Drained, In Pain

Relationships Between Sleep and Pain

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Objectives:

1. Understand the bidirectional relationship between sleep and pain.

2. Recognize the common effects of opioids on sleep in normal adults.

3. Understand the importance of screening for pre-existing forms of sleep disordered breathing in patients for whom opioids are prescribed.

4. Use your knowledge about sleep hygiene and safely prescribing opioids in those at risk of sleep disordered breathing to modulate how you treat pain.
Pain is a Complex Construct Involving:

- **Nociceptive inputs**
  - Genetic Variability
- **Previous experiences of pain**
  - Resolved or persistent
  - Mild to Severe
- **Maladaptive Pain Beliefs**
- **Emotional Impact of Pain**

- **Perception of pain**
  - Expectation of having pain
  - Voluntary/Enjoyable Activity
  - Unexpected
  - Inflicted
  - Workman’s Comp
    - Job Satisfaction
Pain Prone Phenotypes:

- Females
- Trauma in early life
- Personal or family history of chronic pain
- Personal history of central origin symptoms such as:
  - insomnia
  - fatigue
  - memory complaints
  - mood disorders
  - cognitive disorders
Poor Sleep  More Pain

- There is a complex and reciprocal interaction between pain and sleep

- Association between increases in:
  - Poor sleep quality
  - Increased pain intensity

- Pain patients reporting insomnia have:
  - Delayed sleep onset
  - More sleep fragmentation
  - Poor Sleep Quality
  - Shorter Sleep duration
  - EEG Changes in Polysomnography
    - Alpha Intrusion
      - 31% of chronic pain patients
  - Greater pain intensity
  - Increased pain sensitivity
  - More pain related disability
  - Higher rates of depression and anxiety
  - More health problems
  - Poor daytime functioning
A Domino Effect

Sleep Disturbance
- Poor Sleep Initiation
- Sleep Fragmentation
- Sleep Duration

Fatigue
- Decreased Activity

Psychological Morbidity
- Anxiety
- Depression

Compounding Effects On:
- Pain Perception
Better Sleep Helps Mood and Pain

- Sleep and pain have shared mechanisms in the central nervous system
- Serotonergic and Mesolimbic dopamine systems moderate:
  - Regulation of arousal
    - Circadian differences
  - Motor movement and muscle tone
  - Pain sensitivity
  - Mood and Emotion
Improved Sleep May Reduce Pain Through Modulating Inflammatory Responses

Inflammatory processes associated with the sleep cycle can modulate nociception:

• Sleep disruption can trigger pro-inflammatory responses

• Pro inflammatory changes with sleep disturbance
  • IL-6, TNF alpha, IL-1beta
    • Activates hepatic production of C-Reactive Protein
  • Reduced endogenous pain inhibitory control
  • Amplified pain experience
  • Lowered pain tolerance
  • Increased somatic symptoms

• Higher sleep disturbance are found within inflammatory populations:
  • Rheumatalogical conditions
  • Irritable bowel syndrome
  • Fibromyalgia
  • Temporomandibular joint dysfunction

• Remission of insomnia is associated with a significant reduction of C-reactive protein (CRP)
  • Clinically relevant marker of inflammation in rheumatic diseases
  • Prospectively linked to the development of diabetes, hypertension, and cardiovascular disease
Research: Poor Sleep Quality Predicts Pain

- **Prospective longitudinal study**
  - N=1860

- **Examined weather insomnia and sleep duration predicted the onset of chronic multi site musculoskeletal pain**
  - No baseline chronic multi site musculoskeletal pain
  - Followed up for the onset of chronic multi site musculoskeletal pain over six years
  - Examined whether association mediated by depressive symptoms
  - Insomnia determined by Women's health initiative insomnia rating scale greater than nine
  - Sleep duration
    - Short: Less than or equal to six hours
    - Normal: 7 to 9 hours
    - Long: greater or equal to 10 hours
  - Depression assessed at baseline and as a change score over time using inventory of depressive symptomatology

