

**Sleep Disorders:  
What Optometrists  
Need to Know**

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**Disclosures**

- I have spoken for, been on advisory boards for or have been paid consultants for:

Bausch & Lomb, Genentech, Konan, Novo Nordisk, Optos, Optovue, Regeneron, VSP, Zeiss, ZeaVision

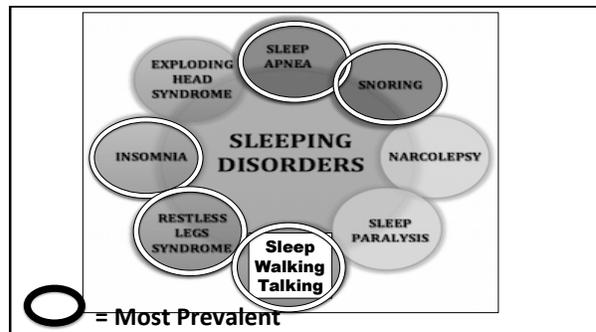
**My Focus**

- Sleep problems are prevalent
- Sleep problems contribute to eye disease & systemic disease that is linked to eye disease
- ECPs can help patients with sleep problems get diagnosed and treated



**It's NOT Just Sleep Apnea**

- Broader Definition of Sleep Disorders
  - Parasomnia:** episodic sleep events including sleep terror disorder, sleep walking and nightmare disorder
  - Dyssomnia:** abnormalities in the amount, duration, quality or timing of sleep; Primary vs Secondary



## Dyssomnia

- **Primary:** Primary insomnia, narcolepsy, circadian rhythm disorders, and sleep disordered breathing including sleep apnea (central, obstructive, mixed forms)
- **Secondary:** sleep disorders caused by psychosocial stressors, anxiety, depression, diet (caffeine/alcohol/nicotine), medications (anti-depressants)

## Epidemiology

- Estimated that **20-40% of Americans experience sleep problems each year**
- **50% of those > 50 years old**
- **25% of fatal motor vehicle accidents are due to sleepiness or driver fatigue**  
MMWR Morb Mortal Wkly Rep. 2014; 63:557-562.
- **Sleep deprivation significantly increases risk of medical errors**  
— **100K deaths in 2006; 250,000 in 2016**  
— Committee on Sleep Medicine, Washington D.C., The National Academies Press 2006  
— Sleep Review, February 27, 2017

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BMJ

Occup Environ Med. 2000 Oct; 57(10): 649-655.  
doi: 10.1136/oem.57.10.649

PMCID: PMC1739867  
PMID: 10984335

Moderate sleep deprivation produces impairments in cognitive and motor performance equivalent to legally prescribed levels of alcohol intoxication

A Williamson and A. Feyer

Occup Enviro

- **17-18.5 hours of wakefulness impairs motor function on a par with or more than a blood alcohol content (BAC) = 0.05%**
- **17.74-19.65 hours without sleep was equivalent to BAC = 0.10%**

## Sleep Duration Across the Lifespan

Sleep Med Rev. 2012 Jun; 16(3): 199-201.

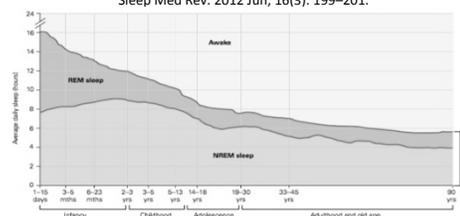


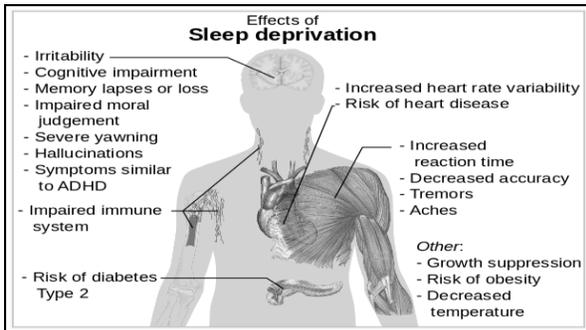
Figure 3.18 The amount of time we spend sleeping decreases as we get older. In addition, the proportion of total sleep time spent in REM sleep decreases markedly from infancy to adolescence, and then remains relatively stable into adulthood and old age. The amount of NREM sleep time also decreases, but compared with the drop in REM sleep up to adolescence, NREM sleep tends to be relatively stable.

