

The Effect of Sleep Apnea on Mental Health

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Disclosure

- ▶ No conflict of interest to disclose

Outline/ Questions to Answer

- ▶ Is there an association between sleep apnea and mood disorders?
- ▶ Is there an association between sleep deprivation and mood disorders?
- ▶ Does treatment of sleep apnea improve mood disorders?
- ▶ Does treatment of mood disorders improve sleep apnea?
- ▶ Can treatment of mood disorders worsen sleep apnea?
- ▶ Is it worthwhile to keep sleep apnea in mind while treating mood disorders?

Definitions

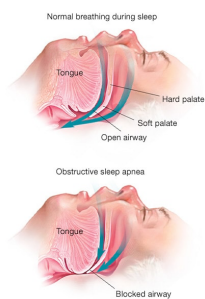
- ▶ The term "Sleep Apnea" was first mentioned in literature in 1965
- ▶ Symptoms of sleep apnea mentioned in literature in 1889 when referring to Pickwickian syndrome (Obesity and sleep problems)
- ▶ *Pickwick Papers*- collection of stories by Charles Dickens ultimately collected into a novel. First stories written in 1836.



Jung et al. Prog Brain Res. 1965;18:140-159
 Britannica. The Edition of Encyclopaedia. "The Pickwick Papers". Encyclopedia Britannica, 7 Dec. 2014

Sleep Apnea

- ▶ Can be divided into Obstructive and Central Sleep Apnea
- ▶ Obstructive Sleep Apnea is repeated collapse of upper airway causing decrease in airflow during sleep with INCREASED respiratory effort
- ▶ Central Sleep Apnea is decrease in respiratory airflow while sleeping and REDUCED respiratory effort
- ▶ Majority of data derived from OSA on this topic and for this talk will be referring to Obstructive Sleep Apnea as **Sleep Apnea**



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Sleep Apnea

Obstructive Sleep Apnea is repeated collapse of upper airway during sleep with increased respiratory effort

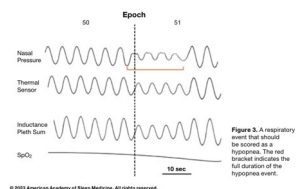
- 1) Leads to disrupted sleep and desaturation
- 2) Non-restorative sleep
- 3) Difficulty initiating or maintaining sleep (Insomnia)
- 4) Daytime sleepiness
- 5) Morning headache
- 6) Many other symptoms
- 7) Nocturia

Jordan et al. Lancet 2014; 22: 383: 736



Definitions

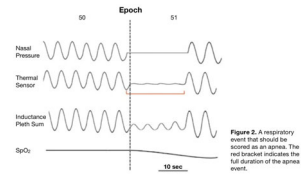
- **Hypopnea**- reduction in airflow > 30% for minimum of 10 seconds with reduction in oxygen saturation of 3% or arousal on EEG



AASM Scoring Manual 2023

Definitions

- **Obstructive Apnea:**
Reduction in airflow of 90% or greater for 10 seconds or more with INCREASED respiratory effort



AASM Scoring Manual 2023

Severity of Obstructive Sleep Apnea

- Combine the number of apneas and hypopneas and divide by number of hours of sleep to get the Apnea Hypopnea Index (AHI)
- **Mild OSA**
 - 5-15 events per hour
 - Treatment typically undertaken if associated symptom:
 1. Hypertension
 2. Excessive daytime sleepiness
 3. Depression
- **Moderate OSA**
 - 15-30 events per hour
 - Treat with or without associated symptoms
- **Severe OSA**
 - >30 events per hour

Prevalence of Sleep Apnea

- Mild Obstructive Sleep Apnea or greater
 - 15-30% of males
 - 10-15% of females
- Moderate Obstructive Sleep Apnea or Mild disease with symptoms
 - 5-15% of patients

Young et al. WJ 2009;108:246
Peppard et al Am J Epidemiol 2013; 177: 1006

Prevalence of Sleep Apnea

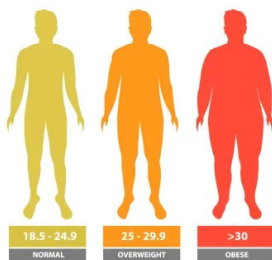
- ▶ Global prevalence of 425 million people with moderate or severe sleep apnea
- ▶ 936 million worldwide with mild sleep apnea or greater
- ▶ >22 million in US with moderate or severe sleep apnea

