Opioids and Sleep Apnea

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Case Presentation

- 58 year old man with history of COPD, hepatitis C, polysubstance abuse on methadone replacement therapy, hypertension, prediabetes, chronic pain on chronic opioid treatment, right hip avascular necrosis, chronic hypoxia thought to be due to obesity hypoventilation on 2-3 L/min nocturnal oxygen supplementation, and severe obstructive sleep apnea.

- **Diagnostic Polysomnogram 2011:**
  - CMS-AHI 43, AASM-AHI 56 and the oxygen nadir was 77%.
    - Due to emergence of central events with CPAP, patient was titrated with BPAP to 20/9 cwp with improved consolidation of sleep, a reduction in respiratory events, and improved oxygenation.
    - At 20/9 cwp with 1 L oxygen bleed average SpO2 84%, nadir 79%.
Repeat Polysomnogram 2016:
CMS-AHI 87, AASM AHI 100, SpO2 nadir 66% with 267 minutes SpO2 ≤ 88%. equal to 88%.

310/620 apneas and hypopneas were CENTRAL or MIXED events.

Biot’s pattern of breathing was noted.
Biot’s Pattern of Breathing Was Also Seen

2-minute PSG epoch NREM 2 sleep with Respiratory rate ~ 9 breaths per minute
Background

  - “Pain is often managed inadequately, despite the ready availability of safe and effective treatments.”
- US Congress declared 2001-2010 as the decade of pain control and research.
- In 2001, the joint commission mandated that health care organizations comply with pain assessment and management standards for accreditation.

- Use of opiates in US doubled in 2011-2013 compared with 2001-2003
- >100% increase in overdose deaths between 1999 and 2009
Distribution of Opioid Receptors

Wide anatomic distribution of sites where opioids shown to decrease neuronal excitability and/or neurotransmitter release which leads to alterations in:

- EEG activity
- Breathing
- Motor control
- Behavioral states

Opioids and Respiratory Depression: Sites of Action

- When overall respiratory drive from ventrolateral medulla \(\downarrow\) \(\rightarrow\) \(\downarrow\) reduced efferent output to spinal motoneurons \(\rightarrow\) \(\downarrow\) intercostal and diaphragmatic activation of the respiratory bellows (\(\downarrow\) alveolar ventilation).

- At same time, \(\downarrow\) respiratory drive \(\downarrow\) reduces efferent output to cranial motoneurons responsible for maintaining upper airway patency (\(\uparrow\) upper airway resistance).
Effect of Opioids on Respiration

Effect on breathing frequency, tidal volume, rhythm, upper airway patency, chemosensitivity to CO$_2$ and O$_2$, arousal response to hypoxia and hypercapnia, inspiratory load, cough reflex, and chest and abdominal wall compliance.

- Central depression of the respiratory rate
- Depressed ventilator response to hypoxia and hypercarbia
- Amplitude and reflex responses
- Reduced ability for arousal
- Upper airway dysfunction
- Hypoventilation
Effects of Opioids on Obstructive Sleep Apnea

• Reduction in airway muscle activation
• Increased arousal threshold by direct sedative effect
• Blunted stimulus of arousal
  • Arousal is result of increasing inspiratory effort
  • Inspiratory effort is modulated by hypercapnic and hypoxic ventilator response
## Acute vs Chronic Effects of Opioids on Respiration

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
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</thead>
<tbody>
<tr>
<td>• Hypoxic/hypercapnic respiratory failure due to decreased respiratory drive and hypoventilation</td>
<td>• Periodic Breathing</td>
</tr>
<tr>
<td></td>
<td>• Hypoxemia</td>
</tr>
<tr>
<td></td>
<td>• Balance between hypoxic and ventilator drive may recover but depression of ventilator drive persists</td>
</tr>
</tbody>
</table>
Abnormal Breathing Patterns Seen with Opioids

**Biot’s Breathing** = high frequency and regular tidal volume breathing with periods of apnea

**Ataxic breathing** = irregular frequency and tidal volume with unpredictable periods of apnea
Hypoxemia and Chronic Opioid Use

