OPIOIDS AND CENTRAL SLEEP APNEA

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CINCINNATI, OH

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He is the Section Editor for Sleep-related Breathing Disorders and Cardiovascular Diseases in the Principles and Practice of Sleep Medicine, the premier book of sleep and sleep disorders. He is on the editorial Board of the Journal Sleep.

Dr. Javaheri has lectured in many countries including China, Japan, Sweden, Finland, Iceland, Tunisia, India, Iran, South Korea, Australia, Italy, Austria, Germany, France, Scotland, Denmark, Brazil, Belgium, Netherlands, Canada, Argentina, Oman and Spain. These lectures have dealt primarily with sleep-disordered breathing, obstructive and central sleep apnea and its relation to congestive heart failure.

He is a member of the American Thoracic Society and American Sleep Disorders Association, and a Fellow of the American College of Chest Physicians.

OBJECTIVES:
Participants should be better able to:

1. To appreciate the differences between opioids-associated sleep apnea VS, sleep apnea in general population;
2. To understand the mechanisms of central sleep apnea caused by opioids;
3. To be able to effectively treat SDB associated with opioids.

SATURDAY, MARCH 24, 2018 8:00 AM
Opioids-Induced Sleep Apnea
Shahrokh Javaheri, MD, FCCP, FAASM, ABSM

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Cincinnati, Ohio
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2018 NAMDRC Meeting

No relevant conflict of interest

2018 NAMDRC Meeting
Opium poppy, opiates and opioids

OPIATES
Alkaloids derived from the opium poppy Papaver somniferum

Morphine, the juice extracted from the opium poppy

OPIOIDS
synthetic or partly-synthetic drugs that are manufactured

Pain Management
Optimal pain management is a national health care priority

Use of opioid therapy for patients with both acute and chronic pain is safer and more effective than ever before. 😊
Opioids Epidemic

In the last decade there has been a major change in the management of chronic pain with a marked increase in the therapeutic use of opioids.

Opiates have become part of contemporary treatment in the management of CNCPC

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Institute of Medicine

Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.
The National Academies Press, Washington, DC, June 29, 2011

- 116 million Americans with pain persisting from weeks to years
- The therapeutic use of oxycodone and methadone have increased by 6-8 fold over the course of 1997 to 2003
- Financial costs ranging from $560 billion to $635 billion per year
**Opioid Epidemic in the United States**

**DISPENSED PRESCRIPTIONS (10^6)**

<table>
<thead>
<tr>
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<th>2008</th>
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<td>Antidiabetics</td>
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<td>Ace Inhibitors</td>
<td>159</td>
<td>163</td>
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<tr>
<td>Beta Blockers</td>
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<td>164</td>
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</tr>
</tbody>
</table>

*Pain Physician 2012; 15:ES9-ES38 • ISSN 2150-1149*

The USA is in the midst of an unprecedented public health crisis of opioid-related morbidity and mortality.

It is estimated that more than 2.5 million Americans have an opioid use disorder (OUD).
Depression that occurs as a result of opioid intoxication or withdrawal is denoted as an opioid-induced mood disorder.

The U.S. Opioid Epidemic: Deaths due to opioids

- Drug overdose deaths are the leading cause of injury death in the United States


Opioids-Related Deaths in USA Quadrupled


Death in Bed Syndrome

• Individuals on opioids are discovered dead in bed during the day

• In most cases the cause of death is unexplained, except opioids in the blood
Question # 1

- Individuals on opioids are discovered dead in bed and in most cases the cause of death is unexplained, except opioids in the blood what is the potential cause?

1. SDB (hypoventilation, CSA, OSA)
2. Torsade
3. both
What are the potential causes of death while asleep in patients on opioids?

1. Arrhythmias/ cardiac arrest

2. Respiratory depression

Polymorphic ventricular tachycardia (PVT) is a form of ventricular tachycardia in which there are multiple ventricular foci with the resultant QRS complexes varying in amplitude, axis and duration.

Torsades de pointes (TdP) is a specific form of polymorphic ventricular tachycardia occurring in the context of QT prolongation.