Young et al. WMJ 2009;108:246
Peppard et al Am J Epidemiol 2013; 177: 1006

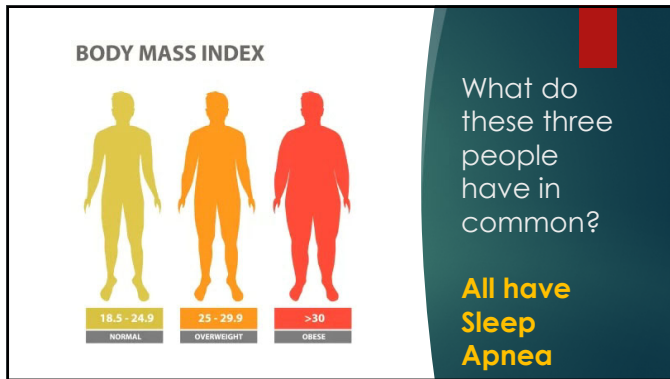
Risk Factors

- ▶ Well defined/established
 - ▶ Age
 - ▶ Male
 - ▶ Obesity
 - ▶ Upper Airway/ Craniofacial Abnormalities
- ▶ Less well defined/established
 - ▶ Family history
 - ▶ Smoking

BODY MASS INDEX



What do these three people have in common?



Sleep Apnea without Obesity

- ▶ 163 consecutive studies at a single academic center were reviewed
 - ▶ 25% diagnosed with OSA had BMI < 25
 - ▶ 54% had BMI < 30
- ▶ Study in Switzerland of 2000 individuals age 40-85 had rate of moderate sleep apnea or greater of 23% in women and 50% in men
 - ▶ Mean BMI of cohort was 25.6
- ▶ **Need to keep sleep apnea in mind even without obesity**

Gray et al. JCSM 2017; 13: 81
Heinzer et al. Lancet Respir Med. 2015 Apr;3(4):310-8

Complications of Sleep Apnea

- ▶ **Excessive daytime Sleepiness/ Sleep Deprivation**
 - ▶ Can worsen hypertension
 - ▶ Increase in complications with major surgery
 - ▶ Hyperglycemia/Diabetes mellitus/ Metabolic syndrome
 - ▶ Increased risk of stroke
- ▶ **Increased risk of sleep deprived partner**

Insomnia and Sleep Apnea

- ▶ 476 patients with OSA at academic sleep center were screened for insomnia with Insomnia Severity Index (ISI)
- ▶ 29% prevalence of co-morbid insomnia with obstructive sleep apnea (ISI >15)
- ▶ **Insomnia and sleep apnea are not mutually exclusive**
- ▶ **Common presentation of sleep apnea to Sleep Clinic is with presenting complaint of insomnia**

Cho et al. JCSM 2018 14:3:409

Sleep Onset vs Sleep Maintenance Insomnia

- ▶ Important to drill down on insomnia
- ▶ Sleep onset vs Sleep maintenance
- ▶ Sleep apnea can be a cause of sleep maintenance insomnia:
 - ▶ "I keep waking up at the same time at night"
 - ▶ "I get to sleep fine but wake up every 3 hours to go to the bathroom"
 - ▶ "I go to sleep very quickly but wake up and my sleep does not feel refreshing"
 - ▶ "I wake up to go to the bathroom at 2am every night"
 - ▶ "Every night I wake up gasping for air a couple of hours after I go to sleep"

Sleep And Mental Health

- ▶ 90% of patients with depression report a sleep disturbance
 - ▶ Daytime sleepiness
 - ▶ Insomnia
 - ▶ Snoring/sleep apnea
- ▶ Adults with depression more likely to have poor sleep efficiency
- ▶ Short sleep time < 6 hours can increase risk for anxiety
- ▶ Sometimes the patient we see with poor sleep quality is the partner of the one who actually has the sleep disordered breathing