• Hypoxemia in absence of apnea can occur during wakefulness in patients without cardiopulmonary disease and who are receiving chronic opioids with and without sleep apnea

• More than 10% of patients on chronic opioids demonstrated resting awake and asleep hypoxemia without apnea
Determining Effects of Opioids on Sleep Complex

• Opioids differ in their receptor agonist repertoire and potency
• When used to treat cancer or non-cancer pain on a chronic basis, it is not usually possible to distinguish the effects of pain vs. the effects of the opioid
• The best information we have comes from
  • Animal subjects, although there are known variations in sleep and respiratory-related CNS structures and function compared to humans
  • Humans treated chronically for addiction with methadone or buprenorphine (±naloxone)
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Clinical Studies of Effects on Chronic Opioid Use on Breathing in Sleep
PSG Studies Characterizing Disruptive Effects of Opioids on Sleep and Wakefulness

<table>
<thead>
<tr>
<th>Study</th>
<th>Opiate</th>
<th>Trade Name(s)</th>
<th>No. of Patients (Female/Male)</th>
<th>Species, Disposition</th>
<th>Wake Time</th>
<th>Light NREM Sleep Duration</th>
<th>Deep NREM Sleep Duration</th>
<th>REM Sleep Duration</th>
<th>Total Sleep Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaw et al., 2005&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Morphine</td>
<td>Avinza, Kadian, MS Contin, Roxanol, Roxanol-T</td>
<td>7 (2/5)</td>
<td>Human 24–28yo, healthy</td>
<td>—</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>—</td>
</tr>
<tr>
<td>Bernards et al., 2009&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Remifentanil</td>
<td>Ultiva</td>
<td>19 (8/11)</td>
<td>Human 38–62yo, moderate OSA</td>
<td>—</td>
<td>↑</td>
<td>NS</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Axelin et al., 2010&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Oxycodone</td>
<td>Tylox, Percodan, OxyContin</td>
<td>18 (7/11)</td>
<td>Human 28–32 weeks, preterm</td>
<td>NS</td>
<td>↑ (NREM only)</td>
<td>↑ (NREM only)</td>
<td>↓</td>
<td>NS</td>
</tr>
<tr>
<td>Dimsdale et al., 2007&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Methadone</td>
<td>Methadose, Dolophine</td>
<td>42 (25/17)</td>
<td>Human 18–60yo, healthy</td>
<td>—</td>
<td>↑</td>
<td>↓</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Gauthier et al., 2011&lt;sup&gt;#&lt;/sup&gt;</td>
<td>Buprenorphine</td>
<td>Buprenex, Suboxone, Subutex</td>
<td>26 (0/26)</td>
<td>Sprague Dawley rat, adult, healthy</td>
<td>↑</td>
<td>↓ (NREM only)</td>
<td>↓ (NREM only)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Williams et al., 2012&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Butorphanol</td>
<td>Stadol</td>
<td>6 (0/6)</td>
<td>Horse, adult, healthy</td>
<td>↑</td>
<td>↓ (SWS only)</td>
<td>↓ (SWS only)</td>
<td>↓</td>
<td>—</td>
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</tbody>
</table>

**FINDINGS:**
- Inhibition of REM sleep
- Decreased duration of slow wave sleep
- Overall sleep disruption
- Decreased sleep consolidation;
- Excluded potentially confounding factors of surgery, pain, drug addiction, or other comorbid conditions.
Different Types of Sleep Disordered Breathing Found on Overnight PSG in Patients on Opioids For Chronic Pain

2014 PSG study of 98 patients on chronic opioid treatment referred for suspected OSA:

- 36% OSA
- 24% CSA
- 21% Combined OSA and CSA
- 4% Sleep apnea classified as indeterminate
- 15% No sleep apnea

