Why am I so tired?

Sleep Disorders – Impact on Mood

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Financial Conflict of Interest

- None

Objectives

- 1. Understand how obstructive sleep apnea affects mood
- 2. Understand how restless leg syndrome affects mood
- Understand how insufficient sleep affects mood

Obstructive Sleep Apnea

- AHI = Apnea Hypopnea Index
  - Number of obstructive apneas and hypopneas per hour
- Sleep Apnea = AHI of 5 or greater with symptoms of sleep apnea (sleepiness, gasping respirations, heart disease, mood disturbance)
- 5 - 15 mild, 15 - 30 moderate, >30 severe

OSA: Left or Right?

Open Airway
Flow Limitation

Snore

Apnea

Sleep Disordered Breathing is Common
- Nightly snoring in 1/3 men, ¼ women
- OSA is present in:
  - 5% of men (20% over age 55)
  - 2% of women (10% over age 55)
  - 2% of children
  - 30% of patients with cardiovascular disease
  - 50% of patients with atrial fibrillation
  - 70% of patients with diabetes type 2
  - 40-70% of patients with stroke/TIA

Sleep study - normal

Sleep study - OSA
Hypoxia
- Gradually increasing hypoxia with apneic episodes
- Hypoxia can cause bradycardia in the absence of airflow
- Increased sympathetic nerve activity which is proportional to the degree of hypoxia
- Vasoconstriction and increased heart rate starting during but peaking after the apnea

Arousal
- Increasing respiratory effort causes an arousal, the critical item that causes the airway to open again
- Arousal contributes to sympathetic drive at the end of the apnea

Apnea Termination
- Increase in stroke volume, heart rate and cardiac output into a constricted arterial system
- Leads to a transient increase in BP
- Pharyngeal collapse recurs with the next apnea
- This may be repeated over and over all night

Sudden Cardiac Death and OSA

Coronary Artery Disease
- OSA is associated with insulin resistance, hypertension, and hypoxia which are all risk factors for coronary events
- Chronic nocturnal hypoxia triggers a systemic inflammatory response
- Increased coronary events (AMI or angina) during nocturnal hours

OSA Treatment in CAD

*Fig. 1 Kaplan–Meier analysis: event-free survival in the group with and without treatment for obstructive sleep apnea.*
Arrhythmias Associated with SDB

- The following have been associated with SDB:
  - Severe bradycardia (sinus arrest, AV block)
  - Atrial and ventricular ectopy
  - SVT, Atrial flutter, Atrial fibrillation
  - Sustained and non-sustained VT
  - Occur mostly with severe OSA and hypoxia

Mechanisms of Arrhythmias in SDB

- Bradycardia due to the diving reflex: increased vagal tone triggered hypoxia
- During obstruction, there is increased myocardial wall tension and O2 demand resulting in possible ischemia
- Hypoxia may result in ischemia
- Hypoxia and hypercarbia result in sympathetic activation and catecholamine release
- Marked changes in intrathoracic pressure from airway obstruction abruptly changes pressure gradients and distorts the atria

Recurrence of AF 12 Months after Cardioversion

[Graph]

Pathophysiology: HTN and OSA

- Sleep deprivation is associated with insulin resistance, which is associated with hypertension
- May be due to chronically increased sympathetic activity due to repetitive hypoxia and chronic tiredness
- Patients with OSA have thicker LV walls (LVH) than patients without OSA

Sleep Apnea and Hypertension

- In resistant hypertension (3 or more drugs) 96% of men and 65% of women have OSA
- LVH regresses with 6 months of treatment of OSA with CPAP

Similarities in OSA and Psychiatric Disorders

- Oxidative stress, inflammation and neurotransmitter imbalances
- Sympathetic hyperactivity and hyperarousal states with sleep fragmentation
- Obesity/metabolic syndrome
- Diabetes
- Cardiovascular disease
- Smoking
Obstructive Sleep Apnea and Psychiatric Disorders

- Gupta and Simpson found 974 manuscripts relating to psychiatric disorders in people with OSA.
- Insufficient reports on the prevalence of OSA in schizophrenia and other psychotic disorders and in anxiety disorders to draw conclusions.
- Despite selection bias there was an increased prevalence of OSA in patients with major depression disorder (median 48.1%) or PTSD (42.7%).
- Median prevalence in bipolar disorder was 19.8%.


Mild OSA may not affect mood

- 239 people in Apnea Positive Pressure Long-term Efficacy Study (APPLES) with no versus mild sleep apnea.
- No significant differences between these two groups on Epworth Sleepiness Scale, Stanford Sleepiness Scale, Hamilton Rating Scale for Depression, Profile of Mood States and Sleep Apnea Quality of Life Index.