Alcantara et al. SLEEP 2016;39(4):915



Association of Sleep Apnea with Depression and Anxiety

- ▶ 264,653 as part of National Survey on Drug Use and Health
- ▶ Those reporting sleep apnea were:
 - ▶ 3.11 times more likely to have depressive symptoms
 - ▶ 2.75 times more likely to have suicidal ideations
 - ▶ 3.68 times more likely to have anxiety

Kaufman et al Sleep Health 2017 3:4: 244

Association of Sleep Apnea with Depression

- ▶ Higher prevalence of depression with sleep apnea vs the general population
- ▶ Prevalence of 5-63% using mostly patient questionnaires (Beck, PHQ-9, HADS-D)

Edwards et al. JCSM 2015;11(9):1029
Diaz et al Innov Clin Neurosci 20118:8:17

Association of Sleep Apnea with Depression

- ▶ Study in 2014 found 46.1% of 178 patients met criteria for depressive symptoms by Beck Depression Inventory Score
 - ▶ Depression score was higher in those with more daytime sleepiness

Rezaei et al. J Res Med Sci 2014;19:205

Table 1

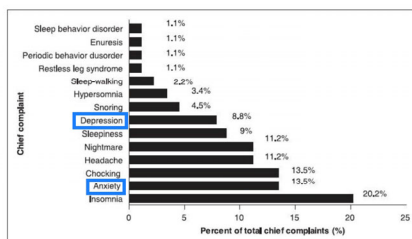
The frequency of the main symptoms of OSAS in males, females, and total population

Symptom	Frequency (%)			P value
	Male	Female	Total population	
Snoring	67.5	58.3	66.3	0.375
Anxiety	53.9	54.2	53.9	0.980
Choking	45.5	58.3	47.2	0.240
Depression	48.1	33.3	46.1	0.178
Insomnia	36.6	33.3	36.2	0.757
Nightmare	16.9	25.0	18.0	0.390
Sleepiness	13.0	25.0	14.6	0.128
Headache	13.0	16.7	13.5	0.538

According to χ^2 test, gender did not affect the frequency of main symptoms of OSAS ($P > 0.05$). OSAS=Obstructive sleep apnea syndrome

Rezaei et al. J Res Med Sci 2014;19:205

Figure 1



The incidences of the common chief complaints in patients with OSAS

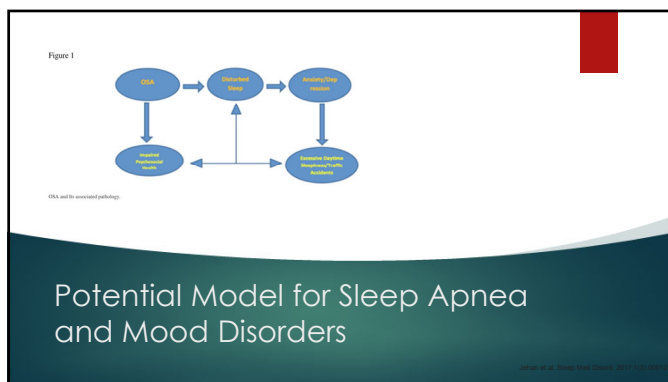
Rezaei et al. J Res Med Sci 2014;19:205

The association of the main symptoms of OSAS and its severity (assessed by AHI)

OSAS severity	Symptom	Frequency (%)			P value
		Mild	Moderate	Severe	
	Anxiety	13.5	19.8	66.7	0.001
	Depression	24.4	23.2	52.4	0.647
	Insomnia	18.8	18.8	62.5	0.192
	Choking	11.9	16.7	71.4	<0.001
	Snoring	16.9	25.4	57.6	0.127
	Headache	16.7	16.7	66.7	0.397
	Nightmare	18.8	18.8	62.5	0.544
	Sleepiness	46.2	30.8	23.1	0.001

OSAS=Obstructive sleep apnea syndrome; AHI=Apnea-hypopnea index; OSAS=Obstructive sleep apnea syndrome. According to χ^2 test, the frequency of anxiety and choking was significantly higher in patients suffering from severe OSAS (P 0.001 in anxiety and <0.001 in choking). On the contrary, sleepiness had a reverse correlation with the severity of OSAS (P 0.001).