- **Outcomes:**
  - Insomnia and short sleep duration each associated with chronic pain onset
    - P < .001
  - Insomnia and short sleep duration are risk factors for developing chronic pain
  - Depressive symptoms partially mediate the effect for insomnia and short sleep with developing chronic pain

# Sleep and Pain: What Are the Odds?

<table>
<thead>
<tr>
<th>Prospective Observational Cohort</th>
<th>LBP tx at Pain Clinic</th>
<th>N=682</th>
<th>Pakpour et al</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Odds of reported non-recovery (OR) At 6 month follow up</strong></td>
<td><strong>Odds of increased pain intensity (OR) At 6 month follow up</strong></td>
<td></td>
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<tr>
<td>Sleep problems reported at baseline evaluation</td>
<td>1.52</td>
<td>2.69</td>
<td></td>
</tr>
<tr>
<td>Sleep problems reported at baseline and 6 month follow up</td>
<td>2.88</td>
<td>3.45</td>
<td></td>
</tr>
<tr>
<td>Developed sleep problems between baseline evaluation and 6 month follow up (25%)</td>
<td>2.71</td>
<td>2.95</td>
<td></td>
</tr>
<tr>
<td>Sleep problems reported at baseline resolved by 6 month follow up (4.5%)</td>
<td>0.5</td>
<td>0.49</td>
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</tr>
</tbody>
</table>
Sleep Affects Treatment Outcomes For Low Back Pain

• Presenting, persistent, and developing sleep problems have a significant impact on recovery for those with low back pain

• People who start with sleep problems:
  • Significant increased risk of poor outcomes and pain intensity

• One quarter of patients developed sleep problems
  • Also associated with poorer outcomes

• The proportion of sleep problems that resolved
  • Notably small proportion of the group (4.5%)
  • Odds ratio supports better recovery and lower pain intensity
    • Does not clarify direction of association
      • Did better recovery and lower pain intensity help improve sleep?
      • Did better sleep contribute to better recovery and less pain?
Research: Impact of Insomnia On Pain In Postmenopausal Women

• Observational study
  • Recruited by phone
  • N= 57 postmenopausal women with sleep complaint, no OSA

• Evaluation of:
  • Subjective info from questionnaire about insomnia
  • Polysomnogram data for objective sleep pattern
  • Sexual function
  • Pain intensity
  • Sleep Split into three groups:
    • Control
    • Subthreshold insomnia
    • Insomnia

• Insomnia affected pain interference but not pain intensity in post menopausal women

• Post menopausal women with insomnia had statistically significant increase of:
  • Pain interference in activities
  • Relationship difficulties
  • Interference in enjoyment of life
  • More severe climacteric symptoms
  • No statistic significant differences in pain intensity and objective sleep patterns

• Women with insomnia perceive pain differently, independently of its intensity

• Post menopausal women have increase chances of having insomnia, sleep apnea, and alterations in objective sleep parameters

Frange C et al. Climact 2017
Research: Cognitive Behavioral Therapy For Insomnia in Knee Osteoarthritis

- **Patients with knee osteoarthritis and insomnia**
  - N= 100

- **Randomized to eight sessions of CBT I or behavioral desensitization**
  - Baseline and Monitoring by:
    - Home sleep apnea test
    - Diary assessment
    - Sensory tests of pain modulation
      - Baseline
      - Post treatment
      - Three months later
      - Six months later

- **Improvement in sleep in both groups of patients**
  - CBT-I group had significantly greater reductions in wake after sleep onset

- **Both groups had a significant reduction in pain over six months**
  - One third reported a 30% reduction in pain severity
  - Clinically significant pain reduction was optimally predicted by achieving approximately 6.5 hours of sleep duration by mid treatment

- Baseline to post treatment reductions in wake after sleep onset predicted subsequent decreases in clinical pain
  - measured by diary and polysomnography

- **Tailoring interventions to increase total sleep time early in treatment may be an effective strategy to promote long-term pain reductions**