TdP has a characteristic morphology in which the QRS complexes “twist” around the isoelectric line.

For TdP to be diagnosed, the patient has to have evidence of both PVT and QT prolongation.
1. Arrhythmogenic death

An association between methadone and torsade de pointes was first described in 2002

This is mediated by a blockade of the human ion channel responsible for the delayed rectifier potassium current

Drugs which reduce the magnitude of outward repolarizing K+ currents, enhance inward depolarizing Na+ or Ca2+ currents, or both, thereby triggering the development of early afterdepolarizations that initiate the tachyarrhythmia

1. Arrhythmogenic death

FDA added a boxed warning for methadone in 2006 about arrhythmia risk followed by a clinical practice guideline in 2009 recommending QTc interval screening

U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) report of adults with QTc prolongation or torsade de pointes and ventricular arrhythmia or cardiac arrest

From November 1997 and June 2011, 1646 cases of ventricular arrhythmia or cardiac arrest and 379 cases of QTc prolongation or torsade de pointes were associated with methadone.

After 2000, methadone was the second-most common primary suspect in cases of QTc prolongation or torsade de pointes and was associated with disproportionate reporting similar to that of antiarrhythmic agents known to promote torsade de pointes.

Antiretroviral drugs for HIV were the most common co-administered drugs.
What are the potential causes of death while asleep in patients on opioids?

1. Arrhythmias/ cardiac arrest

2. Respiratory depression

2. Respiratory Depression

Terminal apnea is sine qua non of death due to opioids

OSA, CSA, hypoventilation, impairment of arousal, combo drugs
Death in Bed Syndrome (DIBS)

- His maid heard him snoring at 12:00 p.m. and he was found dead 3 hours later.
- The medical examiner spokeswoman said:
- "Mr. Heath Ledger died as a result of acute intoxication by the combined effects of oxycodone, hydrocodone, diazepam, temazepam, alprazolam, and doxylamine"
- The only abnormality found was the drug levels noted.
- Mr. Heath Ledger died from opioid-induced respiratory depression and sleep apnea

Respiratory Depression

- Although acute use of opioids may cause CO$_2$ retention, chronic respiratory acidosis, a reflection of long-term respiratory depression is not common or is mild in most cases.

- However, respiratory depression in the form of sleep apneas and hypopneas, both obstructive and central, and hypoventilation are prevalent in patients who are chronically using opioids.
Opioids and sleep apnea (Javaheri, JCSM, 2008)

This is also PB

What is wrong with this patient?

Javaheri, Atlas of Sleep Medicine, 2013
Opioids and sleep apnea
Javaheri et al, JCSM, 2014

Current Prevalence of Sleep Apnea in USA

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI &gt; 5/hr (30-70)</td>
<td>26</td>
<td>34</td>
</tr>
<tr>
<td>AHI &gt; 15/hr (30-70)</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Women (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI &gt; 5/hr (30-70)</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>AHI &gt; 15/hr (30-70)</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>
Question #2

• Comparing SDB in patients on opioids to general population (False or true)

1. Similar to general population, SDB is more common in older people.

2. Similar to general population, SDB is more common in men than women.

3. Central apneas are more common in patients on opioids.

4. The pattern of CSA with opioids is more or less similar to that in HF.

5. Currently, the best treatment for CSA is O₂.
Opioids sleep apnea phenotype compared to general population OSA

1. More prevalent
2. More severe
3. CSA is common
4. No gender predilection
5. Thin OSA common
6. Age not an issue

Retrospective chart review of 98 consecutive patients on chronic opioids in pain clinic (Mogri, Sleep Breath, 2009)

41 of 98 were women

Hypopnea: 30% ↓ in airflow and 3% desat

- 85% in men
- 17% in women

- 34% in men
- 6% in women

- 15
- 50%
- 35%
- 43%
Prevalence of SA in patients on chronic opioids in pain clinic
(140/392 consecutive patients)
Webster et al, Pain Medicine, 2008

Women: 85/140
Hypopnea: 30%↓ in airflow and 3% desat
34% in men
17% in women

<table>
<thead>
<tr>
<th>AHI &lt; 5</th>
<th>AHI ≥ 5</th>
<th>AHI ≥ 15</th>
<th>AHI ≥ 30</th>
<th>CAI ≥ 5</th>
<th>CAI ≥ 15</th>
<th>CAI ≥ 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>75</td>
<td>50</td>
<td>36</td>
<td>33</td>
<td>23</td>
<td>14</td>
</tr>
</tbody>
</table>

13% in men
6% in women

1 % in general population?

