Management of Sleep-Disordered Breathing: case based approach

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• Consultant for Ikaria Pharmaceuticals
Overview

• Introduction and definitions
• Case 1: Diagnosis of obstructive sleep apnea (OSA)
• Case 2: Treatment of OSA
• Case 3: Neurocognitive deficits in OSA
• Conclusion
Introduction

- International Classification of Sleep Disorders-3 (ICSD-3):
  - Obstructive Sleep Apnea disorders
  - Central Sleep Apnea syndromes
  - Sleep related hypoventilation disorders
  - Sleep related hypoxemia disorder
  - Isolated symptoms and normal symptoms
Epidemiology

• Obstructive sleep apnea (OSA) affects approximately 15 million adult Americans (1)
• OSA is seen in a large proportion of patients who have hypertension, coronary artery disease, stroke and atrial fibrillation (2)
• Prevalence of OSA is 2% in women and 4% in men in the 30-60 year age group (3)

(2) Lattimore JD et al, Obstructive sleep apnea and cardiovascular disease J Am Coll Cardiol 2003;41:1429-1437.
(3) Young T et al, The occurrence of sleep-disordered breathing among middle-aged adults, NEJM1993 Apr 29;328(17):1230-5
Definitions

• **Apnea:** ≥ 90% ↓ in airflow for > 10 seconds

• **Hypopnea (AASM definition):** ↓ in airflow by ≥ 30% for 10 seconds with ≥ 3% desaturation or arousal

• **RERA:** ↓ in airflow with an arousal which does not met the definition of apnea/hypopnea

• **Medicare definition of hypopnea:** ↓ in airflow by ≥ 30% for 10 seconds with ≥ 4% desaturation

• **AHI:** apnea-hypopnea index (apneas + hypopneas/hour of sleep)

• **RDI:** respiratory disturbance index (apneas + hypopneas + RERA’s/hour of sleep)
Figure 1. Baseline diagnostic polysomnogram indicating severe obstructive sleep apnea. Patient at baseline demonstrates primarily obstructive sleep apneas during a 2-minute epoch of Stage 2 sleep.
OSA in Adults

- **Mild OSA**: AHI/RDI $\geq 5$ and $< 15$/hour
- **Moderate OSA**: AHI/RDI $\geq 15$ to $\leq 30$/hour
- **Severe OSA**: AHI/RDI $> 30$/hour

- **Treatment for mild OSA** with symptoms or moderate OSA with/without symptoms
Partial and complete airway obstruction resulting in hypopnea and apnea

American Academy of Sleep Medicine

Levels of Evidence
- I: Randomized trials with low $\alpha$ and $\beta$ errors
- II: Randomized trials with high $\alpha$ and $\beta$ errors
- III: Nonrandomized concurrently controlled studies
- IV: Nonrandomized historically controlled studies
- V: Case Series

Levels of Recommendations
- **Standard**: high degree of certainty, level I or strong level II evidence
- **Guideline**: moderate degree of clinical certainty, level II or a consensus of level III evidence
- **Option**: uncertain clinical use, inconclusive or conflicting evidence or conflicting expert opinion
Patients at high risk for OSA (1):
- Obesity (BMI > 35)
- Congestive Heart Failure
- Atrial Fibrillation
- Refractory hypertension
- Type 2 Diabetes
- Nocturnal Dysrhythmias
- Stroke
- Pulmonary Hypertension
- High-risk driving populations
- Preoperative for bariatric surgery

Clinical features of OSA:
- Daytime Sleepiness
- Non-restorative sleep
- Witnessed apneas
- Snoring
- Insomnia
- Memory loss
- Lack of concentration
- Mood changes
- Morning headaches
- Polycythemia
- Hypercapnia
- Nocturia
- Irritability
- Decreased libido

Screen for OSA

Physical exam findings consistent with OSA:
- Mallampati score 3 or 4
- Macroglossia
- BMI ≥ 30
- Tonsillar hypertrophy
- Elongated uvula
- High arched palate
- Large neck circumference

Sleep Study

(1) LJ Epstein et al, JCSM, 2009
Figure 1. The Mallampati score:
Class 1. Complete visualization of the soft palate
Class 2. Complete visualization of the uvula
Class 3. Visualization of only the base of the uvula
Class 4. Soft palate is not visible at all
Higher Mallampati scores are associated with higher overall AHI

Nuckton TJ et al, Sleep, 2006
STOP-BANG questionnaire

- Snoring
- Tiredness
- Observed you stop breathing
- Blood Pressure
- BMI > 35
- Age > 50
- Neck Circumference > 40 cm
- Gender Male

High Risk: Yes to ≥ 3 items → Refer for sleep testing

Chung F. et al, Anesthesiology, May 2008
Prevalence of resistant hypertension increases with OSA severity

**Figure 2.** Prevalence of resistant hypertension by intensity of OSAS.
Case 1

42 years old female patient presented with history of snoring, daytime hypersomnolence (Epworth Sleepiness Score 14) and fatigue

**PMHx:**
- Obesity
- Hypertension
- Diabetes mellitus
- Hyperlipidemia
- SLE
- Fibromyalgia

**Physical exam findings:**
- BP 166/100 mm Hg
- Other vitals normal
- BMI 38
- Upper airway Mallampati 4
### Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations? Answer considering how you have felt over the past week or so.