2015 Meta-analysis of Central Sleep Apnea in 560 Chronic Opioid Users

- Meta-analysis of 8 studies of 560 subjects on chronic opioid therapy) by Correa et al. (2015):
  - Prevalence of central sleep apnea (CSA) 24%.
  - **Risk factors for CSA severity:**
    - Daily morphine equivalent dose (MED) > 200 mg
    - Low or normal BMI
    - Opioids combined with benzodiazepines and/or hypnotics
2016 Meta-analysis of Chronic Opioid Use on SDB

- Meta-analysis of 8 studies (803 patients) with OSA to assess effect of long-term opioid use on Apnea-hypopnea Index (AHI) and Central Apnea Index (CAI).
  - AHI in 320 opioid users vs. 483 non-users and
  - CAI in 315 opioid users vs. 475 non-users.

- FINDINGS:
  - Small increase in AHI = 0.25 (95% CI: .02–.49)
  - Medium increase CAI = 0.45 (95% CI: .27–.63).
  - Moderate heterogeneity (I² = 59% for AHI and I²=29% for CAI).

Filiatrault et al. Journal of Clinical Sleep Medicine, Vol. 12, No. 4, 2016
Prevalence of OSA and CSA in Methadone Maintenance Program Patients with Sleep Complaints

Sharkey KM et al. Drug Alcohol Depend. 2010
Treating Sleep Disordered Breathing in Chronic Opioid Users
Supplemental Oxygen for SDB in Chronic Opioid Users

• Chronic opioid use → ↓ arousal/ventilatory response hypercarbia

• O2 therapy could potentiate hypoventilation or prolong central apneas/hypopneas

• Opioids can stabilize breathing if arousal threshold is low and respiratory controller gain is high associated with pain

• O2 unlikely to cause respiratory suppression
ASV to Treat Opioid Induced Sleep Disordered Breathing

• Recent study compared results of 6 studies evaluating efficacy of PAP therapy to treat opioid-induced SDB:
  • 5 of 6 studies demonstrated ASV reduced AHI and CAI significantly (but AHI was not consistently reduced to < 10/h)
  • Benefits of ASV extended beyond the initial titration night into 3 months of home use

Van Ryswyk E and Antic NA. Opioids and SDB. Chest. Oct 2016;150(4); 934–44
Initial Reports of Adaptive Servoventilation (ASV) in Patients with Opioid-associated CSA

Retrospective analysis of 22 consecutive patients opioid medications ≥6 months AHI ≥20/hout Volume-targeted ASV

5 consecutive patients with CSA 2nd night PSG with CPAP titration
3rd night PSG with volume-targeted ASV titration
CPAP and ASV for Treatment of Sleep Disordered Breathing in Chronic Opioid Use

Prospective multicenter interventional study by Colin et al of chronic pain patients prescribed \( \geq 100 \) morphine equivalents for at least 4 months

- CPAP improved but did not normalize AHI, CAI, or hypopnea index.
- Clinically significant reductions after one night of ASV and ASV manual (PSmin 6).
- After 3 months of ASV home use, the AHI, CAI, and obstructive apnea index (OAI) were significantly reduced when compared to baseline diagnostic levels and even when compared to respiratory disturbance indices with CPAP treatment.
### CPAP vs. ASV Effect on SDB in Chronic Opioid Use