Quan SF et al. Southwest Journal of Pulmonary Critical Care 2014; 9(1):44-56

People with OSA are more likely to develop mood disorders

- National Health Insurance database. 5415 patients diagnosed with sleep apnea between 2000 and 2010.
- People with sleep apnea were 1.82 – 2.07 fold more likely to develop major depression compared to people without sleep apnea.
- People with sleep apnea were 2.15 – 3.24 fold more likely to develop bipolar depression compared to people with sleep apnea.


Treatment of OSA and Psychiatric Disorders

- In major depression treatment with CPAP resulted in improvement in excessive daytime sleepiness.
- Possibility of development of a manic episode when CPAP started on people with bipolar disorder.
- CPAP reduced nightmare frequency in people with PTSD and also PTSD symptoms.
- People with PTSD had poorer CPAP compliance.
- UPPP (ENT surgery) decreased hypersomnia significantly in patients with major depression.


Treatment of Psychiatric Disorders and OSA

- Tranquilizing effects of insomnia medications and benzodiazepines can make apnea worse.
- Atypical antipsychotic medication can worsen metabolic syndrome, weight gain and apnea.

Goday LBM et al. Sleep 2017 Dec 1;40(12)
NoSAS Score

- Ranges from 0 – 17
- 4 points for neck circumference more than 15.75 inches (40 cm)
- 3 points for have a BMI 25 – 30
- 5 Points for having a BMI of 30 or greater
- 2 points for snoring
- 4 points for being 55 years of age or older
- 2 points for being male
- Total 8 points or more suggests higher risk of OSA

NoSAS Score and Depressive disorder

- 1761 subjects with major depression
- 58 +/-11 years old
- 48.7% male
- NoSAS score of 8 or greater identified OSAS in people with major depression with a sensitivity of 0.79, specificity of 0.66, negative predicted value of 0.91 and positive predicted value of 0.41
- Area under the ROC curve was 0.72 for NoSAS, 0.66 for STOP-BANG and 0.69 for the Berlin Score

Guichard K et al. J Affect Disorder 2018 Feb;227:136-140

Treatment Options: Success of Therapy at Reducing AHI to < 5 per hour

- CPAP: 90% if worn nightly (national average 50-70% compliance; SCH Sleep Center 72 - 83% compliance)
- ENT surgery: 50% for UPPP, up to 90% with MMA, Inspire new option
- Mandibular advancement appliances: 50-70% successful in mild-moderate sleep apnea

Restless Leg Syndrome

- Urge to move legs
- Rest worsens symptoms
- Movement helps symptoms
- Worse in evening
- Not caused by another condition

Restless Leg Syndrome

- Prevalence 5 – 15%
- About 3% have RLS that disturbs their sleep at least 3 times a week
- Iron/transferrin and dopaminergic abnormalities
- 50 – 85% complain of insomnia
- Decrease sleep efficiency, increased arousals and reduced sleep time
- Higher risk of developing panic disorder (OR 4.7), generalized anxiety disorder (OR 3.5) and major depression (OR 2.6) *


RLS Diagnosis in People with Mood Disorders

- Complicated by symptom overlap: fatigue, sleep disturbance, diminished concentration and psychomotor agitation
- Causality unclear (bidirectional?)
- Dortmund Health study, n=1122 (DHS); Study of Health in Pomerania, n=3300 (SHIP)
- Depressive disorder patients developed new onset RLS (OR 1.94 DHS and OR 2.37 SHIP)
- RLS patients developed new onset depression (OR 1.82 SHIP)

If you were going to order one blood test for a patient with RLS what would it be?

- Hint: What is a necessary cofactor for tyrosine hydroxylase to convert serotonin to dopamine

Ferritin

- Although the low end of the “normal range” for ferritin is often around 10, the AASM recommends iron supplementation if the ferritin is <75.
- Note that ferritin is an acute phase reactant and can be chronically elevated in those with inflammatory conditions. For that reason checking an iron saturation (normal 20-50%) is reasonable.