## Insomnia

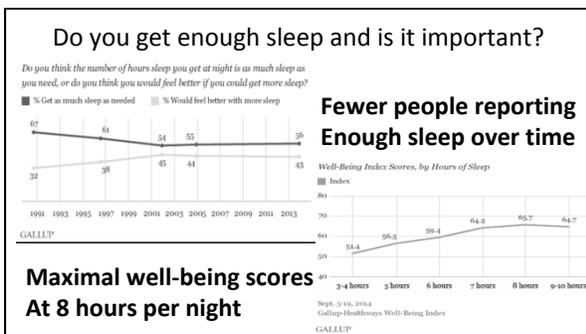
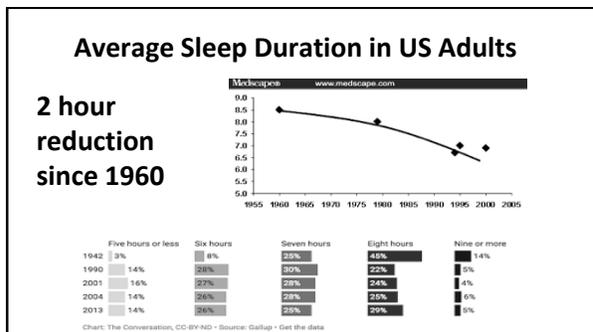
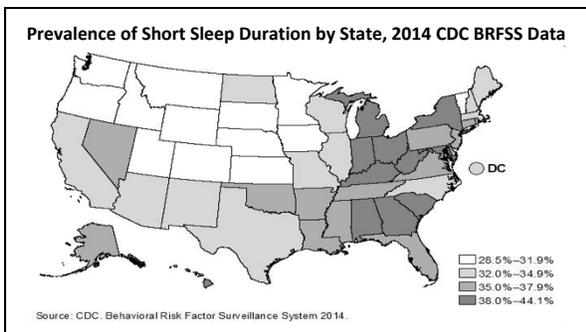
- **Prolonged sleep latency and/or reduced duration of sleep**
  - Acute: **30% of Americans each year ( $\geq 1$  month duration)**
  - Chronic Insomnia Syndrome: **10% each year ( $\geq 3$  months duration)**
  - If adjusted for depression, about **6%/year**
  - By definition, accompanied by interference with wakeful activity (e.g. excessive daytime sleepiness = EDS)

J Clin Sleep Med. 2007 Aug 15; 3(5 Suppl): S7-S10.





- ### Hyposomnia: Short Sleep (< 7h) is Common
- Behavioral Risk Factor Surveillance System 2014
  - 35% of US adults
    - 68% of teens get < 8 hours (NSF recommends 8.5)
  - 46% of African Americans & Native Hawaiians
  - Significantly more common in adults with CAD, stroke, asthma, COPD, diabetes, CKD, depression



- ### My Pa
- 
- 50 yo psychiatrist with T
    - Glaucoma Suspect in fo
    - Falls asleep/snoring 3X
  - 40 yo internist just off o
    - for routine eye exam
    - “How are you doing?”
    - Sobbing b/c he screamed at his favorite nurse



