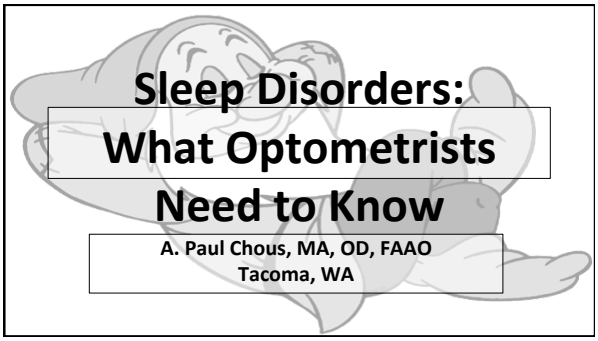
Sleep Disorders:

What Optometists Need to Know



Sleep Disorders: What Optometrists Need to Know

A. Paul Chous, MA, OD, FAAO
Tacoma, WA

Disclosures

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

AIOptics, American Diabetes Association, Bausch & Lomb, EyeNUK, Genentech, Konan, Novo Nordisk, Optos, Optovue, Regeneron, VSP, Zeiss, ZeaVision

Building Your Practice with Vision

- **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**

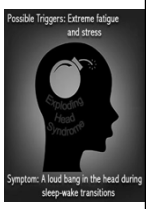
Sleep Disorders – What We Think Of

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

= Most Prevalent

Exploding head syndrome is a rare and relatively undocumented parasomnia event in which the subject experiences a loud bang similar to a bomb **exploding**, a gun going off, a clash of cymbals or any other form of loud, indecipherable noise that seems to originate from inside the **head**.



18% of college students reported at least 1 episode
J Sleep Res. 2015 Aug;24(4):447-9.

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

- **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.

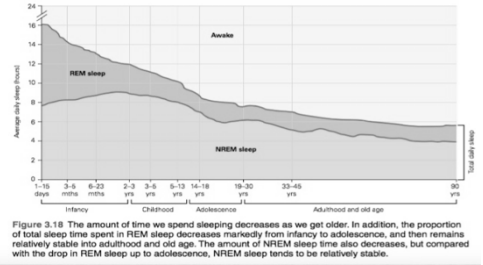
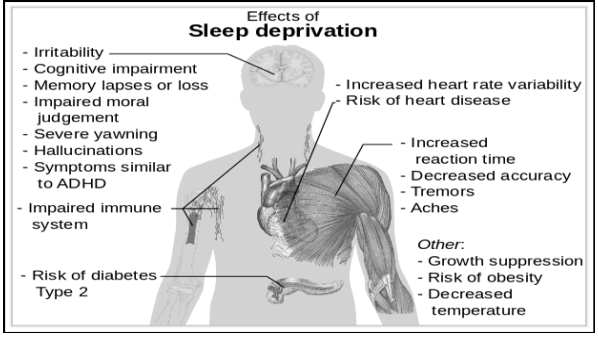


Figure 3.18 The amount of time we spend sleeping decreases as we get older. In addition, the proportion of total sleep time spent in REM sleep decreases markedly from infancy to adolescence, and then remains relatively stable into adulthood and old age. The amount of NREM sleep time also decreases, but 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 (≥ 1 month duration)**
  - **Chronic Insomnia Syndrome: 10% each year (> 3 months duration)**
  - **If adjusted for depression, about 6%/year**
  - **By definition, accompanied by interference with wakeful activity (e.g. excessive daytime sleepiness = EDS)**

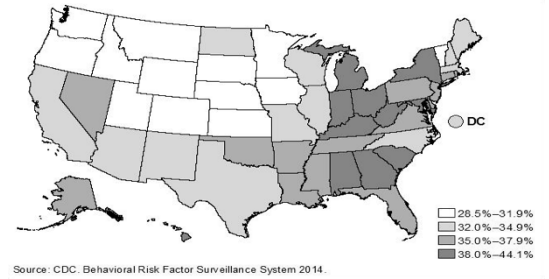
J Clin Sleep Med. 2007 Aug 15; 3(5 Suppl): S7–S10.