Case control Australian study inpatients on methadone
Wang et al, Chest 2006

N=50 patients; 25 women
25 subjects: age, gender and BMI matched: CAI≤ 1

<table>
<thead>
<tr>
<th>CAI &lt; 5</th>
<th>CAI ≥ 5</th>
<th>CAI ≥ 10</th>
<th>CAI ≥ 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>30</td>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>
Buprenorphine and SA

Buprenorphine: a semysynthetic μ- agonist used for opioids dependency
N=70 consecutive patients on Suboxone
Mean age = 32
Mean BMI = 25
Female 60%
Mean values: AHI = 20
CAI = 11
OAI = 2
% time TST, SaO₂ < 90% = 23
Phenotypes of Sleep Disordered Breathing in General Population VS. Patients on Opioids

<table>
<thead>
<tr>
<th>Variable</th>
<th>General population</th>
<th>Opioids</th>
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<tbody>
<tr>
<td>Prevalence</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Irrelevant</td>
</tr>
<tr>
<td>Obesity</td>
<td>Prevalent</td>
<td>Irrelevant</td>
</tr>
<tr>
<td>Age</td>
<td>Relevant</td>
<td>Irrelevant</td>
</tr>
<tr>
<td>AHI, severity of SDB</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>CAI, n/h</td>
<td>Minimal</td>
<td>High</td>
</tr>
<tr>
<td>Pattern</td>
<td>Periodic</td>
<td>Ataxic</td>
</tr>
<tr>
<td>CPAP-emergent CSA</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

Buprenorphine and SA
G Protein coupled receptor (GCPR)
7 transmembrane domain receptors

Many second messengers: cyclic AMP [cAMP], diacylglycerol [DAG], and inositol 1, 4, 5-triphosphate [IP3]

Opioid Receptors

• Opioid ligand binding ► inhibitory IC pathways:
  Closure of voltage sensitive Ca++ channels
  Stimulation of K+ efflux
  ▼cAMP
  Neuronal depression

Few respiratory centers of interest:

1. Hypoglossal motor neuron pool
2. Pro-Botzinger Complex
Opioid-induced ventilatory depression

1. OSA
2. CSA
3. Hypoventilation and nonapneic desaturation

Mechanisms of Opioid-Induced Obstructive Sleep Apnea

Microdialysis perfusion at the hypoglossal motor pool in isoflurane anesthetized rats

In adult rats, application of opioids at the hypoglossal motor neuron pool diminishes the activity of the genioglossal muscle

Hajiha et al, J Physiol, 2009
ACS F, fentanyl and naloxone applied via microdialysis perfusion at the hypoglossal motor pool in isoflurane anesthetized rats

1. Application of the μ-opioid receptor agonist fentanyl at the hypoglossal motor pool causes suppression of tongue respiratory muscle activity
2. This is specific effect on HMNP
3. no effect on diaphragmatic activity
4. No effect on BP
5. This suppression is reversed by application of the μ-opioid receptor antagonist naloxone
Opioid Receptors

- Opioid ligand binding ► inhibitory IC pathways:
  - Closure of voltage sensitive Ca^{++} channels
  - Stimulation of K^{+} efflux
  - ▼ cAMP
  - Neuronal depression

Few respiratory centers of interest:

1. Hypoglossal motor neuron pool (OSA)
2. Pro-Botzinger Complex (CSA)

Javaheri
Determinants of carbon dioxide tension
In: Acid-Base Disorders and Their Treatment
2005; 47-77
In adult rats, ablation of preBotzinger complex neurons with saporin-substance P causes central apnea, initially during sleep and then also during wakefulness (McKay Janczewski Feldman, Nat Neurosci, 2005)
Mechanisms of Opioid-Induced Central Sleep Apnea