Rezaeitalab et al. J Res Med Sci 2014;19:205



Association of Sleep Apnea with Depression

- ▶ 2016 Study looked at 1,784 adults:
 - ▶ The severity of sleep apnea did not predict association with depression
- ▶ Increased depression prevalence when sleep apnea accompanied by daytime sleepiness

Alcantara et al. SLEEP 2016;39(4):915

Association of Sleep Apnea with Depression

- ▶ 2016 study looked at 284 patients with moderate obstructive sleep apnea utilized a Psychiatric interview
- ▶ 21% diagnosed with dysthymia or major depression
- ▶ Depression can also cause daytime sleepiness emphasizing the importance of evaluating mental health among sleepy OSA patients and considering sleep evaluation in sleepy depressed patients

Bjornsdottir et al. JCSM 2016;12(1): 105

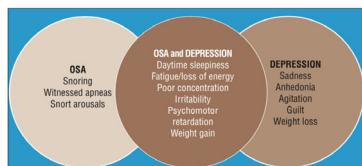
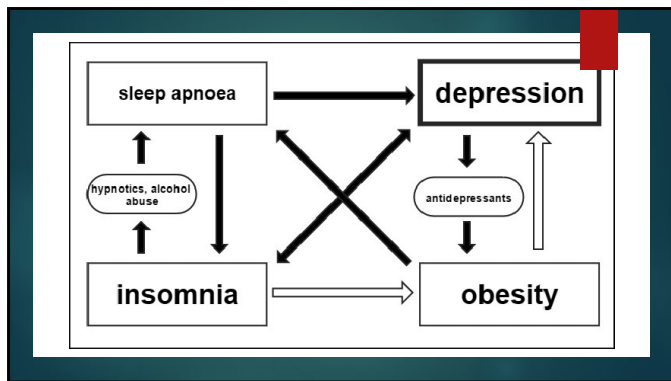


FIGURE 2. Overlapping symptoms of obstructive sleep apnea (OSA) and major depression. Adapted from: American Academy of Sleep Medicine. *International Classification of Sleep Disorders, Second Edition, Diagnostic and Coding Manual*. Westchester, IL: American Academy of Sleep Medicine; 2005.¹⁴ American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Association; 2000.¹⁵ and Kryger, MH, Roth T, Dement WC (eds). *Principles and Practice of Sleep Medicine, Fourth Edition*. Philadelphia, PA: W.B. Saunders; 2005.¹⁶

Pathophysiology

- ▶ Sleep deprivation and disturbance can cause psychological stress
- ▶ Excessive sleepiness, fatigue, and inability to concentrate can limit enjoyment of social interactions and can lead to isolation and feeling abandoned
- ▶ Impaired sleep can lead to impaired physical health and cognitive ability and work can suffer leading to a vicious cycle

Jehan et al. Sleep Med Disord. 2017;1(3):00012



Depression and Sleep Apnea have Cardiac Consequences

- ▶ 4918 patients studied and divided in to categories
- ▶ Cardiovascular disease defined as:
 - ▶ Hospitalized acute MI, known CAD, Stroke, Angina, CHF, Coronary Bypass Graft (CABG)

Lou et al. Journal of Sleep research 2023 February. Early Access

Depression and Sleep Apnea have Cardiac Consequences

- ▶ Risk of CVD
 - ▶ 24.5% in Healthy without Depression or Sleep Apnea
 - ▶ 31% in Depression
 - ▶ 31.6% in Sleep Apnea
 - ▶ 41.7% in Sleep Apnea and Depression
- ▶ This was consistent across different Sleep Apnea severities

Lou et al. Journal of Sleep research 2023 February. Early Access



Does Treating Sleep Apnea with CPAP help Depression?

- ▶ Study in 2020 on 468 patients diagnosed with OSA and prescribed CPAP were surveyed using Hospital Anxiety and Depression Score- D (HADS-D)
 - ▶ In patients with baseline score >8, reduction in score by 1.8 (10.64→8.84)
 - ▶ Reduction in score seen in CPAP adherent patients only
- ▶ Suggests role of CPAP in reducing depressive symptoms