Hyposomnia: Short Sleep (< 7h) is Common

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

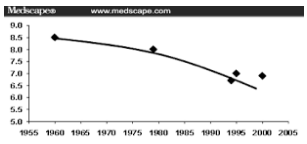
Prevalence of Short Sleep Duration by State, 2014 CDC BRFSS Data



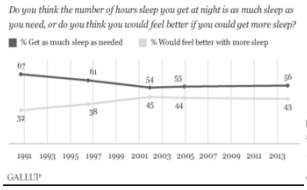
Source: CDC. Behavioral Risk Factor Surveillance System 2014.

Average Sleep Duration in US Adults

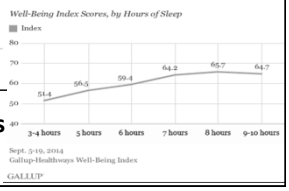
2 hour reduction since 1960



Do you get enough sleep and is it important?



Fewer people reporting Enough sleep over time



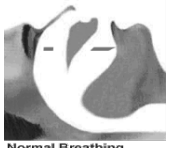
Maximal well-being scores At 8 hours per night

My Pa

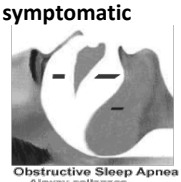
- **50 yo psychiatrist with T**
  - **Glaucoma Suspect in fo**
  - **Falls asleep/snoring 3X**
- **40 yo internist just off o for routine eye exam**
  - **"How are you doing?"**
  - **Sobbing b/c he screamed at his favorite nurse**

Sleep Apnea

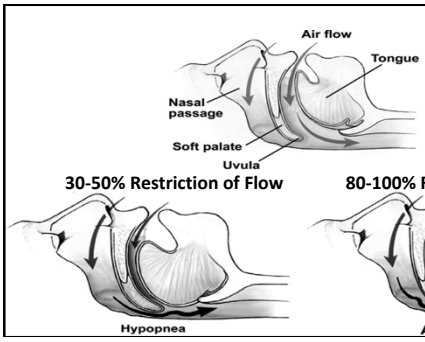
- **Cessation of breath during sleep**
- **About 20% of US adults**
- **Roughly 15% of these are symptomatic**



Normal Breathing
- Airway is open
- Air flows freely to lungs



Obstructive Sleep Apnea
- Airway collapses
- Blocked air flow to lungs



Sleep Apnea

- **Most case are Obstructive (OSAS)**
  - **22% of men / 17% of women → 22 million Americans**
  - **Rates increase with age & obesity → 80% unDx**
- **< 10% are central - <1% of population**
  - **Decreased or absent ventilatory effort (neurologic)**
- **Apnea: temporary cessation of breathing (≥ 10 seconds) during sleep with reduced O_2 saturation [≥ 4% drop]**
- **Hypopnea: decreased airflow ≥ 10 sec with reduced O_2 saturation (partial obstruction)**
  - **Elevated Apnea-Hypopnea Index (AHI)**

J Thorac Dis. 2015 Aug; 7(8): 1311–1322

AHI

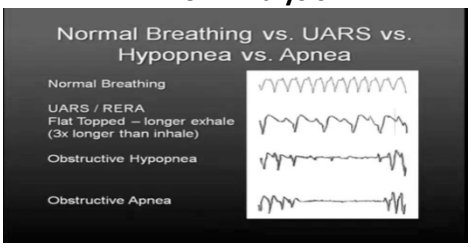
apneic + hypopneic episodes
time asleep (in hours)

- **AHI ≤ 5 = normal**
- **AHI > 5 ≤ 15 = mild apnea**
- **AHI > 15 ≤ 30 = moderate apnea**
- **AHI > 30 events/hour = severe apnea**

- **15% of all OSA is moderate or worse by AHI**
- **Milder OSA far more likely to be positional**

Eur Resp J 2016;47: 23-26 Chest 2005 Oct;128(4):2130-7

Airflow Analysis

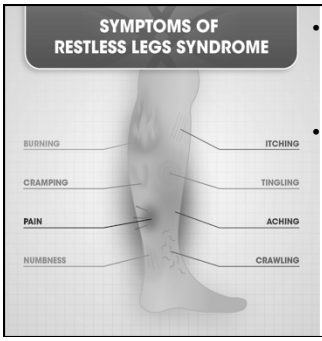


UARS = Upper Airway Resistance Syndrome
RERA = Respiratory Effort-Related Arrousal

Other Sleep Disorders

- **Restless Leg Syndrome**: leg discomfort coupled with compulsive movement; Symptoms worse when stationary; females > males; 5.5% of the population Sleep Med 2011;12(7): 623-34
- **Narcolepsy**: excessive daytime sleepiness, sleep paralysis, hallucinations,+/- cataplexy; females > males; 79.4 cases per 100,000