Salwen JK et al. Sleep 2017
Meta-analysis: Interventions Targeting Sleep For Adults Who Reported Long-term Pain

Inclusion Criteria:

- Original Randomized Controlled Trial with a control group
- Eleven RCTs involving 1,066 participants
- In adults (aged 18 years)
- With painful health conditions
  - Musculoskeletal pain
  - Arthritis
  - Fibromyalgia
  - Headache
  - Cancer
- Included an outcome measure of sleep and
  - At least one other health and well-being outcome
- Intervention differed in dose and duration
  - Most sleep treatments tested adopted a face-to-face approach
    - i.e. 7 weekly sessions of 120-minute intervention
  - Of the 9 studies that involved face-to-face contact with health care professionals:
    - 3 delivered the treatment individually
    - 6 offered the treatment in group
  - 2 delivered the intervention using the phone or internet
    - i.e. 3 telephone intervention sessions totaling an average of 69 minutes over 60 days
- Tested a non-pharmacological intervention that targets sleep
  - Sole or combined use of components of cognitive behavior therapy for insomnia (CBT-I).
    - Psychoeducation
    - Sleep hygiene
    - Stimulus control therapy
    - Sleep restriction therapy
    - Sleep scheduling
    - Relaxation techniques
    - Paradoxical intention
    - Imagery
    - Cognitive therapy
- Included if the interventions being evaluated were designed to address insomnia specifically:
  - Physiotherapies
  - Exercise
  - Yoga
  - Qigong
  - Mindfulness meditation
  - Massage
  - Acupuncture
  - Hormone therapy
  - Hypnosis

Tang NK et al. Sleep 2015
Meta Outcomes:

- Means and standard deviations were extracted for the sleep treatment and control groups at: baseline, post-treatment and final follow-up (3-12 mo)

- Non-pharmacological sleep treatments in chronic pain patients at follow up were associated with:
  - **Large improvement in sleep quality**
    - (standardized mean difference = 0.78, 95% Confidence Interval [0.42, 1.13]; P < 0.001)
  - **Small reduction in pain**
    - (0.18 [0, 0.36] P < 0.05)
  - **Moderate improvement in fatigue**
    - (0.38 [0.08, 0.69]; P < 0.01)
  - The effects on sleep quality and fatigue were maintained at follow-up when a moderate reduction in depression was also observed
    - (0.31, [0.09, 0.53]; P < 0.01)

- Both cancer and non-cancer pain patients benefited from non-pharmacological sleep treatments

- Face-to-face treatments achieved better outcomes than those delivered over the phone/internet.

- **Non-pharmacological sleep interventions can help optimize treatment outcomes in patients with chronic pain**
  - Body of evidence was small

Tang NK et al. Sleep 2015
Painsomnia

- An estimated 50% to 90% of chronic pain patients report insomnia of a severity that warrants clinical attention
- Those with chronic pain and insomnia often have an undiagnosed sleep disorder
  - Obstructive sleep apnea
  - Restless leg syndrome
Spielman’s 3 Factor Model of Insomnia

Sleep Disturbance Intensity

Baseline | Acute | Early | Chronic

Predisposing | Precipitating | Perpetuating

Sleep Hygiene

- Avoid Moderate to heavy alcohol use in late evening
- Avoid nicotine use within 4 hours of bedtime
- Do not go to bed hungry
- Cut down caffeine
- Avoid exercise right before bed
- Avoid TV, eating, and working in bed or just prior bedtime
- Comfortable, dark, quiet sleep environment
- Avoid “clock watching”
Stimulus Control Therapy

- Decrease conditioned arousal for those who associate the bed, or sleep in general, with a negative response
  - Bed for sleep and sex only
  - Go to bed only when tired
  - Leave room if not falling asleep in 15-20 minutes
  - Avoid daytime napping
Insomnia Overview and Summary