Comparison of respiratory variables across diagnostic PSG and titration studies (CPAP, ASV, and ASV manual (PSmin 6))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diagnostic PSG (N=31)</th>
<th>CPAP (N=31)</th>
<th>ASV (N=31)</th>
<th>ASV manual (PSmin 6) (N=31)</th>
<th>Overall p value (Friedman test)</th>
<th>CPAP vs. ASV</th>
<th>CPAP vs. ASV manual (PSmin 6)</th>
<th>ASV vs. ASV manual (PSmin 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>32.5 (38.8 ± 31.1)</td>
<td>10.1 (17.4 ± 20.1)</td>
<td>1.4 (4.5 ± 7.3)</td>
<td>2.1 (7.6 ± 16.7)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.009</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>CAI</td>
<td>6.4 (16.1 ± 18.8)</td>
<td>2.4 (8.4 ± 12.4)</td>
<td>0.0 (0.2 ± 0.8)</td>
<td>0.0 (0.2 ± 0.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>OAI</td>
<td>1.9 (9.7 ± 15.2)</td>
<td>2.8 (4.5 ± 6.3)</td>
<td>0.0 (0.3 ± 0.5)</td>
<td>0.0 (0.5 ± 1.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>HI</td>
<td>10.2 (14.8 ± 12.6)</td>
<td>2.8 (4.5 ± 5.1)</td>
<td>1.4 (4.6 ± 7.4)</td>
<td>3.2 (7.9 ± 16.2)</td>
<td>0.441</td>
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</tr>
<tr>
<td>ODIa</td>
<td>24.2 (32.8 ± 29.2)</td>
<td>6.0 (15.1 ± 20.2)</td>
<td>1.9 (5.9 ± 8.6)</td>
<td>2.6 (9.5 ± 19.2)</td>
<td>0.161</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td>Av. O₂ saturation</td>
<td>93.4 (92.9 ± 3.4)</td>
<td>94.9 (94.6 ± 2.3)</td>
<td>94.6 (94.6 ± 2.6)</td>
<td>94.6 (94.5 ± 3.2)</td>
<td>0.627</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td>Min. O₂ saturation</td>
<td>80.5 (79.9 ± 7.8)</td>
<td>85.0 (85.5 ± 6.0)</td>
<td>85.0 (82.9 ± 6.0)</td>
<td>86.6 (79.7 ± 22.8)</td>
<td>0.991</td>
<td>--</td>
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</tr>
</tbody>
</table>
Comparison of Respiratory Indices Between CPAP Titration and After 3 Months At-Home Use in Chronic Pain Patients

<table>
<thead>
<tr>
<th>AHI (N=24)</th>
<th>CAI (N=24)</th>
<th>OAI (N=24)</th>
<th>HI (N=24)</th>
<th>Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All days</td>
</tr>
<tr>
<td>CPAP titration</td>
<td>11.3 (20.3 ± 21.8)</td>
<td>2.6 (10.3 ± 13.5)</td>
<td>3.0 (5.2 ± 6.7)</td>
<td>3.5 (5.3 ± 5.5)</td>
</tr>
<tr>
<td>ASV home use\textsuperscript{a}</td>
<td>5.8 (8.6 ± 7.9)</td>
<td>0.8 (1.5 ± 2.0)</td>
<td>0.7 (1.4 ± 1.7)</td>
<td>3.8 (5.7 ± 5.3)</td>
</tr>
<tr>
<td>\textit{p value}\textsuperscript{c}</td>
<td>0.021</td>
<td>0.006</td>
<td>0.002</td>
<td>0.648</td>
</tr>
</tbody>
</table>

- Prospective multi-center interventional study recruited chronic pain patients prescribed > 100 morphine equivalents for at least 4 months.

Randomized crossover trial of 33 patients after bariatric surgery on 30% oxygen in PACU.

- Evaluated AHI under atmospheric pressure and CPAP (8 to 10 cm H₂O) after self-administration of opioids;

- 64% of patients demonstrated SDB (AHI greater than 5/h) early after recovery from anesthesia.

**CPAP treatment**

- Decreased AHI (8 ± 2/h vs. 25 ± 5/h, \( P < 0.001 \))
- Decreased oxygen desaturations (5 ± 10/h vs. 16 ± 20/h, \( P < 0.001 \))
- Increased the mean oxygen saturation by 3% (\( P = 0.003 \))
- Significant decrease of respiratory-depressant effects observed during wakefulness–sleep transitions without affecting hemodynamics

Risk Mitigation Strategies

• Opioid dose reduction
• Trial of non-opioid therapies (NSAIDs, antiepileptic drugs, physical therapy, antidepressants etc) in lieu of opioids
• Avoiding use of benzodiazepines, sedatives, hypnotics
• Caution against alcohol use
• Sleep medicine consultation and treatment of SDB