Sleep 2018;41 (suppl 1): A227



- **Often worsened by antihistamines, melatonin, alcohol, SSRIs**
- **RLS increases the risk of suicide and self-harm by up to 4-fold after all adjustments**
  - **24+K RLS patients followed over 8 years**

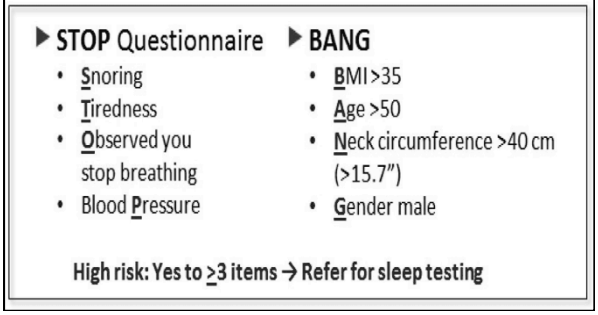
. *Neurotherapeutics*. 2012;9(4):776–790

JAMA Netw Open. 2019;2(8):e199966. Epub 2019 Aug 2

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)**

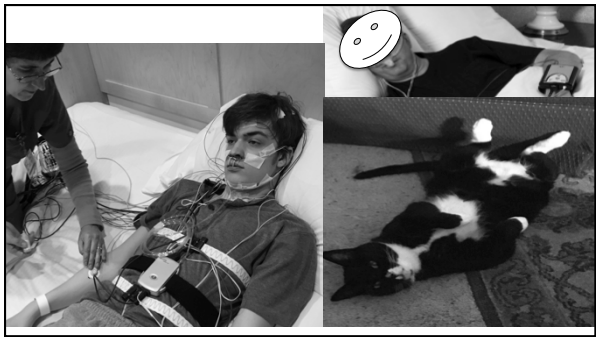
Int J Prev Med. 2018 Mar 9;9:28



Polysomnography (PSG)

- **Gold standard for diagnosis of most sleep disorders (except Restless Leg Syndrome)**
- **Overnight measurement of breathing, pulse, $P0_2$, EEG, REM, leg movements**
- **Home sleep studies record pulse, $P0_2$, breathing**
  - **Good correlation with PSG for Dx of OSA**
  - **Costs are typically $200-500 versus $1500-2000**

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



Actigraphy

- Lower-cost, wearable sensors for measuring activity, pulse and pulse variability, breath, oxygenation during wakeful and sleep hours
  - Sleep duration
  - Wakefulness after sleep onset (WASO)
  - 7 devices have peer-reviewed sleep validation study evidence
  - American Academy of Sleep Medicine guidelines advocate their use for chronic insomnia & circadian rhythm sleep disorders

J Clin Sleep Med. 2018 Jul 15;14(7):1209-1230.

"Phygama"

- Actigraphic sleepwear using pressure points to measure movement, breath and pulse during sleep

Comig to a Bedroom near you!

- Ballistic measurements where embedded sensors within textiles meet wearers' skin

Source: University of Massachusetts, Amherst

Actigraphy/Actometers

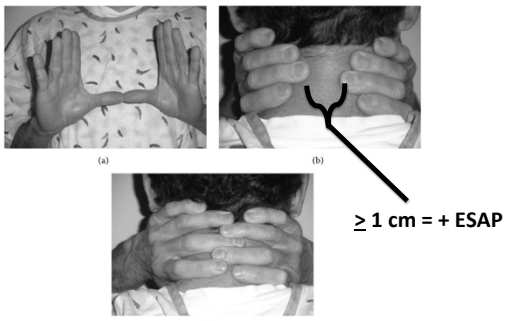
- **<u>Limitations</u>**
- Over-estimates WASO and sleep latency compared to PSG
- Low reliability for patients with restricted movement or mobility

Front. Psychiatry, 10 June 2020

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 <u>≥</u> 35 and + STOP-BANG
- A positive ESAP was defined as a 1+ cm gap when a patient encircled their hands around the neck

Sleep Disord. 2019; 2019: 3184382.