- Early Insomnia
  - Caffeine
  - Anxiety
  - Poor sleepy hygiene
  - Medications
  - Restless leg syndrome
  - Delayed sleep phase

- Middle Insomnia
  - Pain
  - Repeated stimulus effect
  - Substance withdrawal
  - Nightmares

- Terminal Insomnia
  - Major depressive disorder
  - OSA
  - Circadian phase shift

- Acute insomnia often resolved when precipitant is resolved

- Chronic Insomnia can be
  - Lifelong
  - Formed by habit
  - Due to other medical or behavioral factors
  - Worsened by other sleep disorders

- Behavioral interventions are most effective
  - Predisposing
  - Precipitating
  - Perpetuating
Obstructive Sleep Apnea

- Complete or partial upper airway obstruction occurring during sleep
- Often results in reductions in oxygen saturation
- Often terminated by brief arousals from sleep
- Increased sympathetic activation
  - Fight or flight across the night
Sleep Apnea Cycle

- Physiologic stressors:
  - Cyclic hypoxemia
    - 11,911 adults — 41% systemic hypertension
  - Strenuous respiration
  - Sympathetic activation
  - Reduced total sleep time

Tkacova, Eur Respir J. 2014
Sleep Disordered Breathing and Pain

• Main focus on OSA centers around pauses in breathing and drops in oxygen during the night

• HOWEVER: American Academy of Sleep Medicine diagnostic criteria includes airflow limitation that leads to sleep disruption
  • Upper Airway Resistance Syndrome (UARS)
  • Many patients with chronic pain syndromes have OSA or UARS
    • Chronic tension-type headache (TTH)
    • Fibromyalgia
    • Chronic fatigue syndrome
    • Decrease in slow wave sleep (“deep sleep”) and rapid eye movement (REM)
    • Alpha intrusion
  • Airway resistance contributes to inflammatory markers in the blood and lower pain threshold in those with:
    • Chronic tension type headaches
      • particularly those who report waking with headaches
    • Temporomandibular joint (TMJ) pain
    • Teeth clenching during the night
      • protective mechanism to try to keep the airway open
      • keeps jaw and tongue from sliding toward the back of the throat
The Nightly Struggle

- Oxygen at 92%
- Can not open airway
- Oxygen drops below 50%
- 155 Seconds
Physical Findings on Exam Which May Predispose to OSA

BMI > 35

Neck Circumference
- > 16 in women
- > 17 in men
Physical Findings on Exam Which May Predispose to OSA

- Chronic Nasal Congestion
- Nasal Speech
- Obligate mouth breathing
  - Due to adenoidal hypertrophy
- Mandibular retrognathia
- Mid face hypoplasia
- Ectropion (floppy eyelids)
  - 38/45 patients
    - 85% had OSA
    - 65% had severe OSA
Physical Findings on Exam Which May Predispose to OSA

Crowded Oropharynx

- Large uvula
- Large Tongue
- Tonsil hypertrophy
- Small Airway
- High arched narrow palate
- Low laying palate

http://yoursmileyourstyle.com/files/2014/05/What-your-dentist-looks-for-in-diagnosing-sleep-apnea.jpg
Physical Findings on Exam Which May Predispose to OSA
STOP-BANG: Quick Screening Tool for OSA

Answer each of the following “yes” or “no”:

- **S**nore loudly (louder than talking or loud enough to be heard through closed doors)?
- Do you often feel **T**ired, fatigued, or sleepy during daytime?
- Has anyone **O**bserved you stop breathing during your sleep?
- Do you have or are you being treated for high blood **P**ressure?
- **B**MI more than 35?
- **A**ge over 50 years old?
- **N**eck circumference > 15.75 inches?
- **G**ender male?

