Effects are heterogeneous and depends on formulation, duration of action, dosing time, and acute/chronic ingestion
Sleep Disturbances from Adjuvant Analgesics

- Tricyclic antidepressants
  - Increase slow wave sleep
  - Markedly decrease REM sleep
  - Decrease nocturnal awakenings
  - Effects begin with start of therapy
- Selective serotonin reuptake inhibitors
  - Increase sleep latency
  - Delay onset of REM (fluoxetine, paroxetine, sertraline)
  - Suppression of REM sleep
  - Increased nocturnal awakenings
  - Decrease slow wave sleep


Carbamazepine

- Increases stage 1 and 2 NREM sleep
- Depresses REM sleep
- Marked reduction in sleep latency


Gabapentin

- Increase in sleep stages 3 and 4
- Fewer nocturnal awakenings
- Improves sleep efficiency
- Improved sleep quality per patient
- Effective for restless legs
- Extended-release 1800 mg decreased pain and improved sleep in postherpetic neuralgia

**Tiagabine**

- GABA reuptake inhibitor
- 3-month, open-label trial of 91 patients with chronic pain
- Randomized to receive tiagabine (up to 24 mg/day) or gabapentin (2400 mg/day)
- Tiagabine and gabapentin reduced pain intensity and improved sleep quality at 3 months ($p < 0.01$)
- Improvements in sleep quality greater with tiagabine vs. gabapentin


**Tiagabine**

- Dose-response effects of tiagabine on sleep in adults with primary insomnia
- Randomized, double-blinded, parallel-group
- Tiagabine 4, 6, 8, 10 mg or placebo
- Increase in stage 3 and 4 sleep in 6, 8, 10 mg doses ($p < 0.01$)
- Stage 1 sleep showed greater decrease for all doses compared with placebo ($p < 0.01$)
- Psychomotor performance and daytime function wose with 10 mg tiagabine
- No changes in wake after sleep onset, latency to persistent sleep or total sleep time


**Pregabalin**

- In patients with fibromyalgia
  - Starting dose of 75 mg twice daily, with last dose 1 hour before bed
    - Increased to 150 mg twice daily on day 4
    - If tolerated, dose increased to 225 mg twice daily
    - Target dose 300-450 mg/day
  - Reduction in polysomnographic sleep efficiency
  - Improvement in pain score
  - ADRS of dizziness, somnolence, headache

Pregabalin

- In patients with diabetic peripheral neuropathy or postherpetic neuralgia
  - Review of 9 clinical trials
    - 2399 patients
    - Dose of pregabalin 75-600 mg/day
    - Some trials allowed benzodiazepines
    - No studies reported objective sleep measures
  - Pregabalin 150-600 mg/day significantly reduced pain and improved pain-related sleep disturbance

Others

- Trazodone
  - Decreases sleep latency
  - Increases slow wave sleep
- Quetiapine
  - No alteration in sleep efficiency
  - No change in sleep continuity
  - Suppression of REM
  - Increase in non-REM sleep, especially stage 2

Benzodiazepines

- Hasten onset of sleep
- Decrease nocturnal awakenings
- Increase total sleep time

**BUT**

- CHANGES IN SLEEP ARCHITECTURE
  - Light sleep (stages 1 and 2) is prolonged
  - Duration of deep slow wave sleep is reduced
  - REM is reduced
- 86% of pain patients taking benzodiazepines continue to report problems sleeping
Sodium Oxybate (SXB)

- Acts as a neuromodulator/neurotransmitter to affect neuronal activity of other neurotransmitters and stimulates the release of growth hormone
- Rapidly absorbed and has a plasma half-life of 30 - 60 min, necessitating twice-nightly dosing
- Approved by FDA in 2002 for treatment of narcolepsy with cataplexy
- Difficult to use clinically and available from a single, specialty pharmacy
- Well-designed trials in fibromyalgia
  - Significantly improved fibromyalgia
  - Improved sleep
    - Increased slow-wave sleep duration
    - Reduced frequent night-time awakenings
    - Reduction in fatigue
- Despite its proven efficacy, SXB did not receive FDA approval for the management of fibromyalgia in 2010, mostly because of concerns about abuse

Management of Sleep Complaints

- Thorough history and physical
- Uncover comorbid pain condition
- Assessment of sleep disturbances
- Suspected primary sleep disorder (sleep apnea or periodic limb movement) or excessive daytime sleepiness
  - Diagnostic sleep study
  - Multiple sleep latency test

Cognitive Behavioral Therapy

- Sleep hygiene
  - Environment
  - Sleep cycle
  - Lifestyle
  - External factors
- Progressive muscle relaxation
- Guided imagery
- Biofeedback
- Stimulus control
- Restriction of time in bed
Cognitive Behavioral Therapy