Lundström et al. *Sleep and Breathing* 2021;25:1277

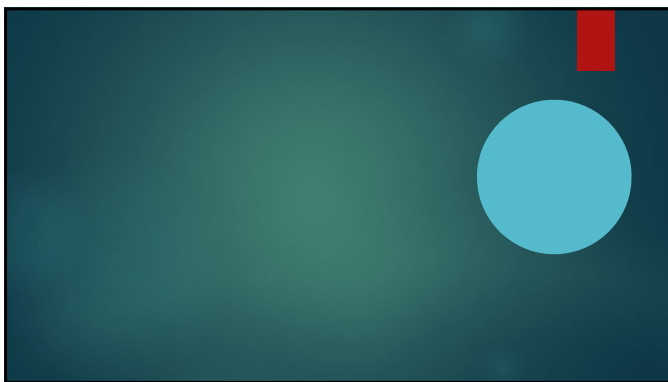
Does Treating Sleep Apnea with CPAP help Depression?

- ▶ Meta-analysis looked at SAVE Trial (Sleep Apnea Cardiovascular Endpoints)
- ▶ 2410 patients with CV disease and OSA (Moderate or greater)
- ▶ 221 with depressive symptoms on CPAP and 295 in usual care arm
- ▶ Significant decrease in depressive symptoms with CPAP

Zheng et al. *EClinicalMedicine* 2019;11:89

Depression/ Sleep Apnea/ and CPAP

- ▶ Possible roles for CPAP improving symptoms:
 - 1) reduction in daytime sleepiness
 - 2) Reduction in sleep fragmentation caused by apnea
 - 3) Reversal of hypoxemia
- ▶ Majority of studies driven by patient survey/standardized scoring
- ▶ Overall favor decrease in depressive symptoms with significant reduction in scores



Does Treatment with CPAP decrease anxiety

- ▶ Study in 2020 on 468 patients diagnosed with OSA and prescribed CPAP were surveyed using Hospital Anxiety and Depression Score- A (HADS-A)
 - ▶ 82 of these patients had a HADS-A score of 8 or greater
 - ▶ Reduction in score in these patients of 1.28 significant with $p < 0.001$
 - ▶ Entire cohort had reduction in score of 0.4, significant with $p < 0.001$

Lundström et al. Sleep and Breathing 2021;25:1277

Does Treatment with CPAP decrease anxiety

- ▶ Meta-analysis looked at SAVE Trial (Sleep Apnea Cardiovascular Endpoints)
- ▶ 2410 patients with CV disease and OSA(Moderate or greater)
- ▶ Treatment with CPAP improved depression but **NOT** Anxiety

Zheng et al EClinicalMedicine 2019;11:89

Does Treatment with CPAP decrease anxiety

- ▶ **Conflicting Studies with no definitive evidence that treatment with CPAP decreases anxiety or anxiety symptoms**

Sleep Deprivation

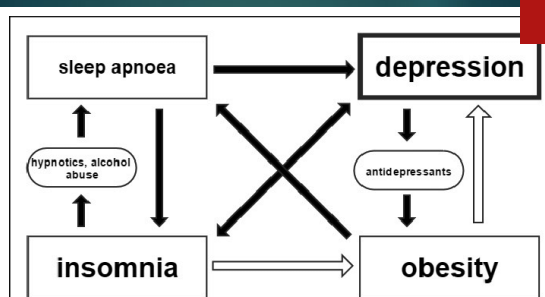
- ▶ Quantity and Quality of sleep must be kept in mind
- ▶ American Academy of Sleep Medicine recommends 7 hours of sleep per night
- ▶ Less than 7 hours of sleep led to cumulative deficits in alertness and vigilance
- ▶ Sleep deprived individuals take longer to respond to stimuli

Belenky et al. J Sleep Res. 2003 Mar;12(1):1-12.