### Tools for Assessing Sleep Symptoms

- **Epworth Sleepiness Scale (ESS)**
  - Questions about sleepiness during wake activity
- **Pittsburgh Sleep Quality Inventory (PSQI)**
  - Questions about sleep latency, quality, breathing
- **Little correlation between ESS & PSQI**
- **Both poor predictors of milder obstructive sleep apnea (OSA) & other sleep disorders** Sleep Med. 2014 Apr;15(4):422-9.
- **Berlin Obstructive Sleep Apnea Survey**
- **STOP-BANG Apnea Questionnaire (snore/tired/observed/pressure – BMI/age/neck circumference/gender)** Int J Prev Med. 2018 Mar 9;9:28

### ▶ STOP Questionnaire ▶ BANG

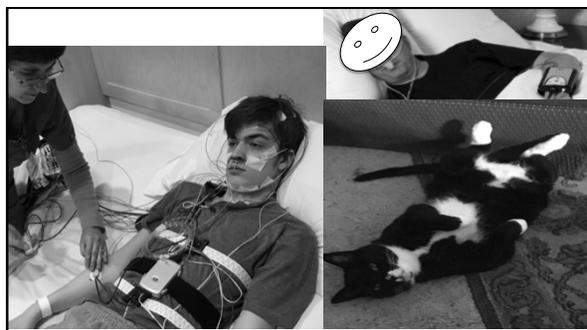
- |                                       |  |
|---------------------------------------|--|
| • <u>S</u> norring                    | • <u>B</u> MI >35                            |
| • <u>T</u> iredness                   | • <u>A</u> ge >50                            |
| • <u>O</u> bserved you stop breathing | • <u>N</u> eck circumference >40 cm (>15.7") |
| • <u>B</u> lood <u>P</u> ressure      | • <u>G</u> ender male                        |

High risk: Yes to  $\geq 3$  items → Refer for sleep testing

### Polysomnography (PSG)

- **Gold standard for diagnosis of most sleep disorders (except Restless Leg Syndrome)**
- **Overnight measurement of breathing, pulse,  $P_{O_2}$ , EEG, REM, leg movements**
- **Home sleep studies record pulse,  $P_{O_2}$ , breathing**
  - Good correlation with PSG for Dx of OSA
  - Costs are typically \$200-500 versus \$1500-2000

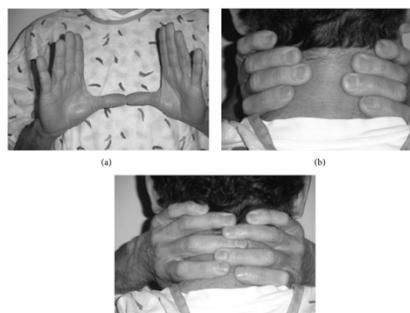
Respirology. 2010 Feb;15(2):336-42



### ESAP: Easy Sleep Apnea Predictor

- 100% specificity for mild OSAS in T2DM (n = 43) when compared with PSG
- Neck circumference > 17/16 inches in males/females also 100% specific
- Both more specific but less sensitive than BMI  $\geq 35$  and + STOP-BANG
- A positive ESAP was defined as a 1cm gap when a patient encircled their hands around the neck

Sleep Disord. 2019; 2019: 3184382\_



### Sleep Disorders Associated with Risk of Multiple Systemic Pathologies

- Cardiovascular Disease
- Diabetes/Insulin Resistance/Obesity
- Intestinal Dysbiosis
- Hypertension
- Sub-optimal response to treatment of the above

[https://www.cdc.gov/sleep/about\\_sleep/chronic\\_disease.html](https://www.cdc.gov/sleep/about_sleep/chronic_disease.html)