≥ 3 “yes” answers = High-risk for OSA
< 3 “yes” answers = Low-risk for OSA

Obstructive Apnea

Central Apnea

Mixed Apnea

We classify sleep apnea in a PSG based upon INSPIRATORY effort during absent airflow.
Central Sleep Apnea

- A lack of effort to breathe
- Respiratory drive under metabolic control in NREM sleep
  - Mu receptors sense CO2 in brainstem
  - Breath is triggered CO2 hitting threshold (individual)
- Dysregulation due to:
  - Brain Lesion
    - Stroke, anatomical, vascular, tumor
  - Genetic
    - Oden’s Curse (“forget” to breathe)
  - Medication
    - Narcotics block Mu receptor
  - Poor Cardiac Function
    - Congestive Heart Failure, Atrial Fibrillation
    - Signal to brain is “old news”
### Sleep-disordered Breathing in Patients Receiving Buprenorphine/Naloxone

- Consecutive admissions to inpatient detoxification facility underwent PSG
- Buprenorphine dose ranged from 2.0 to 76.0 mg (mean ± sd total dose) 18.5 ± 13.9 mg

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>All</th>
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<tbody>
<tr>
<td>Subjects</td>
<td>28</td>
<td>42</td>
<td>70</td>
</tr>
<tr>
<td>AHI</td>
<td>15.2±26.3</td>
<td>23.9±35.6</td>
<td>20.4±32.3</td>
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<td>(0.0–106.2)</td>
<td>(0.0–180.0)</td>
<td>(0.0–180.0)</td>
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<tr>
<td>CAI</td>
<td>6.3±19.0</td>
<td>14.9±32.6</td>
<td>11.4±28.1</td>
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<tr>
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<td>(0.0–176.4)</td>
<td>(0.0–97.6)</td>
<td>(0.0–176.1)</td>
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<tr>
<td>OAI</td>
<td>2.0±2.3</td>
<td>2.5±4.7</td>
<td>2.3±3.9</td>
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<td>(0.0–8.6)</td>
<td>(0.0–26.5)</td>
<td>(0.0–26.5)</td>
</tr>
<tr>
<td>HI</td>
<td>6.9±4.8</td>
<td>6.5±9.6</td>
<td>6.6±11.8</td>
</tr>
<tr>
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<td>(0.0–71.8)</td>
<td>(0.0–42.6)</td>
<td>(0.0–71.8)</td>
</tr>
<tr>
<td>Baseline $S_{pO2}$ %</td>
<td>92.7±3.0</td>
<td>91.0±3.5</td>
<td>91.7±3.4</td>
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<tr>
<td></td>
<td>(86.0–98.0)</td>
<td>(83.0–98.0)</td>
<td>(83.0–98.0)</td>
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<tr>
<td>% of TST where $S_{pO2}$ &lt;90%</td>
<td>13.4±22.4</td>
<td>29.8±36.6</td>
<td>23.2±32.5</td>
</tr>
<tr>
<td></td>
<td>(0.0–76.2)</td>
<td>(0.0–100.0)</td>
<td>(0.0–100.0)</td>
</tr>
</tbody>
</table>

Chronic Opioid Use is a Risk Factor for the Development of Central Sleep Apnea and Ataxic Breathing

- Prevalence of ataxic breathing, patients vs. controls: 70.0% vs. 5.0%, \( p < 0.001 \)
- Odds ratio for presence of ataxic breathing for morphine dose equivalent \( \geq 200\text{mg} \): 15.4 (95% C.I., 1.6 – 145.5, \( p < 0.017 \))
- Prevalence of ataxic breathing in patients, morphine dose equivalent of \( \geq 200\text{mg} \) vs. <200mg: 92% vs. 61%

Opioid-induced Sleep-disordered Breathing: Is it a Cause of Death?