Sleep Deprivation

- ▶ Chronic sleep deprivation can lead to:
 - 1) Elevated cortisol production
 - Correlations with anxiety and depression
 - 2) Decreased testosterone levels
 - Testosterone enhances function of GABA and serotonin systems
 - Possible causal link with depression and anxiety
- ▶ **Best treatment is to ensure adequate quality sleep**

Hanson et al STAT Pearls 2022 Jan





Drugs that can worsen Sleep Apnea

- ▶ Opiates
 - Respiratory depression
 - Cause relaxation of tongue and upper airway muscles
- ▶ Benzodiazepines
 - Klonopin may cause increase in apnea
 - No evidence the shorter acting benzos change AHI
 - Multiple studies saw lower oxygen saturation

Drugs that can worsen Sleep Apnea

- ▶ Baclofen
 - ▶ Best to avoid if possible in OSA
 - ▶ Relax upper airway muscles
 - ▶ Depresses respiratory drive
- ▶ Testosterone
 - ▶ Increases AHI
 - ▶ Increases time with low saturations

Desayes et al. Br J Clin Pharmacol 2017; 83: 688

Drugs that can worsen Sleep Apnea

► Drugs that induce weight gain:

- 1) Neuroleptics
- 2) Tricyclic antidepressants
- 3) MAO inhibitors
- 4) SSRI
- 5) Mirtazapine
- 6) Valproate, Gabapentin, carbamazepine
- 7) Steroids

Desayes et al., Br J Clin Pharmacol 2017; 83: 688

Using anti-depressant to treat Sleep Apnea?

- Reboxetine has been tested in combination with oxybutynin and more recently as mono therapy
- Hypothesis that norepinephrine reuptake inhibitors affects upper airway stability
- Effects tone in NREM sleep
- Also decreases REM sleep
- Reduction in AHI by 5
- Small study with more to follow

Altire et al., JCSM 2023;19[1]:85

Screening for Sleep Apnea in the Office

- ▶ Multiple validated questionnaires in **symptomatic** patients
- ▶ No validation in **asymptomatic** patients
- ▶ Berlin, STOP-BANG, STOP questionnaires



STOP

S	So you snore loudly (louder enough to be heard through closed doors or louder than talking)?	Yes	No
T	Do you often feel tired , fatigued or sleepy during the daytime?	Yes	No
O	Has anyone observed you stop breathing or choking or gasping during your sleep?	Yes	No
P	Do you have or are you being treated for high blood pressure ?	Yes	No

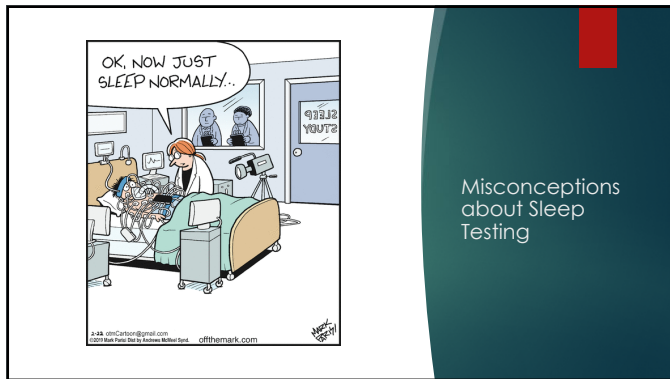
Bang

B	BMI more than 35?	Yes	No
a	Age – over 50 years old?	Yes	No
n	Neck circumference – is it greater than 17" if you are a male or 16" if you are a female?	Yes	No
g	Gender – are you a male?	Yes	No

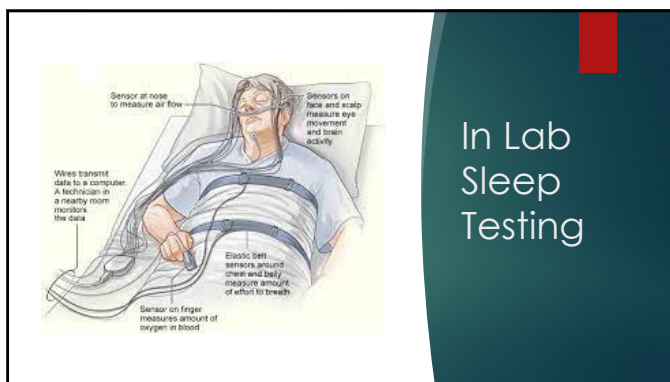
When to think about Sleep Apnea

- ▶ Can use screening questionnaire if symptomatic
 - ▶ Daytime sleepiness
 - ▶ Snoring
 - ▶ Apneas
- ▶ If asymptomatic
 - ▶ Not responding to anti-depressant therapy
 - ▶ Adding multiple medicines to try and get control of symptoms