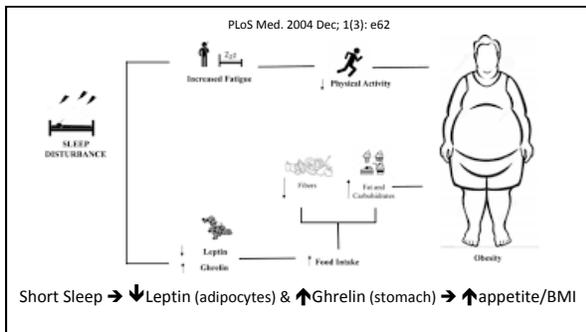
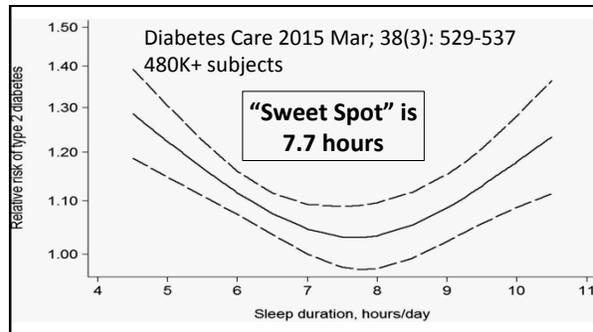
### CVD

- Obstructive sleep apnea increases the risk of stroke and MI more than 3-fold, but CPAP doesn't lower risk of recurrent events per multiple analyses\*  
Eur J Clin Invest. 2018 May;48(5):e12908.
- Meta-analysis shows sleep apnea doubles the risk of MACE after stent placement  
Medicine (Baltimore). 2018 Apr;97(17):e0621
- Untreated OSAS increase risk of heart failure by 140% via hypoxic damage to cardiac muscle  
Tex Heart Inst J. 2018 Jun; 45(3): 151-161
- 10-year analysis shows Insomnia increases risk of MI and stroke by 13%  
Neurology 2019 Dec 3;93(23):e2110-e2120

\* MORE on this LATER

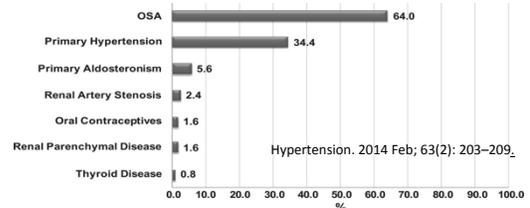
### Diabetes

- Short sleep (< 5.5 hours) triples the likelihood of T2DM in observational studies after all controls  
Curr Diab Rep. 2018 Aug 17;18(10):82.
- Severe obstructive sleep apnea increased incident diabetes 71% over 13 years independently of adiposity  
Sleep Med. 2016 Sep;25:156-161
- Both short (<5.5 hrs) and long (> 9 hrs) sleep duration are significantly associated with adiposity & insulin resistance  
Diabetes Res Clin Pract. 2018 May;139:195-202



### HTN and OSA

- 50% of hypertensive patients have OSA
- Drug-resistant HTN is highly associated with severe OSA



### OSA + High Fat Diet → Dysbiosis, HTN

- Rats with tracheal balloon- induced apnea and high-fat diet develop **significant decrease in butyrate-producing bacterial flora** and 29 mm Hg BP increase after 2 weeks
- Fecal transplantation into normal rats resulted in a 32 mm Hg increase in BP at 2 weeks
- Suggests a causal nexus for HTN between sleep apnea, dysbiosis and fat intake Hypertension. 2016 Feb; 67(2): 469-474.

### Reductions in butyrate producing bacteria are prevalent in T2DM & HTN

Med Sci (Basel). 2018 Jun; 6(2): 32  
Microbiome. 2017; 5: 14.

### Gut Microbiome Affects Sleep

- **Antibiotics totally inactivate tryptophan-serotonin signalling in mice**
- **Higher tryptophan but little serotonin**
- **Significantly more REM to non-REM sleep transitions**
- **Improving gut health & diversity (↓saturated fat and ↑fermented foods, probiotics) may improve sleep**

Gut microbiota depletion by chronic antibiotic treatment alters the sleep/wake architecture and sleep EEG power spectra in mice. *Scientific Reports*, 2020