- All cases of opioid overdoses in Ferrara, Italy 1991-1998
- 110 lethal overdoses
- Presumptive time of death by report or necropsy
- Peak time of death occurred between 0300 and 0859, p=0.002

![Circadian rhythm of death risk for opioid overdose](image)

Adaptive Servoventilation (ASV) in Patients with Opioid-associated CSA

- Retrospective Analysis of consecutive patients; N= 22
- Opioid medications ≥6 months
- AHI ≥20/hour

Adaptive Servoventilation (ASV) in Patients with Opioid-associated CSA

- Patients with CSA; N=5
- Second NPSG with CPAP titration
- Third NPSG with volume-targeted ASV titration

Opioid Induced CSA Summary

• Contrary to popular belief, **tolerance does not develop to the effects of opioids on respiratory control**

• Chronic opioid use can lead to obstructive and central apneas and hypopneas as well as an ataxic (Biot’s) breathing pattern

• The prevalence of sleep apnea is proportional to dose

• Some form of PAP treatment can be effective

• Patients with ataxic, or Biot’s breathing, are more difficult to treat

• May be a significant cause of death from opioid use
Opioids Change Sleep Architecture

- **Acute opioid use**
  - Increases stage N2
  - Decreases stage N3 (slow wave sleep)
  - Decreases REM
  - Increases REM latency (time it takes to get to REM)
  - Increases wakefulness
  - Increases arousals
  - Reduces total sleep time (TST)
  - Decreases sleep efficiency

- **Chronic Opioid Use**
  - Abnormalities in sleep architecture tend to normalize
  - Subjective sleepiness increases

Normal Sleep Architecture:
- Stage N1------------------2-5%
- Stage N2-----------------45-50%
- Stage N3---------------13-23%
- Stage REM--------------20-25%
- Wake---------------------5%

To a great extent, the literature is inconsistent and difficult to interpret!

Case: Ms. Roxy

Ms. Roxy is a 28 year old obese female who is treated for pain and anxiety related to a motor vehicle accident during which she sustained a traumatic brain injury and broken back. Her husband reports that she has had a few “scary” episodes where he wakes and thinks she is dead because he can’t see her breathing. She notes sometimes waking with a racing heart. She requests something to help with her anxiety at night.
Opioids Can Worsen Obstructive Sleep Apnea

- Opioids can raise arousal threshold by direct sedative effect
  - Blunt the stimulus that causes arousal
    - Arousal is the result of increasing inspiratory effort
      - Modulated by hypercapnic and hypoxic ventilatory response

- Respiratory depressants can further block the arousal process
  - Alcohol
  - Benzodiazepines
  - Barbiturates
Sleep Apnea and Death: Respiratory Depressants May Block the Arousal Process

Alcohol/Medications may block the brains ability to arouse

Oxygen drops below 50%
Case: Ms. Roxy

Key Points

• Brain injuries can effect the sleep wake circuitry and breathing centers in the brainstem
  • Insomnia
  • Central sleep apnea
  • Arousal system
• Opioid medications decrease respiratory drive during sleep
  • Brain forgets to send a signal to lungs to breathe
• Decreased capacity to arouse when hypoxemic
• Those at risk for OSA are at higher risk of death with narcotic use
• Concurrent use of benzodiazapines and narcotic medications are a “double whammy”
  • Increased OSA risk from loss of muscle tone
  • Central sleep apnea from blocking mu receptors
Summary

• Sleep and pain have a bidirectional relationship
• Targeting poor sleep may help with treatment of pain
• Insomnia is related to predisposing precipitating and perpetuating factors
• Sleep hygiene and cognitive framing are important parts of treating insomnia
• Those with chronic pain often have undiagnosed sleep apnea
• Sleep apnea increases adverse outcomes in those using narcotic medications
• Use of narcotic medications increases risk of CSA and respiratory depression
  • Dose dependent relationship
• Patients with chronic pain should be screened for OSA and CSA
  • Increases likelihood of better sleep and better pain treatment
  • Decreases health risks and death associated with sleep apnea and narcotic use
Thank You!

Questions?
References:

- Salwen JK, Smith MT, Finan PH. Mid-Treatment Sleep Duration Predicts Clinically Significant Knee Osteoarthritis Pain Reduction at 6 Months: Effects from A Behavioral Sleep Medicine Clinical Trial. *Sleep*. 2017 Feb. 1;40(2)