<u>≥</u> 1 cm = + ESAP

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

CVD

- **Untreated obstructive sleep apnea increases the risk of stroke and MI more han 3-fold, but CPAP doesn't lower risk of recurrent events per some 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 increass 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**

Napping Protects Against MI?

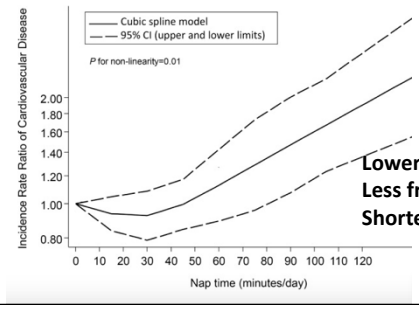
- Once or twice weekly daytime napping associated with a 48% decreased risk of MI, stroke & heart failure
  - 3400+ Swiss adults free of CVD followed 5+ years
- Unaffected by confounders including age, HTN, dyslipidemia, OSAS, nap duration
- More frequent napping (6-7/wk) associated with increased risk but this was attenuated after adjustments for other risk factors

pii: heartjnl-2019-314999. doi: 10.1136/heartjnl-2019-314999. [Epub ahead of print]

To Nap or Not to Nap

- Meta-analysis of 11 prospective cohort studies with 150+ thpusand subjects
- Nap duration associated with major adverse cardiovascular events
- 80% increased risk for habitual napping > 60 minutes

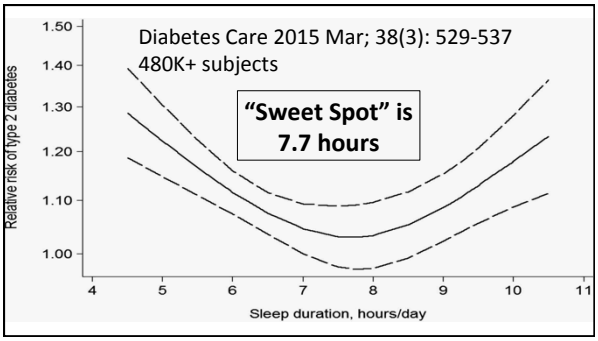
Sleep. 2015 Dec 1; 38(12): 1945–1953.

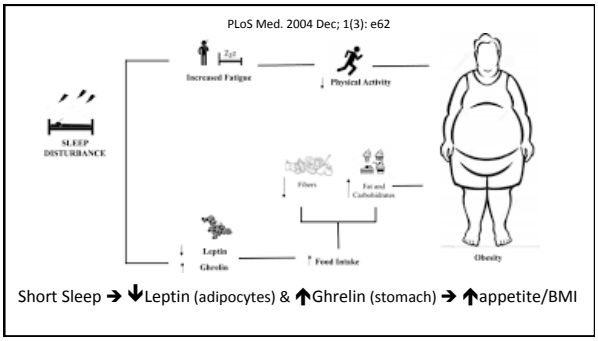


Lower risk with Less frequent & Shorter nap duration

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

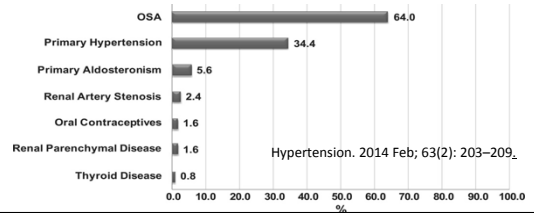




Short Sleep → ↓Leptin (adipocytes) & ↑Ghrelin (stomach) → ↑appetite/BMI

HTN and OSA

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



Hypertension. 2014 Feb; 63(2): 203–209.

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-serontonin 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**

90-95% of serotonin made in gut

PLoS One. 2019; 14(10): e0222394.

Mental Health: Sleep, Diet & Exercise

- Cross-sectional study of 1,111 young adults (18-25) from US and New Zealand
- Assessed for depressive symptoms and indices of well-being via validated tools
- Best predictor of well-being/absence of depression was reported sleep quality
  - ↑ Fruit/vegetable intake was second best and only dietary predictor

Front. Psychol., 10 December 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

Does CPAP Compliance Matter in DR?