Genetics: approximately half of all people with RLS have a first degree relative with RLS

- There are now 6 genes mutations that have been found to be cause RLS/PLMD
- It is not completely understood what each of these do
- Low ferritin levels can run in families
- If a child has RLS there is a 90% chance one of the biologic parents do also

Medications for RLS

- Mirapex/pramipexole (DA agonist; renally excreted)
- Requip/ropinirole (DA agonist; metabolized in liver)
- Neupro/rotigotine patch (DA agonist; metabolized by conjugation and N-dealkylation)
- Horizant/gabapentin enacarbil (binds to the δ subunit and reduces calcium’s flow through voltage-gated calcium channels; renally excreted)
- Lyrica/pregabalin (not FDA approved for RLS but recommended by AASM; δ subunit-containing voltage-gated calcium channel agonist. It increases extracellular GABA concentrations by producing a dose-dependent increase in L-Glutamic acid decarboxylase, the enzyme responsible for making GABA; renally excreted)

Non-medication treatments for RLS

- Regular bedtime and sleep schedule
- Treat any obstructive sleep apnea
- Avoid alcohol and caffeine within 6 hours of bedtime
- Make sure ferritin (measure of body iron stores) is greater than 75 ng/mL – supplement with iron if not and consider adding some Vitamin C which aids in the absorption of the iron
- Short walk or leg massage before bedtime
- Try wearing thigh high compression socks to bed
- Relax (vibrating pad)
- Avoid medications that make RLS worse (SSRI, SNRI, Tricyclics, MAOIs, mirtazapine, metoclopramide). Buproprion does NOT make RLS worse (Norepinephrine Dopamine Reuptake Inhibitor)

Side effects

- Dopamine agonists: nausea, fatigue, headache, dizziness, daytime sleepiness, sleep attacks, impulse control disorders (compulsive shopping/gambling), augmentation
- Rotigotine patch: dopamine agonist side effects and rash at patch site
- Alpha 2 delta ligands: dizziness, fatigue, drowsiness, peripheral edema, tremor, weight gain, suicidal ideation
Dopamine agonist effect on RLS and Mood

- In patients with RLS and mood disturbance pramipexole improved RLS while also improving RLS-related impairment at 12 weeks
- Beck Depression Inventory version II, -7.4 +/-0.4 with pramipexole and -5.8 +/-0.5 placebo (p=0.0199)


Gabapentin Enacarbil effect on RLS and Mood

- 600 mg significantly improved the Profile of Mood Stated Mood Brief Form (POMS-B) vigor activity but not other scores versus placebo at week 12
- 1200 mg significantly improved POMS scores for total mood disturbance, depression-dejection, fatigue-inertia, vigor-activity and confusion-bewilderment versus placebo at 12 weeks

Pooled data from 3 placebo controlled trials
Avidan AY et al. CNS Drugs 2016 April;30(4):305-16

Insufficient Sleep

- Myalgias
- Memory issues
- Depression
- Headache
- Perioral puffiness
- HTN
- Diabetes
- Weight gain
- Irritability
- Yawning
- Mania
- Hostility

Motomura et al. Sleep 2017 Oct 1;40(10)

Sleep Deprivation

- Myalgias
- Memory issues
- Depression
- Headache
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Motomura et al. Sleep 2017 Oct 1;40(10)

Insufficient Sleep in Adolescents and Young Adults

- Adolescent sleep loss poses a serious risk to the physical and emotional health, academic success and safety of our nation’s youth.
- “The prevalence and effects of insufficient sleep may be further magnified in high-risk adolescents.”
- “Many of the factors that have been shown to contribute significantly to the current “epidemic” of insufficient sleep in teenagers, such as electronic media use, caffeine consumption and early start times, are potentially modifiable and, as such, are important intervention points in anticipatory guidance in the clinical setting.”

School Start Time
- Adolescents normally develop a later evening peak of sleepiness.
- Multiple professional sleep organizations now recommend that no middle or high school should open before 8:30 am. Currently in the US only 7% of middle and high schools do.
- Doing so decreases tardiness, truancy, depression, suicide rate, drop out rate and motor vehicle accidents.
- Doing so increases grades and athletic performance.

Good Sleep Habits
- Bedroom should be quiet, dark and cool.
- Regular schedule.
- Do not spend too long in bed.
- Avoid napping.
- Avoid bright lights, computers, or TV just before bedtime.
- No caffeine, alcohol or nicotine within several hours of bedtime.
- If insomnia starts after initiating a medication see if it causes insomnia (e.g. fluoxetine, stimulants, prednisone).

I have tried everything I can think of and I still can’t get to sleep. How about one of those pills?
- OTC: diphenhydramine, doxylamine, valerian, melatonin.
- FDA approved for insomnia: zaleplon, zolpidem, eszopiclone, temazepam, doxepin, ramelteon, suvorexant.
- FDA approved but not for insomnia but still used for insomnia anyway: trazodone, amitriptyline, mirtazapine.
- There is no FDA approved sleep aid for children.

What’s the Best Treatment for Chronic Insomnia
- Skip the pills and find a sleep psychologist: 75-80% success rate after 4 visits.
- Sleep Logs.
- Sleep Education.
- Sleep Habits.
- Bed Restriction.
- Stimulus Control.
- Relaxation Therapy.
- Cognitive Behavioral Therapy.

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