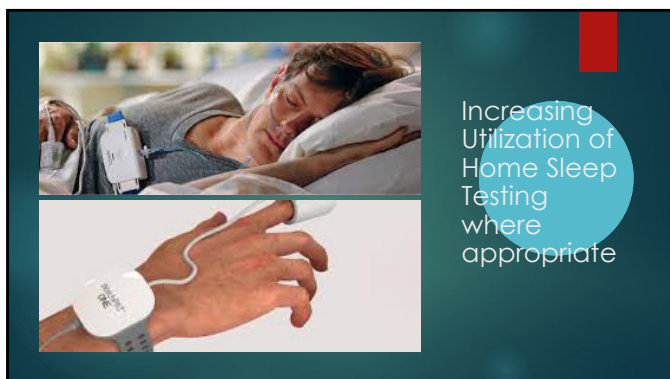




Misconceptions about Sleep Testing

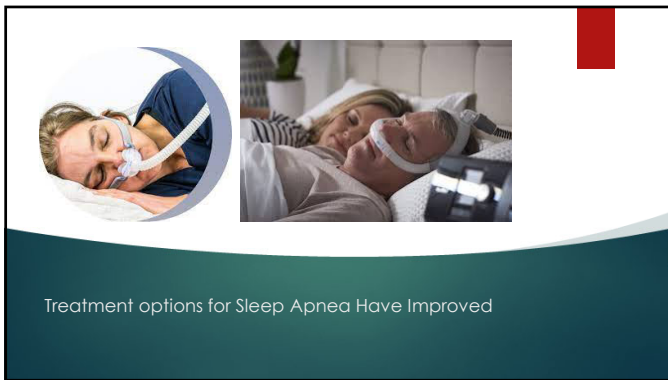


In Lab Sleep Testing

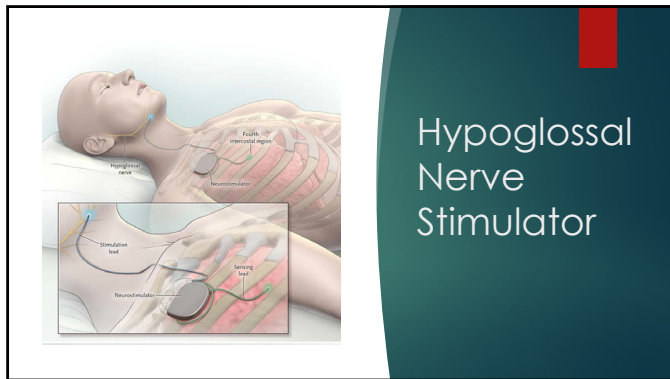


Increasing Utilization of Home Sleep Testing where appropriate









Summary

- ▶ The relationship between depression, sleep apnea, and sleep fragmentation can lead to diagnostic confusion
- ▶ Not addressing sleep apnea in patients with depression can lead to excess anti-depressant therapy or persistent depressive symptoms
- ▶ Not recognizing depression/anxiety in sleep apnea patients can rely therapy and make CPAP adherence worse

Outline/ Questions to Answer

- ▶ Is there an association between sleep apnea and mood disorders?
 - ▶ Yes, well established
- ▶ Is there an association between sleep deprivation and mood disorders?
 - ▶ Yes
- ▶ Does treatment of sleep apnea improve mood disorders?
 - ▶ Yes with Depression/ Not clear with Anxiety

Outline/ Questions to Answer

- ▶ Does treatment of mood disorders improve sleep apnea?
 - ▶ Not proven/ Clinical trial with reboxetine
 - ▶ Controlling anxiety may help with CPAP adherence
 - ▶ REM suppression with some anti-depressants can potentially ~~lead to~~ *lead to* with REM predominant sleep apnea
- ▶ Can treatment of mood disorders worsen sleep apnea?
 - ▶ Yes, through weight gain
- ▶ Is it worthwhile to keep sleep apnea in mind while treating mood disorders?
 - ▶ I hope we have established the importance of this

Other Take Home Points

- ▶ Keep in mind the patient may be the sleepy partner and not the one with sleep apnea
- ▶ The diagnosis for large portion of patients has gotten easier
- ▶ The treatment of sleep apnea has gotten better with improvements in CPAP comfort and alternative options to CPAP

Thank You

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