- The Veterans Affairs Continuous Positive Airway Pressure Use and Diabetic Retinopathy Study.
  - Cross-sectional analysis of 321 T2DM patients with OSA at Maine VA (Optometry & Pulmonary Clinics)
  - CPAP compliance (≥ 4 hrs 70% of nights) ↓ OR of DR by 46% (p = 0.04) after all controls (HbA1c, BP, disease duration, lipids, renal function, insulin use, smoking, BMI, AHI)
  - Not powered to assess DR severity & CPAP compliance

Optom Vis Sci. 2019;96(11):874-878

OSA and DME Risk

- Case-control study of T2DM patients in Taiwan
  - n = 99 DME = 38 no DME = 61
  - no stat sig difference in age/BMI (67 yrs/30 kg/m^2)
  - Overnight PSG
- **Mean AHI significantly different between the groups**
  - 43.9 versus 35.2 events/hour (p = 0.034)
  - 71% vs 51% had severe OSA (AHI > 30) (p = 0.049)
  - Cumulative time with O_2 saturation < 90% was significantly associated with DME
- **Subjects with severe OSA were 9X more likely to have DME**

Retina. 2019 Feb;39(2):274-280

Does CPAP Improve VA in DME?

- UK prospective study of 131 subjects with DME & VA loss (20/40-20/200) and severe OSA (mean AHI = 36 events/hr)
- Randomized to usual care +/- CPAP clinic x 12mos
- mean age/BMI were 64 yrs and 35 kg/m^2
- No statistically significant difference in BCVA at 12 mos between the two groups (mean 20/63 for both)
- Mean CPAP use = 1.78+/- 2.18 hrs
- Only "usual care intervention" reported was macular photocoagulation – no data on anti-VEGF!

Eur Respir J. 2018 Oct; 52(4): 1801177.

Does CPAP Improve VA in DME?

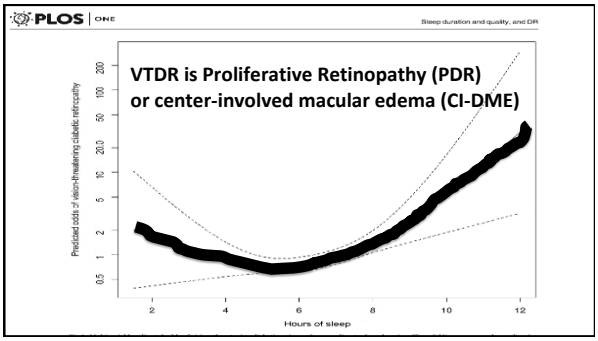
?

- Higher CPAP time of use might matter
- CPAP + anti-VEGF likely better than CPAP + laser
- Preventative CPAP use might beat therapeutic CPAP use for DME

DR & Hypersomnia

- **1231 T2DM patients in Singapore**
- **Long sleep duration (> 8 hrs) & EDS were independently associated with VTDR (3-fold)**

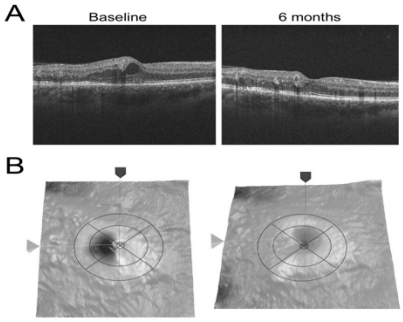
  PLoS One. 2018; 13(5): e0196399
- **Hypothesis: Retinal O_2 demand is predominantly driven by rod metabolism; increased sleep may be a hypoxic stimulus to worsening retinal disease**



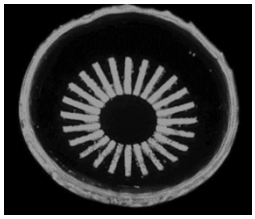
A novel approach to DR

- **Inner retinal hypoxia is primarily responsible for DR and vision loss**
- **Rods are primarily responsible for most retinal O_2 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.



SCL with LED for Dx and Tx

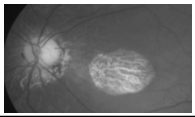


- ✓ Measures blood glucose in conjunctival blood vessels (animal model)
- ✓ Significantly reduced angiogenesis in DR

Nat Rev Mater **5,** 149–165 (2020)

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.