### Sleep Disorders Associated with Multiple, Prevalent Eye Diseases

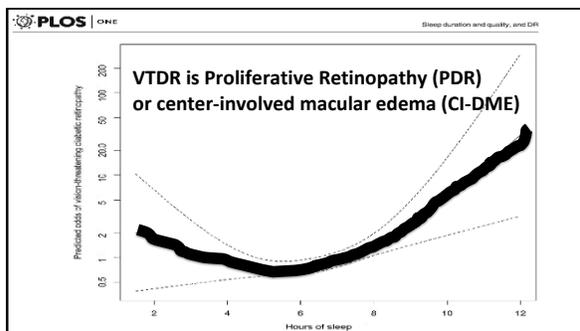
- **OSA: normotensive glaucoma, NAION, DR & DME, Poor response to anti-VEGF Tx in nvAMD & DME, Floppy Eyelid Syndrome**
- **Insomnia : AMD**
- **Hyposomnia: nvAMD, POAG, dry eye, myopia**
- **Hypersomnia (excessive sleep duration): Sight-threatening DR, AMD with geographic atrophy, POAG**

### Apnea in Diabetic Retinopathy/DME

- STDR rates were 2-2.5X higher in T2DM patients (n = 230) with untreated/under-treated OSA followed for 4 yrs
- After all adjustments, OSA increased odds of progressing to severe NPDR/PDR 5-fold
- **AHI > 11.9 vs < 4.8 increased odds of STDR 7.5-fold**  
Am J Respir Crit Care Med. 2017 Oct 1;196(7):892-900.
- CSME patients with confirmed OSA & Tx with grid laser gained an extra line of VA if treated with CPAP > 2.5 hrs/night @ 6 months  
Respiration. 2012;84(4):275-82
- DME patients (n = 30 receiving Avastin), the probability of OSA symptoms was directly proportional to the # of required injections  
Retina. 2014 Dec;34(12):2423-30

### DR & Hypersomnia

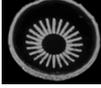
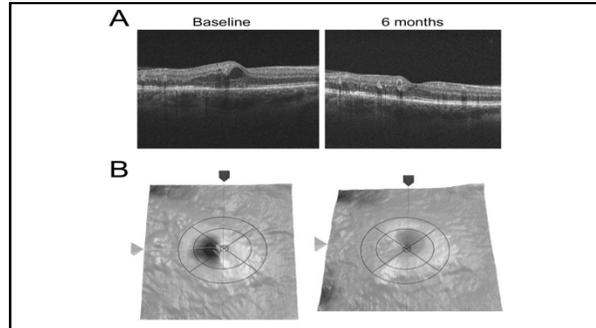
- **1231 T2DM patients in Singapore**
- **Long sleep duration (> 8 hrs) & EDS were independently associated with VTDR (3-fold)**  
PLoS One. 2018; 13(5): e0196399
- **Hypothesis: Retinal O<sub>2</sub> demand is predominantly driven by rod metabolism; increased sleep may be a hypoxic stimulus to worsening retinal disease**



### A novel approach to DR

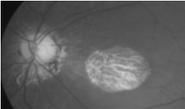
- Inner retinal hypoxia is primarily responsible for DR and vision loss
- Rods are primarily responsible for most retinal O<sub>2</sub> consumption during dark
- Limiting rod metabolism with a green LED reduces hypoxic stress in animals and improved DME in 17/26 eyes versus 3/26 control eyes

Diabetic retinopathy and a novel treatment based on the biophysics of rod photoreceptors and dark adaptation.  
Editors In: Kolb H, Fernandez E, Nelson R, editors.

### Geographic Atrophy

- After all adjustments, long sleep (> 8 hours) increased the risk of GA 7.1 times compared to patients without AMD
- 1003 consecutive pts in a San Francisco retina practice surveyed about sleep history
- Hours sleeping was not associated with nvAMD



Retina. 2016 Feb;36(2):255-8\_

### ? nvAMD

- In a case control study of AMD pts with self-reported short sleep (< 6 hours), relative risk of CNVM with self-reported short sleep (< 6 hrs; 3.29 v. 7-8 hrs; 2.25 for 6-7 hrs; 1.39 for > 8 hrs (n=165)
- HR = 3.1 for short sleep after all controls (p < 0.01)

Ophthalmic Epidemiol. 2016;23(1):20-6.