- 28 patients with chronic pain were assigned to CBT or a contact control condition
- 8 weeks of CBT including sleep restriction, stimulus control, sleep hygiene, and one session of cognitive therapy devoted to catastrophic thoughts about the consequences of insomnia
- Outcomes included sleep diary assessments of sleep continuity, post-measures of insomnia severity, pain, and mood
- Subjects receiving CBT (n=19), as compared to control subjects (n=9), exhibited significant decreases in sleep latency, wake after sleep onset, number of awakenings, and significant increase in sleep efficiency. The groups did not significantly differ on mood measures or measures of pain severity.
- CBT was successfully applied to patients experiencing chronic pain
  - Significant improvements were found in sleep
  - Extent to which pain interfered with daily functioning


Cognitive Behavioral Therapy

- 21 adults with co-occurring chronic pain and chronic insomnia were randomized to either CBT for pain, CBT for insomnia, combined CBT for pain and insomnia, or a wait-list control condition
- Combined CBT intervention was feasible to deliver
  - Significant improvements in sleep
  - Improvement in disability from pain, depression and fatigue
- The combined intervention appeared to have a strong advantage over CBT for pain on most outcomes, modest advantage over both CBT for insomnia in reducing insomnia severity in chronic pain patients


CASE II

- A 56-year-old female patient with chronic pain from fibromyalgia and insomnia
- Pain level today is a 5/10
- Sleep complaints are described as taking 2 hours to fall asleep, multiple awakenings, and daytime fatigue
- Current medications
  - Minalcipran 50 mg twice daily
  - Hydrocodone with acetaminophen 7.5/325 mg every 6 hours prn pain
  - Buspiron 30 mg twice daily
- Polysomnography
  - Increased stage 1 sleep
  - Increased number of awakenings
  - Low sleep efficiency
  - Increase in alpha–EEG activity during stages 3 and 4 sleep
  - No sleep apnea is present
- What pharmacotherapy changes would you consider?
CASE III

- A 62-year-old male patient with chronic pain from failed back surgery and complaints of excessive daytime sleepiness
- Pain level today is a 8/10
- Sleep complaints are described as multiple awakenings during the night and daytime fatigue. Wife says he snores like a freight train.
- Current medications
  - Methadone 10 mg four times daily for chronic pain
  - Atorvastatin 40 mg daily for cholesterol
  - Lisinopril/HCTZ 40/25 mg daily for blood pressure
  - Clonazepam 1 mg at HS for sleep
- Polysomnography
  - Increased stage 1 sleep
  - Increased number of awakenings
  - Average 18 apneic episodes per hour; 12% of time with SaO₂ 80-90%
- What non-pharmacologic and pharmacologic recommendations do you make?

A 62-year-old patient with chronic pain syndrome from diabetic peripheral neuropathy presents with complaints of difficulty falling asleep and multiple nighttime awakenings. Which of the following medications has been shown in controlled trials to improve subjective sleep satisfaction and be effective in the treatment of pain and sleep interference in this type of patient?

1. Nortriptyline
2. Gabepentin
3. Oxcarbazepine
4. Methadone

Clinical Recommendations for Management of Pain and Sleep Complaints

1. Assess sleep with sleep diary and validated sleep questionnaires. Interview bed partner or caregiver.
2. Review sleep hygiene of the patient. Ensure no daytime naps or unnecessary nocturnal interruptions of sleep. Propose individualized physical activities to meet the needs and preferences of each patient.
3. Polysomnography in select patients; ambulatory polysomnography may be used. Sleep apnea and periodic limb movements are TREATABLE.
4. Consider withdrawing medications known to disturb sleep.
5. Reevaluate patients taking analgesic medications frequently for drug efficacy during initiation, titration, or change in dose.
6. Opioids may induce or worsen sleep apnea.

Clinical Recommendations for Management of Pain and Sleep Complaints

7. Treat pain during the night properly - use acetaminophen instead of aspirin or NSAIDS. Preferentially, use antidepressants and anticonvulsants with beneficial effects on sleep.

8. Consider cognitive-behavioral treatment for both insomnia and pain.

9. Combine non-pharmacologic strategies with pharmacotherapy for added value.

10. Use hypnotics in select patients - traditional agents help with initiating and maintaining sleep but DO NOT provide restorative sleep or reduce pain
   - Limit use to 2-4 weeks
   - Use non-benzodiazepine agents preferentially (eszopiclone, zolpidem, zaleplon)
   - Benzodiazepines may worsen pain in some patients

11. Adjuvant analgesics such as tiagabine, gabapentin, and pregabalin may be helpful in decreasing pain and improving slow wave sleep (restorative).


Discussion

• Share a case where you had successful outcomes treating a patient with chronic pain and sleep dysfunction.

Conclusions

• Chronic pain and sleep seem to have a bidirectional relationship
• Thorough evaluation of each complaint is imperative for appropriate treatment
• Unclear from evidence if pain or sleep should be addressed first
• Cognitive behavioral therapy is first-line therapy
• Avoid medications with adverse effects on sleep architecture
• Follow clinical recommendations when treating a patient with comorbid sleep and pain problems
QUESTIONS and DISCUSSION