Short Sleep ↑ nvAMD

- **In a case ontrol study of AMD pts with self-reported short sleep (< 6 hours), relative risk of CNVM was 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

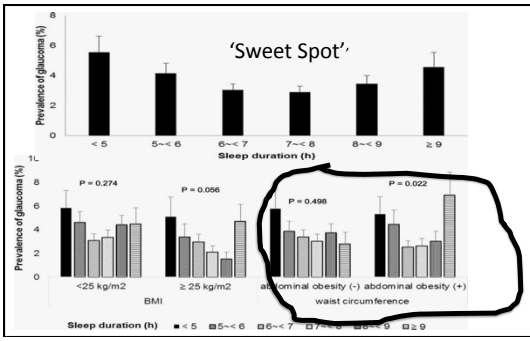
In 38 patients with nvAMD and OSA confirmed by PSG, CPAP + Avastin improved VA (20/40 vs 20/100), CST by -78μ and cut required AVT in half compared to Avastin alone (8 vs 16 injections)

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**

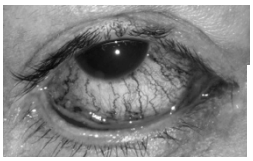
J Glaucoma. 2014 Jan;23(1):e81-5.

Sleep Apnea & Glaucoma

- Studies show POAG patients are more likely to have OSAS
- More severe OSAS is linked to worsening glaucoma
- Worsening NFL and visual field may be seen more often in CPAP-using patients

Graefes Arch Clin Exp Ophthalmol 2014 Sep;252(9):1345-57.

Increased thoracic venous pressure ➔increased episcleral venous Pressure



The Goldmann Equation

$$Po=(F/C)+Pv$$

Po, intraocular pressure in millimeters of mercury; F, rate of aqueous formation; C, facility of aqueous outflow; Pv, episcleral venous pressure

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

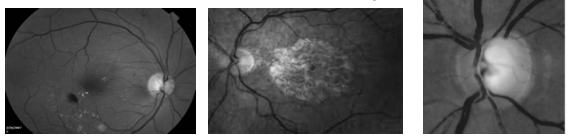
- **Nocturnal IOP was significantly higher in 21 CPAP subjects measured Q2h**
  - **Mean trough/peak spread increased from 6.7 to 9.0 mm Hg after 1 month**
  - **Decreased IOP was seen after 30 minutes CPAP cessation** Invest Ophthalmol Vis Sci. 2008 Mar;49(3):934-40.

Time for an Anecdote

- **54 yo male w T1DM: AHI = 18.3 events/hr**
- **Baseline IOP 19 mm in AM x 3 mornings**
- **After 6 hrs CPAP, IOP increased to 23-26 mm with mean CPA pressure of 11 mm Hg (AHI mean = 3.4)**
- **Addition of oral appliance to CPAP reduced IOP to baseline, mean CPA pressure to 5 mm, & AHI mean = 0.5 events/hr)**

My Simpleton Conclusion for Posterior Segment Disease & Sleep

- **Sick retinas and optic nerves need adequate sleep-time oxygenation to mitigate ongoing damage**
- **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 (≤ 4 hrs)**
  - **16K fom KNHANES** Sleep Med. 2015 Nov;16(11):1327-133
- **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?

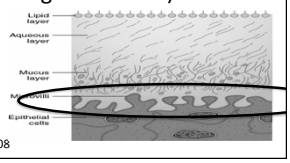
- **Experimental sleep deprivation (mice) induces lacrimal gland hypertrophy and reduces tear production after 10 days**
  - **Reversed after 14 days of rest**

  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-α (mouse model)
- Topical fenofibrate (anti-lipid agent Tricor™) activates PPAR-α 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

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

Is Caffeine Really Problematic?

- Jackson Heart Sleep Study
  - 785 African Americans using actigraphy (wearable activity monitor) x 1 week
- Self-reported use of alcohol, nicotine and/or caffeinated beverages within 4 hours of bedtime
- Both nicotine and alcohol significantly disrupted sleep, but low-dose caffeine did not (≤ 1 cup of caffeinated coffee/tea) Sleep. 2019 Aug 6. pii: zsz136

Caffeine cntd

- There is considerable variability in caffeine metabolism and sensitivity Psychopharmacology (Berl). 2010 Aug;211(3):245-57
  - Modulated by genes influencing dopamine and adenine receptors
- Cross-sectional Analysis of 880 college students
  - Caffeine consumption after 6 PM had no effect on self-reported sleep quality (PSQI)
  - Higher weekly caffeine consumption affected sleep quality ONLY in those NOT consuming after 6 PM
  - → **hypersensitive subjects self-selected for no evening consumption**

J Sleep Res. 2018 Oct;27(5):e12670.

