Sleep Disorders: What Optometrists Need to Know

A. Paul Chous, MA, OD, FAAO


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

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

Sleep Walking Talking

Exploding Head Syndrome
Narcolepsy
Insomnia
Sleep Paralysis
Most Prevalent
Restless Legs Syndrome
Sleep Apnea
Snoring
Insomnia
Sleeping Disorders

10/31/19
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 WSU students reported at least 1 episode


**Exploding head syndrome**

**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

- 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

**Sleep Duration Across the Lifespan**


- 17-18.5 hours of wakefulness impairs motor function on a par with or more than a blood alcohol content (BAC) = 0.10%

**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)

Hyposomnia: Short Sleep (< 7h) in Adults & Teens 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

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


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
Sleep Apnea

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

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 O₂ saturation
- Hypopnea: decreased airflow ≥ 10 sec with reduced O₂ saturation (partial obstruction)
  - Elevated Apnea-Hypopnea Index (AHI)

AHI

apeic + 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

Other Sleep Disorders

- Restless Leg Syndrome: leg discomfort coupled with compulsive movement;
  Symptoms worse when stationary; females > males; 5.5% of the population
  (PLMD = 3.9%)

Sleep Med 2011;12(7): 623-34

- Narcolepsy: excessive daytime sleepiness, sleep paralysis, hallucinations, +/- cataplexy; males < females; 79.4 cases per 100,000 prevalence (0.05% of the population)

Sleep 2018;41 (suppl 1): A227

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


- Berlin Obstructive Sleep Apnea Survey
- STOP-BANG Apnea Questionnaire (snore/tired/observed/pressure – BMI/age/neck circumference/gender)


Symptoms of Restless Legs Syndrome

- 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


Polysomnography (PSG)

- Gold standard for diagnosis of most sleep disorders (except Restless Leg Syndrome)
- Overnight measurement of breathing, pulse, P0₂, EEG, REM, leg movements
- Home sleep studies record pulse, P0₂, breathing
  - Good correlation with PSG for Dx of OSA
  - Costs are typically $200-500 versus $1500-2000

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

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

• 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*
  
  * More on this LATER

• Meta-analysis shows sleep apnea doubles the risk of MACE after stent placement
  
  Medicine (Baltimore). 2018 Apr;97(7):e12908

• Women with insomnia have higher BP and serum markers of inflammation
  
  (Am Heart Assoc. 2018 Jun 9;7(12)

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, sleep duration

• More frequent napping (6-7/wk) associated with increased risk but this was attenuated after adjustments for other risk factors

Diabetes

• Short sleep (<5.5 hours) triples the likelihood of T2DM in observational studies after all controls
  

• 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
  

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

Diabetes Care 2015 Mar; 38(3): S29-S37

480K+ subjects

“Sweet Spot” is 7.7 hours

Reducions in butyrate producing bacteria are prevalent in T2DM & HTN


Studium; 2017, 5:14
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

- STDs rates were 2-2.5X higher in T2DM patients (n = 230) with 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 STDs 7.5-fold

DR & Hypersomnia

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

Hypothesis: Retinal O2 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 O2 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

**? nvAMD**
- In a case control 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


**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)


**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;55(52):e5704

**Normotensive Glaucoma**
- NTG appears to be more prevalent in OSA
- 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


**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 (< 4 hrs)
  - 16K from 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

Mechanisms?

- Experimental sleep deprivation (mice) induces lacrimal gland hypertrophy and reduces tear production after 10 days
  - Reversed after 14 days of rest
- Sleep apnea significantly associated with persistent/severe dry eye symptoms in a study of 120 US Veterans (3.8 X)
  - CPAP use not reported

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

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, nasolacrimal air flow

Does CPAP Increase IOP?

- No difference in mean IOP at baseline and after 7 hours in 31 subjects w OSA +/- CPAP
- 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
Time for an Anecdote
- OSA was present in 46% of 200 consecutive T1DM patients (30% normal weight/60% overweight/obese) J Diabetes Complications. 2017 Jan;31(1):156-161
- 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)

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

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 Drug Therapy
- Physical activity
  - Insomnia → Sonata, Lunesta
  - Night terrors → clonazepam
- Identify & treat OSA
  - RLS → carbidopa, gabapentin, Fe

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)

Caffeine contd
- There is considerable variability in caffeine metabolism and sensitivity
  - 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

---

Sleep. 2019 Aug 6; pii: xat136
Sleep Res. 2018 Oct;27(5):e12670
**Bottom Line**

- Avoid alcohol and 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
  

- Indoor and outdoor nighttime 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
  
> Am Acad Sleep Med 2014

- Increased light at night exposure significantly elevated BP 4/3 mm Hg in Japanese subjects
  - 6% increased mortality -10K additional deaths
  
> Chronobiol Int. 2014 Jul;31(6):779-86

- Increased LAN also significantly associated with increased rates of obesity and dyslipidemia independently of melatonin levels affects microbiome activity
  
> Cell. 2016 Dec 1;167(6):1495-1510

**Bacterial metabolites affect host energy metabolism and appetite....**

- Recognized as essential host energy sources and act as signal transduction molecules via G-protein coupled receptors (FFAR2, FFAR3, OLFR78, GPR109A), as epigenetic regulators of gene expression by the inhibition of histone deacetylase (HDAC), and directly influence appetite via Ppde YY

> Nutrients. 2015 Apr; 7(4): 2839–2849

Improving Adolescent Hyposomnia

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

Improving Adolescent Hyposomnia

- Passive light therapy: 3 ms flash Q 20 seconds x 2 hrs @ 4-6 AM (programmable bridge beacon)
  - Increased sleepiness but not sleep duration (n = 72)
- Light therapy + 4 sessions of cognitive behavioral therapy (CBT)
  - Self-selected goal of improving academics, athletic performance, physical appearance
  - Teens slept 43 minutes longer, went to bed 50 minutes earlier & were 6X more likely to maintain consistent bedtimes with dual Tx

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)

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)


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

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 tone

- Playing a double-reed instrument

- Play didgeridoo
  - comparable to CPAP for mild-moderate OSA

- Weight Loss

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

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;16(5):641-649A

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