CAVEAT: It is not possible to selectively achieve the desired opiate effect of diminishing states of pain and anxiety without causing the unwanted side effects of disrupting breathing and states of sleep and wakefulness

Pain Med. 2015 October; 16(0 1): S22–S26
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

Appendix
Control of Breathing During Sleep

- Absent cortical influence on brain stem
- Respiration is under **metabolic** control
- Reduction in lung volume
- Decreased effect of CO$_2$
- Response to hypoxia preserved
- $\rightarrow$ $\uparrow$ upper airway resistance $\rightarrow$ unmasking of CO$_2$ induced apneic threshold $\rightarrow$ apneas
Control of Breathing During Sleep

• **Pre-Bötzinger complex:**
  • Central chemoreception of CO2 generating inspiration;

• **Glomus cells of carotid body:**
  • Breath-by-breath control by providing rapid feedback from periphery to CNS regarding \( O_2 \), \( CO_2 \), \( H^+ \) and \( K^+ \)

• **Bulbospinal inspiratory and expiratory premotor neurons:**
  • Project to phrenic, intercostal and abdominal motoneurons.

• **Hypoglossal motor nucleus:**
  • Maintains upper airway patency during sleep.
Metabolic Breathing Control

- Central chemoreceptors in brainstem (nucleus solitarius, dorsal respiratory group, medulary raphe, Pre-BOTC, RTN/PFRTC)
  - Stimulated by PaCO$_2$
  - Hypercapnic ventilatory response slope → degree of ventilator stimulation for given PaCO$_2$ above eupnea

- Peripheral chemoreceptors in carotid bodies
  - Detect changes in PaO$_2$
  - Hypoxic ventilatory response → ventilator stimulation for given level of paO$_2$
  - Peripheral chemoreceptors → inputs to central respiratory centers → input to motor neurons that innervate respiratory muscles
Opioids and Their Receptors

Opioids interact with variety of G-coupled protein receptors to reduce neuronal excitability: delta, mu, kappa, nociception/orphanin FQ peptide

- All are involved in the analgesic effects
- Mu and kappa receptors mediate sedation
- Mu and delta receptors play a key role in the respiratory depression
- Opioid receptors can combine to form dimers and/or oligomers with unique functional roles.

- Most commonly used opioids are relatively selective for mu receptors but there can be significant variability.

### Mu (μ) Receptor Activation

- **Full agonist**: Morphine
  - Full activation of μ receptor site

- **Partial agonist**: Buprenorphine
  - Partial activation of μ receptor site

- **Antagonist**: Naloxone
  - Prevents or reverses activation of receptor site

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Opioid Effects

- Morphine, heroin, fentanyl, codeine and dihydrocodeine $\rightarrow$ Full $\mu$ receptor agonists
  - Weak agonist activity at $\delta$ and $\kappa$ receptors

- Buprenorphine $\rightarrow$ Partial $\mu$ receptor agonist
  - Antagonistic activity at $\mu$ receptor $\rightarrow$ enhances $\mu$ mediated analgesia

- Meptazinol $\rightarrow$ $\mu$ receptor agonist
  - Agonist activity on muscarinic acetylcholine receptors

- Tramadol $\rightarrow$ $\mu$ receptor agonist
  - Inhibits re-uptake of norepinephrine and serotonin $\rightarrow$ enhances analgesic activity

- Methadone $\rightarrow$ $\mu$ receptor agonist
  - Inhibits re-uptake of norepinephrine and serotonin $\rightarrow$ enhances analgesic activity
  - Glutamatergic NMDA receptor antagonist $\rightarrow$ further inhibits the transmission of pain
Geriatrics and Opiate induced Respiratory Depression

- Increased rates of sleep disordered breathing and pain
- Change in pharmacokinetics and pharmacodynamics with age
- Increased mean elimination half life
- Increased brain sensitivity
- Decreased volume of distribution
- Decreased clearance
- Decreased protein binding
- Reduction in renal function
- Worst effect in 70-90s: 2.8-8.7 times increased risk of critical ventilatory failure