Alcohol within 4 hours of Sleep

- Decreases sleep latency
- Decreases REM sleep duration
- Decreases total sleep duration
- Increases likelihood of sleep apnea
- Increases daytime sleepiness

. Subst Abus. 2005;26(1):1-13.

Sleep medicine vol. 42 (2018): 38-46.

How About Cigarettes?

Table 3.

Adjusted mean differences in sleep parameters by smoking status

Sleep parameter	Adjusted mean difference comparing smokers vs. nonsmokers (%95 CI)	*p*-value
Sleep duration (minutes)	1.51 (−15.88 to 18.89)	0.865
WASO (minutes)	**8.01** (1.94 to 14.07)	0.010
Sleep efficiency (%)	**−1.74** (−3.00 to −0.48)	0.007

Significant p values are bolded. Adjusted for age, sex, BMI, education, work/school next day, depressive symptoms, anxiety, stress.

Sleep. 2019 Nov; 42(11): zsz136.

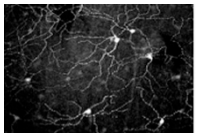
Bottom Line

- **Avoid alcohol an nicotine before bed**
- **Avoid caffeine consumption before bed, especially if it experientially interferes with your individual sleep quality**

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 nightime lighting affects sleep quality and quantity** Sleep. 2016 Jun 1; 39(6): 1311–1320

RGCs in control



ipRGCs

- **Intrinsically photosensitive retinal ganglion cells (1-3% of RGCs)**
- **The 3rd photoreceptor containing the photopigment, melanopsin**
- **Synchronize circadian rhythms to the 24-hour dark/light cycle**
- **Regulate pupil size in ambient light**

ipRGCs Respond to Blue Light

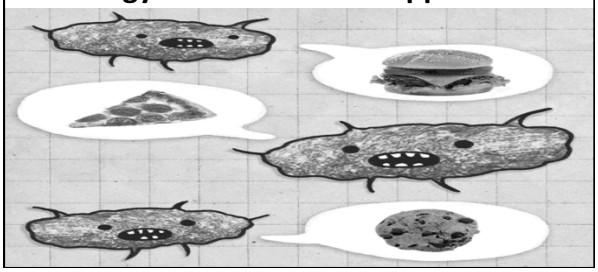
- Contain the photopigment, melanopsin with peak spectral sensitivity of 460-520 nm
- Blue light absorption by ipRGC melanopsin down-regulates production of melatonin by the pineal gland
- Melatonin suppression results in increased wakefulness and alertness

Light At Night (LAN)

- Increased blue light exposure during the evening meal increases hunger & decreases insulin sensitivity x 2 hours
- Increased light at night exposure significantly elevated BP 4/3 mm Hg in Japanese subjects
  - 6% increased mortality -10K additional deaths
- Increased LAN also significantly associated with increased rates of obesity and dyslipidemia independently of melatonin levels→ affects microbiome activity

Am Acad Sleep Med 2014
Chronobiol Int. 2014 Jul;31(6):779-86
J Clin Endocrinol Metab. 2013 Jan;98(1):337-44

Bacterial metabolites affect host energy metabolism and appetite….

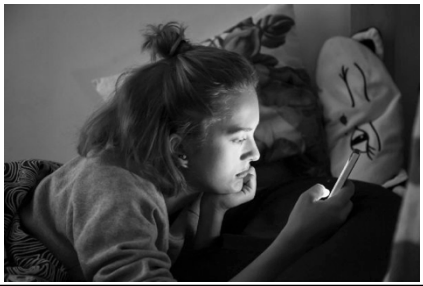


Gut Microbiome Affects Sleep

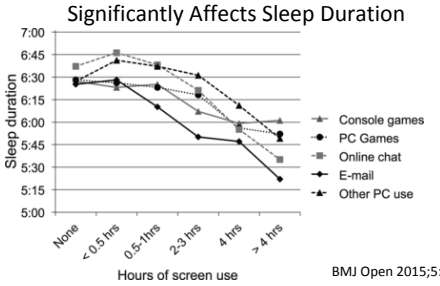
- Antibiotics totally inactivate tryptophan-serontonin signalling in mice
- Higher tryptophan but little serotonin
- Significantly more REM to non-REM sleep transitions
- Improving gut health & diversity (↓saturated fat and ↑fermented foods, probiotics) may improve sleep via ↑IL-6

Gut microbiota depletion by chronic antibiotic treatment alters the sleep/wake architecture and sleep EE power spectra in mice. *Scientific Reports*, 2020 PLoS One. 2019; 14(10): e0222394.