#### Poor Response to AVT in Untreated OSA

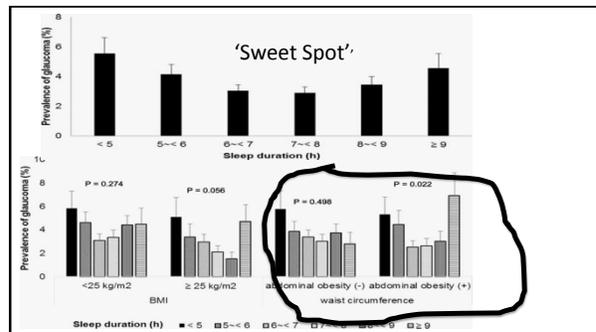
In 38 patients with nvAMD and OSA confirmed by PSG, CPAP + Avastin improved VA (20/40 vs 20/100), CST by -78µ and cut required AVT in half compared to Avastin alone (8 vs 16 injections)

Retina. 2016 Apr;36(4):791-7\_

### Glaucoma

- POAG was associated with short (< 5 hrs) and long (> 9 hrs) sleep duration (p = 0.07)
- When stratified by abdominal obesity & BMI, overweight subjects were 2.4X more likely to have POAG if sleep duration was ≥ 9 hrs or < 7 hrs after adjustments for age/gender/IOP/HTN/smoking/drinking/income/depression (p = 0.036)
- 9400 subjects from KNHANES 2012

Medicine (Baltimore). 2016 Dec;95(52):e5704\_



### Normotensive Glaucoma

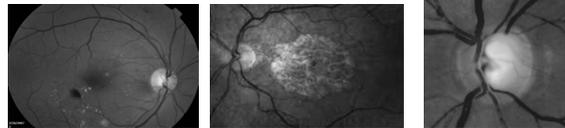
- **NTG appears to be more prevalent in OSA and vice versa** J Glaucoma. 2007 Jan;16(1):42-6 BMC Ophthalmol. 2014 Mar 10;14:27
- **Presence of floppy eyelid syndrome in pts with OSA associated with a 4-fold+ increase in glaucoma (NTG & POAG)**
  - 23% vs 5%  $p = 0.04$
  - 150 FES patients



J Glaucoma. 2014 Jan;23(1):e81-5.

### My Simpleton Conclusion

- Sick retinas and optic nerves need to breathe
- Sick retinas and optic nerves need adequate sleep, but not too much or too little sleep



### Dry Eye

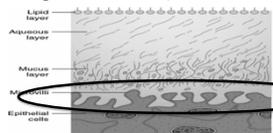
- **Short and very short sleep duration increased odds of dry eye symptoms**
  - HR = 1.2 (5 hrs) and 1.29 ( $\leq 4$  hrs)
  - 16K fom KNHANES Sleep Med. 2015 Nov;16(11):1327-1333
- **Clinical and subjective dry eye significantly more common in patients with poor PSQI scores**
  - Osaka study n = 672 Japanese office workers
  - 730 pts at Tokyo eye clinic Clin Ophthalmol. 2016; 10: 1015–1021. Neuropsychiatr Dis Treat. 2015; 11: 889–894

### Mechanisms?

- **Experimental sleep deprivation (mice) induces lacrimal gland hypertrophy and reduces tear production after 10 days**
  - Reversed after 14 days of rest Exp Mol Med. 2018 Mar 2;50(3):e451
- **Sleep apnea significantly associated with persistent/severe dry eye symptoms in a study of 120 US Veterans (3.8 X)**
  - CPAP use not reported JAMA Ophthalmol. 2016 Dec 22.