1. IV administration of fentanyl results in depression of respiratory rate
2. Localized in vivo application of μ-opioid receptor agonists to preBötC produces respiratory depression or fatal apnea
3. Local application of the μ-opioid receptor antagonist naloxone to the preBötzingen Complex prevents RR depression

Montandon et al, J Neurosci, 2011
non-REM sleep

<table>
<thead>
<tr>
<th>Condition</th>
<th>RR (50)</th>
<th>Diaph EMG</th>
<th>Neck EMG</th>
</tr>
</thead>
<tbody>
<tr>
<td>aCSF</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAMGO 20 μM + aCSF</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naloxone 100 μM + aCSF</td>
<td>100</td>
<td></td>
<td></td>
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</tbody>
</table>

1 sec
Mechanisms of Opioid-Induced Central Sleep Apnea

- Localized *in vivo* application of µ-opioid receptor agonists to preBötzinger Complex produces respiratory depression or fatal apnoea

- In vitro, µ-opioid receptor agonists preferentially inhibit preBötzinger Complex neurons expressing neurokinin-1 receptor

- Depression is most pronounced in states of anaesthesia and sleep

- Montandon et al, J Neurosci, 2011

Mechanisms of Opioid-Induced Central Sleep Apnea

1. IV administration of fentanyl results in depression of respiratory rate

1. Localized in vivo application of µ-opioid receptor agonists to preBötzinger Complex produces respiratory depression or fatal apnoea

3. Local application of the µ-opioid receptor antagonist naloxone to the preBötzinger Complex prevents RR

4. Depression is most pronounced in states of anaesthesia and sleep
Treatment of SA
Associated with the Use of Opioids

- Withdrawal of opioids
- PAP devices
  - CPAP/bilevel: not recommended
  - Bi-level with back up rate
  - ASV
- Phrenic N stimulation
- Drugs
  - Naloxone, ampakines, naltrexone
  - O₂, acetazolamide, theophylline

A 44-year-old female was referred for evaluation of possible sleep apnea. She complained of habitual snoring, witnessed apnea, frequent nocturnal awakenings, nocturia, non-restorative sleep, and excessive daytime sleepiness. She scored 17 our of 24 on the Epworth Sleepiness Scale.

She was on OxyContin® 40 mg TID and Vicodin® up to 4 times daily for chronic pain stemming from a craniotomy and decompression for Chiari malformation six years ago. She was also on Cymbalta® 20 mg daily for depression at the initial visit.

Her BMI was 33.5 kg/m²

<table>
<thead>
<tr>
<th>Evolution of sleep apnea before and after detoxification</th>
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<tbody>
<tr>
<td><strong>On opioids</strong></td>
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<tr>
<td>Type of Study</td>
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<tr>
<td>Date</td>
</tr>
<tr>
<td>AHI, n/hr</td>
</tr>
<tr>
<td>OAI, n/hr</td>
</tr>
<tr>
<td>CAI, n/hr – Total</td>
</tr>
<tr>
<td>CAI, n/hr – Non-REM</td>
</tr>
<tr>
<td>CAI, n/hr – REM</td>
</tr>
</tbody>
</table>

Opioids Cause Central and Complex Sleep Apnea in Humans: Reversal with Discontinuation
### Treatment of SA Associated with the Use of Opioids

#### Withdrawal of opioids
- There are 3 cases of opioids–induced sleep apnea reversed with detoxification
  
  2 with PSG and 1 with oximetry


### Treatment of SA Associated with the Use of Opioids

- Withdrawal of opioids
- PAP devices
  - CPAP/bilevel: not recommended
  - Bi-level with back up rate
  - ASV
- Phrenic N stimulation
- Drugs
  - Naloxone, ampakines, naltrexone
  - \(O_2\), acetazolamide, theophylline
1. Treatments of OSA