Improving Adolescent Hyposomnia



Adolescent Use of Electronic Devices Significantly Affects Sleep Duration



BMJ Open 2015;5:e006748.

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

Treating OSAS

- **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 ≥ 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

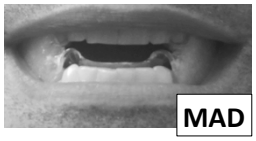
CPAP/BIPAP/auto-PAP

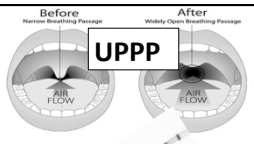
- CPAP (continuous positive airway pressure)
  - Constant air pressure during inhalation and exhilation
- BIPAP (bi-level positive airway pressure)
  - Higher inhalation pressure (IPAP) and lower exhalation pressure (EPAP)
  - Favored for patients with CHF and/or CAD, pulmonary disease (COPD) and disorders affecting CNS breathing (e.g. central sleep apnea, myasthenia gravis)
- Auto-titrating PAP (auto-PAP)
  - Continuous sensors regulate real-time IPAP/EPAP allowing for change in sleep position or weight status; expensive and CI in CHF

J Clin Sleep Med. 2019;15(2):301-334. *Respir Care*. 2010;55(9):1216-1229

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**





Dtsch Arztebl Int. 20. 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
BMJ. 2006 Feb 4; 332(7536): 266–270

Targeted Hypoglossal Neurostimulation

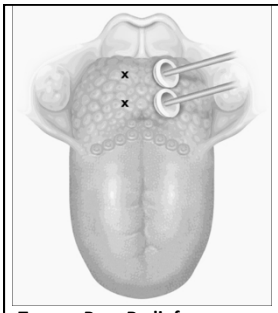
- **Minimally invasive surgery**
- **Intercostal pacemaker with a multi-contact electrode to CN XII**
  - **43% with significant improvement in AHI & O_2 saturation at 6 mos**
  - **BMI < 35 and AHI < 65 predicted good response**
  - **At 1 year, 'responders' had mean AHI decrease from 28.6 to 9.5 events/hour**
  - **> 50% reduction in AHI at 5 years**

Laryngoscope. 2016 Nov;126(11):2618-2623
Laryngoscope. 2018 Feb;128(2):509-515
Otolaryngol Head Neck Surg. 2018 Jul;159(1):194-202

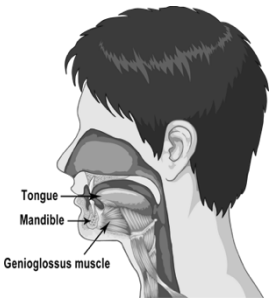
Mandibular Advancement Devices (MAD)

- Reduce required positive airway pressure when used in combination with CPAP
- Combo Tx better tolerated by many patients
- **Patients without severe upper airway collapsibility and with a weaker reflex of throat muscles were more likely to benefit from MAD** (measured by PSG)
  - 93 adults with moderate to severe OSA
  - **OSAS severity & BMI did NOT predict response to MAD**

PLoS One. 2017 Oct 26;12(10):e0187032.
Annals of the American Thoracic Society, 2019; DOI: 10.1513/AnnalsATS.201903-190OC



Tongue Base Radiofrequency



Genioglossus Advancement

Excess Body Weight

Sleep Disorders

Nat Sci Sleep. 2013; 5: 27–35

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

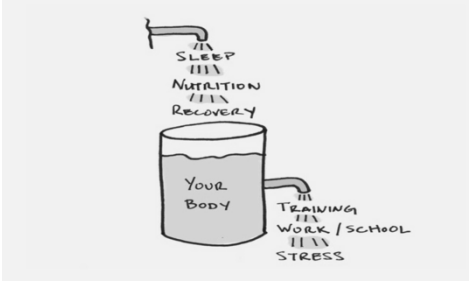
- **Decreased visceral fat (600 Kcal deficit +/- exercise) significantly improved sleep symptoms (insomnia, EDS, apnea) in overweight/obese**

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**

Summary



Thank You!

Paul Chous

dr_chous@diabeticeyes.com