### Sleep Deprivation Dry Eye (SDE)

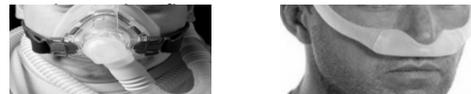
- SDE results from changes in morphology of corneal epithelial microvilli and ↓ tear stability resulting from inhibition of the protein PPAR- $\alpha$  (mouse model)
- Topical fenofibrate (anti-lipid agent Tricor™) activates PPAR- $\alpha$  and normalizes microvilli & tear film stability



Invest Ophthalmol Vis Sci. 2018 Nov 1;59(13):5494-5508

### CPAP use & OSD

- **Conjunctival squamous metaplasia increased & TBUT decreased in right eyes only after 4 months of CPAP (n = 80)** Cornea. 2012 Jun;31(6):604-8
  - Positional effect? (mask vs habitual sleep position); mask leakage, mask displacement,





### EyeEco's Eyeseals 4.0

Sleep Review 2016  
Interview of Art Epstein, OD, FAAO

### Does CPAP Increase IOP?

- No difference in mean IOP at baseline and after 7 hours in 31 subjects w OSA +/- CPAP

Graefes Arch Clin Exp Ophthalmol. 2015 Dec;253(12):2263-71

- Nocturnal IOP was significantly higher in 21 CPAP subjects measured Q2h
  - Mean trough/peak spread increased from 6.7 to 9.0 mm Hg after 1 month
  - Decreased IOP was seen after 30 minutes CPAP cessation

Invest Ophthalmol Vis Sci. 2008 Mar;49(3):934-40.

### Hyposomnia & Myopia

- 3625 Korean adolescents (12-19 yo)
- Myopia was inversely associated with sleep duration after controls (0.1 D/hour)
- Compared to subjects getting < 5 hrs, OR for myopia > -0.50D < 6.00D in those getting > 9 hrs was 0.59 (p = 0.006)
- No relationship was seen for myopia > 6 diopters

Acta Ophthalmol. 2016 May;94(3):e204-10.

### How Do We 'Fix' Poor Sleep?



### Combatting Poor Sleep

- Remove local factors (quiet/dark room; avoid caffeine/nicotine/alcohol & light at night)
  - Blue light suppresses melatonin, impairs sleep latency, duration of REM – 559 studies in 5 yrs
- Identify & treat psycho-social stressors (anxiety/depression)
- Avoid napping, shift work and variable bed/waking times
- Physical activity
- Identify & treat OSA

#### •Drug Therapy

insomnia → Sonata, Lunesta  
night terrors → clonazepam, prazosin  
RLS → carbidopa, gabapentin, Fe

National Sleep Foundation

### Avoid Light-at-Night

- LAN disrupts the circadian rhythm and metabolism, increasing rates of obesity and metabolic disorders Endocr Rev. 2014 Aug;35(4):648-70.
- Indoor and outdoor nighttime lighting affects sleep quality and quantity Sleep. 2016 Jun 1; 39(6): 1311-1320



### School Start Times

- The American Society of Pediatrics recommends that middle and high schools start no earlier than 8:30 AM
- Very few schools do so

**SCHOOL START TIMES & TEEN SLEEP**  
 Pediatricians recommend schools begin classes at 8:30 a.m. to help students get 8.5 hours of sleep. Most schools do not. States by percent of public schools with starting times before 8:30 a.m.:

Less than 25%
  50%-74%
  75%-100%

TEEN SLEEP PATTERNS

### Treating OSA

- CPAP is the gold standard, but compliance rates are low (50% discontinue within the first year and another 25% by year 3)
- Females, > 55 yo and improved daytime sleepiness (ESS) predict compliance past 6 mos Respir Care. 2010 Sep;55(9):1230-9
- CPAP did NOT improve MACE or mortality in pts with established CVD (mean nightly use only 3.3 hrs on 70% of nights) Sleep Apnea. N Engl J Med. 2016 Sep 8;375(10):919-31