CPAP is the treatment of choice

CPAP-emergent central sleep apnea may occur

Opioids, OSA, CPAP-emergent CSA

**Inclusion Criteria**

- Opioid use ≥ 12 months
- Diagnosis of OSA on diagnostic PSG (AHI > 5)
- Age ≥ 18 y; mean age = 46 y; 50% women
- Mean BMI= 25.5 kg/m²
- Naïve to positive airway pressure treatment or surgical treatment for OSA
- Absence of heart failure, CAD, renal failure, CVA, neurologic disease, history of head trauma

Guilleminault, Cao, Yue, Chawla, Lung 2010
Results: (All 42 pts underwent Bilevel with back-up rate)

**Diagnostic PSG:**
AHI= 44; 31 of 42 had AHI ≥ 30/ h of sleep
CAI 0.6

**CPAP titration:** (mean pressure 14 ± 2 cm H₂O)
Mean OAHI = 0
Mean CAI = 14

**Bilevel titration:** (mean IPAP 17, EPAP 12)
Mean CAI = 12

**Bilevel with back up rate:**
Mean CAI = 2

Guilleminault, Cao, Yue, Chawla, Lung 2010
Treatment of opioid-induced central sleep apnea

2 phenotypes

1. CPAP emergent central sleep apnea
2. CSA present in the diagnostic PSG

Treatment of CSA
Associated with the Use of Opioids

PAP devices
CPAP/bilevel: not recommended
Bi-level with back up rate
ASV
### Sleepiness in Patients on Opioids

<table>
<thead>
<tr>
<th>Epworth Sleepiness Scale</th>
<th>12 ± 4 (mean ± SD)</th>
<th>4-20 (range)</th>
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</thead>
<tbody>
<tr>
<td>Falling asleep while,</td>
<td>Watching television</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Reading</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Driving</td>
<td>16</td>
</tr>
</tbody>
</table>

Sleep apnea associated with opioids (Javaheri, JCSM, 2014)

[Graph of sleep apnea associated with opioids]
Sleep apnea associated with opioids
CPAP (5 cm H₂O)

CPAP (10 cm H₂O)
### SA in 9 consecutive patients

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>CPAP 1</th>
<th>CPAP 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>45 ± 22</td>
<td>34 ± 19</td>
<td>33 ± 18</td>
</tr>
<tr>
<td>CAI</td>
<td>20 ± 21</td>
<td>20 ± 14</td>
<td>19 ± 17</td>
</tr>
</tbody>
</table>

CPAP was not recommended for the remaining 11 patients.

### ASV

![ASV Diagram]
Central apnea index (CAI) across the night on PAP devices compared to baseline for the 20 patients

Long-term FU

1 patient refused using ASV and 2 lost to follow up in less than a month.

17 patients were followed for a minimum of 9 months and up to 6 years.
   Mean± SD = 25±5.2 months

The mean long-term adherence was 5.1±2.5 hours.

Home AHI = 3.3±3.4 (range was 0 to 8.7) in 6 patients whose device had the related algorithm.

The mean ESS was 12.4±4.6 at baseline
   10.7±5.8 on CPAP
   10.4±4.6 on ASV at final FU
Conclusions and future directions

1. CNCPC are common and opioids have become part of contemporary management of chronic pain patients.
2. Chronic pain is common and a large number of patients are on opioids.
3. Individuals on opioid are found dead in bed without a cause at autopsy except drugs.
4. Cause of death: cardiac or respiratory.
5. Opioids-associated sleep apnea can be effectively treated with PAP devices.
6. RCT with various drugs badly needed: Ampekines.

Morphine, Morpheus, Hypnos, Nyx and Thanatos

- Morpheus was one of the many sons of Hypnos. In Greek mythology Hypnos was the god of sleep. The Romans called him Somnus (somnology).
- Hypnos was kind and gentle with good sleep hygiene! He had the power to induce sleep even in gods.
- Appropriately, his mother, Nyx was the goddess of night.
- Hypnos had many sons; Morpheus was the most famous. Morpheus would take the shape of humans and appear in their dreams.
- Morphine, the juice extracted from the opium poppy Papever somniferum, is named after Morpheus.
- Morpheus’ uncle was Thanatos, the god of death.
How beautiful and how deadly
The opium poppy
Papaver somniferum