0 = Would never doze  
1 = Slight chance of dozing  
2 = Moderate chance of dozing  
3 = High chance of dozing

<table>
<thead>
<tr>
<th>Number</th>
<th>Activity</th>
<th>Score</th>
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<tbody>
<tr>
<td>1</td>
<td>Sitting and reading</td>
<td></td>
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<tr>
<td>2</td>
<td>Watching TV</td>
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<tr>
<td>3</td>
<td>Sitting inactive in a public place (e.g., theater or meeting)</td>
<td></td>
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<tr>
<td>4</td>
<td>As a passenger in a car for an hour without a break</td>
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<tr>
<td>5</td>
<td>Lying down to rest in the afternoon when able</td>
<td></td>
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<tr>
<td>6</td>
<td>Sitting and talking to someone</td>
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<tr>
<td>7</td>
<td>Sitting quietly after a lunch without alcohol</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>In a car while stopped for a few minutes in traffic</td>
<td></td>
</tr>
</tbody>
</table>

Johns MW, Sleep 1991
Which of the following tests would NOT definitively exclude a diagnosis of OSA:

A. Attended polysomnogram (PSG)
B. Unattended portable polysomnogram
C. Portable monitor
D. Nocturnal oximetry

D. Nocturnal oximetry
Types of Sleep Studies

• **Type I**: in-lab attended polysomnogram (gold standard, ≥7 channels)
• **Type II**: comprehensive portable unattended polysomnogram (≥7 channels)
• **Type III**: modified portable sleep apnea testing (cardiorespiratory sleep studies, 4-7 channels)
• **Type IV**: 1 or 2 channels, oximetry is 1 channel

Practice parameters for the use of portable recording in the assessment of obstructive sleep apnea. Sleep 1994
Types of sleep studies

- Diagnostic PSG
  - AHI ≥40/hour or 20-40/hour with low SO2
- Split PSG
- Titration PSG
  - Physician specified AHI
You choose to screen an asymptomatic individual for OSA. A portable monitor (home sleep apnea test) would be the best testing modality for this purpose:

A. True
B. False
Clinical Guidelines for the Use of Unattended Portable Monitors in the Diagnosis of Obstructive Sleep Apnea in Adult Patients

Portable Monitoring Task Force of the American Academy of Sleep Medicine

Task Force Members: Nancy A. Collop, M.D. (Chair); W. McDowell Anderson, M.D.; Brian Boehlecke, M.D., M.S.P.H.; David Claman, M.D.; Rochelle Goldberg, M.D.; Daniel J. Gottlieb, M.D., M.P.H.; David Hudgel, M.D.; Michael Sateia, M.D.; Richard Schwab, M.D.

Collop, N. et al, JCSM, October 2007
Indications for Portable Monitoring

• PM is done only in conjunction with a comprehensive sleep evaluation
• PM is only indicated in patients with a high pre-test probability of moderate to severe OSA
• No PM in patients with co-morbid conditions or other sleep disorders
• PM is NOT for screening asymptomatic individuals
• PM measures AHI/total recording time, so underestimates AHI

Collop, N. et al, JCSM, October 2007
Case 2

- A 50 years old morbidly obese (BMI 50) male patient had a diagnostic polysomnogram which showed an apnea-hypopnea index of 50/hour, a SO2 nadir of 70% and an end tidal CO2 of 70 mm Hg. The patient has come for a follow up visit to discuss treatment options for OSA.
Which of the following would NOT be an effective therapeutic option for this patient:

A. Mandibular-maxillary advancing appliance
B. Genioglossal-hyoid advancement
C. Positive airway pressure
D. Tracheostomy
Treatment of OSA

Positive Airway Pressure
- CPAP
- BIPAP
- BIPAP ST
- APAP

Oral appliances
- Tongue retaining device
  - Mandibular repositioning device

Upper airway surgery
- UPPP
- Adenotonsillectomy
- Genioglossus advancement
- Hyoid suspension
- Mandibular advancement
- Tongue reduction
- Maxillomandibular advancement
- Tracheostomy

New treatments
- Hypoglossal nerve stimulation
- Provent

Adjunctive therapy
- Bariatric surgery
- Leukotriene inhibitors
- Nasal steroids
AASM guidelines on Positive Airway Pressure treatment