### Dose May Be Critical for CPAP

- The SAVE Study did show a 44% reduction in stroke risk for those with 'good compliance'
  - > 4 hrs on 70% of nights
- CPAP use  $\geq$  4 hours/night does significantly reduce MACE in meta-analysis
  - 4 RCTs, 3780 patients  $p = 0.02$

Am J Cardiol. 2017 Aug 15;120(4):693-699

### Other OSA Tx Options

- Mandibular Advancement Devices (MAD)
  - comparable to CPAP for mild OSA (50-60% lower AHI)
- Uvulopalatopharyngoplasty (UPPP)
  - removal of tonsils, posterior soft palate, uvula
- Targeted Hypoglossal Neurostimulation
  - improves tongue muscle tonus
- Playing a double-reed instrument (e.g. an oboe)
  - lower prevalence of OSA
- Play didgeridoo - comparable to CPAP for mild-moderate OSA
- Weight Loss

**MAD**

**THN**

**UPPP**

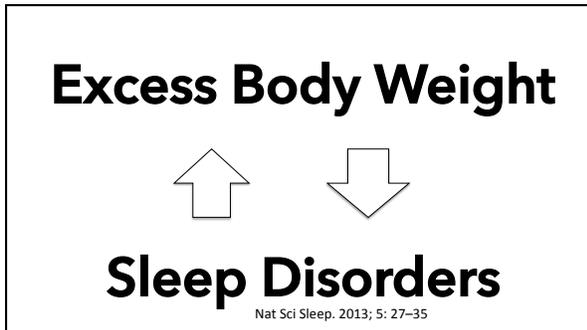
**Oboe**

**Didgeridoo**

Dtsch Arztebl Int. 2018 Mar; 115(12): 200-207  
 Mayo Clin Proc. 2009 Sep; 84(9): 795-800.  
 Sleep. 2015 Oct 1; 38(10): 1593-1598  
 J Clin Sleep Med. 2012 Jun 15; 8(3): 251-255

**Tongue Base Radiofrequency**

**Genioglossus Advancement**

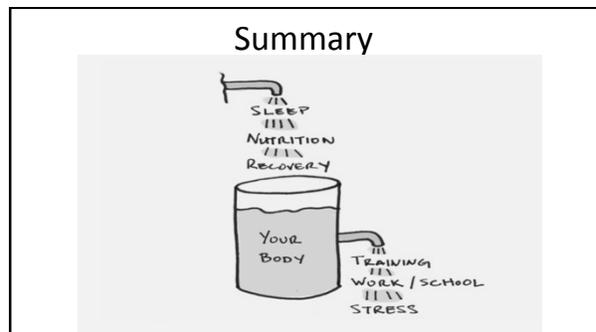


**Weight Loss Improves Dysomnia**

- Overweight/Obese T2DM patients (mean BMI = 36.7) and OSA who lost 30 lbs over 1 year reduced their mean AHI from 23.2 to 13.5
- Improved OSA scores persisted after 4 yrs (mean change AHI = -7.7) despite (mean = 15 lbs) weight gain  
Arch Intern Med. 2009 Sep 28; 169(17): 1619-1626. Sleep. 2013 May 1;36(5):641-649A
- Decreased visceral fat (600 Kcal deficit +/- exercise) significantly improved sleep symptoms (insomnia, EDS, apnea) in overweight/obese  
Behav Sleep Med. 2016 May-Jun; 14(3): 343-350.

**Conclusions**

- Sleep disorders are prevalent and contribute to vision loss and mortality
- ECPs should ask pts/partners about sleep quality/quantity (STOP-BANG)
- ECPs should initiate referral for Dx of high-risk patients
- ECPs should assess/treat ocular sequelae of sleep disorders as well as possible CPAP-related ocular adverse events
- ECPs should educate on sleep hygiene & therapies



Thanks, sleep!

**Thank You!**

**Paul Chous**

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