• CPAP is indicated for moderate to severe OSA (standard) and for mild OSA (option)
• CPAP is indicated for improving self-reported sleepiness in OSA patients (standard)
• CPAP is recommended as adjunctive therapy to lower blood pressure in hypertensive patients with OSA (option)
• Heated humidification should be added (standard)
• BIPAP can be used where high pressure is needed with difficulty on exhalation and with coexisting central hypoventilation (guideline)

Kushida CA et al, Sleep 2006
AASM guidelines on auto-titrating devices (APAP)

• APAP should not be used in patients with (standard):
  - congestive heart failure
  - significant lung disease like COPD
  - low SO2 due to conditions other than OSA
  - patients who do not snore
  - patients with central sleep apnea

• APAP devices may be used to identify a single CPAP pressure or for unattended treatment in moderate to severe OSA without significant comorbidities (option)

Morgenthaler TI et al, Sleep 2008
Decreased C-Reactive Protein is seen in weight loss and weight loss + CPAP groups at 24 weeks
↓ insulin resistance and serum triglyceride levels are seen in weight loss and weight loss + CPAP groups and ↓ blood pressure is seen in all 3 groups at 24 weeks.

Chirinos JA et al, NEJM, June 2014
CPAP produces greater reduction in blood pressure than oxygen or a healthy lifestyle

<table>
<thead>
<tr>
<th>Variable</th>
<th>CPAP (N=90)</th>
<th>NSO (N=94)</th>
<th>HLSE (N=97)</th>
<th>CPAP vs. HLSE</th>
<th>NSO vs. HLSE</th>
<th>CPAP vs. NSO</th>
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<tr>
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<td>87.7±9.3</td>
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<tr>
<td>12 Wk</td>
<td>87.8±8.1</td>
<td>90.2±11.1</td>
<td>89.0±11.2</td>
<td>−2.4 (P=0.04)</td>
<td>0.4 (P=0.71)</td>
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<td>24-Hr mean systolic blood pressure</td>
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<tr>
<td>Baseline</td>
<td>124.7±13.5</td>
<td>125.3±16.9</td>
<td>123.6±14.3</td>
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<tr>
<td>12 Wk</td>
<td>123.4±12.8</td>
<td>126.9±16.5</td>
<td>124.7±16.4</td>
<td>−1.9 (P=0.25)</td>
<td>1.2 (P=0.45)</td>
<td>−3.1 (P=0.06)</td>
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<td>24-Hr mean diastolic blood pressure</td>
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</tr>
<tr>
<td>Baseline</td>
<td>72.0±7.7</td>
<td>70.8±8.3</td>
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<td></td>
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<tr>
<td>12 Wk</td>
<td>69.8±7.5</td>
<td>71.7±9.8</td>
<td>70.9±10.1</td>
<td>−2.8 (P=0.005)</td>
<td>−0.1 (P=0.95)</td>
<td>−2.8 (P=0.006)</td>
</tr>
</tbody>
</table>

Gottlieb DJ et al, NEJM, June 12, 2014
Oral Appliances

• Less effective than CPAP but may be preferred by patients over CPAP
• Indicated for mild to moderate OSA in patients unable to use CPAP and for primary snoring
• Follow up polysomnography or attended type III study should be done to confirm efficacy
• May aggravate temporo-mandibular joint disease and cause dental misalignment

Ferguson KA et al, Sleep 2006
Mandibular-Maxillary Advancing Appliance

Orthodonticreviews.blogspot.com,
www.sleephelpnw.com
Uvulopalatopharyngoplasty (UPPP)

Mandibular advancement surgery

4fraziers.com
Dentalmandibulartori.blogspot.com
Treatment of OSA in adults

1. PAP (1st line)

   - Oral Appliances for mild-moderate OSA (3rd line)
     - Upper airway surgery
   - Upper airway surgery for severe OSA (3rd line)
     - Tracheostomy

2. Upper airway surgery (2nd line)

3. Adjunctive therapy
Positive airway pressure intolerance

- **Dry mouth**: heated humidification, chinstrap
- **High pressure**: ramp, EPR, bipap
- **Mask intolerance/leak**: use a different interface
- **Rhinorrhea**: nasal saline, nasal steroids, antihistamines, heated humidification
- **Noise**
- **Bed partner complaints**
- **Unattractive appliance and headgear**
The patient is started on bipap 18/12 cm H2O and is struggling with it. He enquires about “a new implantable pacemaker for breathing”. You explain to him that hypoglossal nerve stimulation:

A. Is not a good choice for him as his sleep apnea is just too severe

B. Cannot be used for him due to his morbid obesity

C. Would be an effective treatment for him
Upper-Airway Stimulation for Obstructive Sleep Apnea

Patrick J. Strollo, Jr., M.D., Ryan J. Soose, M.D., Joachim T. Maurer, M.D., Nico de Vries, M.D., Jason Cornelius, M.D., Oleg Froymovich, M.D., Ronald D. Hanson, M.D., Tapan A. Padhya, M.D., David L. Steward, M.D., M. Boyd Gillespie, M.D., B. Tucker Woodson, M.D., Paul H. Van de Heyning, M.D., Ph.D., Mark G. Goetting, M.D., Oliver M. Vanderveken, M.D., Ph.D., Neil Feldman, M.D., Lennart Knaack, M.D., and Kingman P. Strohl, M.D., for the STAR Trial Group*

NEJM, January, 2014
Hypoglossal Nerve Stimulation

- No anatomy alteration
- Works with patients physiology
- Standardized implant technique
- Fast post operative recovery
- No facial apparatus
- Patients start, stop or pause therapy using a sleep remote
- Therapy is titrated non invasively under the care of a sleep physician
Hypoglossal Nerve Stimulation

Drug Induced Sleep
Hypoglossal Nerve Stimulation
Stimulation On
Hypoglossal Nerve Stimulation effect during sleep study

Therapy turned on

Courtesy Inspire Medical Systems Inc.
Phase III Pivotal Study (STAR), n=126

**Study Design**
Prospective, multi-center single-arm trial with a randomized, controlled therapy withdrawal phase

**Key Patient Selection Criteria**

**Inclusion:**
- CPAP failure or intolerant
- Moderate to severe OSA

**Exclusion**
- BMI > 32 kg/m²
- Complete concentric collapse at the level of soft palate
- Significant central sleep apnea

**Study Endpoints**

Primary Endpoints at 12 months
- AHI and ODI reductions

Secondary Endpoints at 12 months
- Quality of life questionnaires
- Randomized withdrawal effect
• Use objective measures of OSA severity (AHI and ODI) for primary efficacy endpoint
• Long-term follow up at 12/18 months to evaluate sustained effect
• Randomized controlled withdrawal phase to confirm therapy effects
Hypoglossal Nerve Stimulation Decreased Median AHI at 12 Months

Strollo P, et. al., NEJM, 2014
Hypoglossal Nerve Stimulation improved Functional Outcomes of Sleep Questionnaire and Epworth Sleepiness Scores

Strollo P, et al., NEJM, 2014
Withdrawal of Hypoglossal Nerve Stimulation Returns Patients to Baseline Status

Strollo P, et. al., NEJM, 2014
FDA Indications for Hypoglossal Nerve Stimulation

- Age ≥ 22 years
- AHI 20-65/hour with < 25% central events
- Inability to use CPAP
- Free of complete concentric collapse at the palate
- BMI < 32
Case 3

A 52 year old male patient presented to the ED with new onset left sided hemiparesis

**PMHx:**
- Hypertension
- Hyperlipidemia
- Diabetes mellitus
- Obesity
- Tobacco abuse

**Physical exam:**
- BP 162/90 mm Hg
- Other vitals stable
- BMI 38
- Truncal obesity, ↑ neck circumference
- Cyclical oxygen desaturation to the mid 70’s during sleep
Case 3

• **Diagnostic PSG findings:** AHI 60/hour (obstructive), SO2 nadir 74%, 50 minutes of total sleep time with SO2 < 90%

• Patient was intolerant of CPAP

• He presents again 6 weeks later with memory impairment and daytime hypersomnolence

• Neuropsychological testing confirmed impairments in vigilance and memory
You tell the patient that his memory problems are related to:

A. His underlying stroke
B. OSA
C. Excessive sleepiness
D. All of the above
E. None of the above

D. All of the above
Proposed model for pathogenesis of CI in OSAS

Lal, C et al, Chest 2012
The Association between Obstructive Sleep Apnea and Neurocognitive Performance—The Apnea Positive Pressure Long-term Efficacy Study (APPLES)

- Cross-sectional study
- n=1204 patients
- Inclusion criteria: AHI ≥ 10/hour, age ≥ 18 years
- Neurocognitive data collected at baseline

Limitations:
- No control group
- High education level of study cohort
- OSA defined by 3% desaturation

Quan SF et al, Sleep 2011
Functional MRI results in 4 OSA+ subjects on task-switching compared to resting state

Average of impaired and unimpaired subjects

impaired > unimpaired subjects

unimpaired > impaired subjects

p=0.001 corrected (according to fixed effects analysis)
Conclusions

• OSA is a common disease with a significant impact on health and overall quality of life
• High risk patients should be assessed for OSA with a comprehensive clinical evaluation
• Hypoglossal nerve stimulation is a new treatment for moderate to severe OSA in patients who fail CPAP
• Neurocognitive decline in OSA is a real and unique syndrome and needs further study