Clinical Sleep Medicine Update: Year in Review

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MASM Fall 2016 Meeting
October 14, 2016
OBJECTIVES

Review and understand key medical literature published in the following topics between 2015 – 2016, in order to incorporate them into medical practice:

• Pediatrics
• Insomnia (including pharmacological & non-pharmacological management options)
• Sleep and its relationship to other medical disorders
• Alternative treatments for obstructive sleep apnea
Year in Review:
Pediatric Sleep

Cindy Nichols, PhD, DABSM, FAASM, CBSM
Clinical Director
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Traverse City, MI
Conflict of Interest Disclosures for Speakers

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Review Process

• SLEEP and JCSM titles from all volumes and issues in 2015 and 2016 were reviewed.
• Expert opinion articles without original data were excluded.
• Articles with original data were reviewed using the GRADE critical appraisal technique.
• Systematic review and meta-analyses were included, but were excluded from the GRADE evaluation.
Results Review

- Systematic reviews and/or meta-analysis: 3
- Scoring update: 1

High level evidence:
- RCT: 2

Low level evidence:
- Case series: 3
  - Prospective observational studies: 4
  - Pre-post design: 3
  - Matched case control design: 8
  - Cross sectional design: 6
  - Retrospective observational design: 1
Topics

- Mental and behavioral health: 2
- Sleep-disordered breathing: 10
- Sleep duration: 1
- Insomnia: 2
- CPAP adherence: 1
- General development: 4
- Infant sleep scoring: 1
- Narcolepsy/IHS: 3
- Sleep deprivation: 4
- Sleep and cognition: 2
- Circadian rhythm: 1
- Sleep in other medical illness: 2
- Sleep education: 1
Sleep-Disordered Breathing

• While AT reduces the AHI significantly even in obese children, obese children do not lose weight after undergoing upper airway surgery (Com G et al, 2015).

• OSA is not routinely screened for by anesthesia providers prior to ambulatory pediatric surgery, and paradoxically, patients with undiagnosed OSA who would benefit the most from screening were the least likely to be screened (Ishman S et al, 2015).

• Adenotonsillar hypertrophy causes elevated airway resistance/upper airway loading that may contribute to the increased frequency of respiratory diseases in untreated children with OSA. Airway resistance loading was higher in children with OSA vs. normal controls, but both groups had normal spirometry. Airway resistance decreased to that of normal controls following AT (Tapia I et al 2016).
Sleep-Disordered Breathing

• 39% of children treated with AT, nasal surgery, or nasal corticosteroids still had significant SDB 3 years after treatment (Walter L, et al 2015).

• Obstructive, central, mixed, and total AHI were not significantly higher in obese adolescents with and without metabolic syndrome (Erdim I et al 2015).

• Pre-AT and post-AT high-sensitivity C-reactive protein (an inflammatory biolmarker) is predictive of residual OSA following AT (Bhattacharjee R et al 2016).

• 66.4% prevalence of OSA in children with Down syndrome, and even those with a “negative” history for OSA symptoms, prevalence is 53.8% (Maris M et al 2016).
Sleep-Disordered Breathing

- Neck circumference-height ratio may improve the ability to triage children and adults at risk for OSA. In children, the odds ratio of AHI >2 was 3.47 for NHR>0.25; however, in adults the odds ratio of AHI>5 was 18 for NHR>0.25 (Ho A, et al 2016).
- Obstructive events in children age 12-18 are still predominantly in REM and in the supine position; AA adolescents have more REM obstructive events. El-Kersh K, et al 2016.
- Children with micrognathia, but not children with isolated cleft palate prior to repair (+/- cleft lip) are more likely to have OSA when compared to controls (Cielo C et al 2016).
PAP Adherence

- Females and children with developmental delay are more likely to be adherent with CPAP, particularly females with Down syndrome.
- Only 49% of patients used CPAP for at least 4 hours on at least 70% of nights.

Hawkins S et al 2016
Insomnia

- Use of the JuSt method (6 group sessions – 5 for children, 1 for parents; utilizing cognitive and behavioral interventions (sleep hygiene, SC therapy, relaxation/guided imagery/self-hypnosis, anxiety management techniques, psychoeducation) was effective for children ages 11-16. Treatment effects were maintained at 3, 6, and 12 month follow up (Roeser K et al 2016).

- Pubertal maturation is associated with a progressive increase in prevalence of insomnia symptoms with the emergence of female preponderance (Zhang J, Chan N, Lam S 2016).
Circadian Rhythms

• Early March DST onset affected sleep and vigilance in high school students, with an average of 32 minutes less sleep per night during the week following DST, resulting in increased daytime sleepiness, reduced reaction times, and increased lapses on the PVT. (Medina D et al 2015).
Narcolepsy and Idiopathic Hypersomnia

• Children with type 1 narcolepsy may have flattening of the circadian rhythm, demonstrating increased motor activity during the night and blunted activity in the afternoon (Filardi M et al 2016).

• Children with type 1 narcolepsy were compared with normal controls and children with idiopathic epilepsy. Narcoleptic children had worse psychosocial health, increased internalizing problems, and behavioral problems than children with epilepsy or normal controls. These problems were significantly correlated with sleepiness (Rocca F et al 2016).

• Children with IHS continue to experience a range of significant psychosocial consequences (academic performance, QoL, wellness, sleepiness, participation in extracurricular activities) even after a diagnosis has been made and treatments initiated (Avis K et al 2015).
Chronic Fatigue Syndrome

• Systematic review of 6 case-controlled studies; all were low quality evidence
• Most found that children and adolescents with CFS had more sleep complaints when compared to healthy controls.
• Further research should focus on identifying specific sleep symptoms, consequences of sleep disturbance, and effective interventions in this population

• Snodgrass K et al 2015
• Delayed school start times (45 minutes) improved tardiness and disciplinary issues that persisted until the end of the academic year, but at the end of the year students total sleep time returned to baseline levels with a delay in bedtime (Thacher P et al 2016).

• Meta analysis of PSG in11 studies on sleep and ADHD found few differences in sleep between children with ADHD and controls, with a possible trend toward more N1 in children with ADHD (Diaz-Roman A et al 2016).
Sleep in Medical Illness

• Critically ill children in the PICU, ventilated and treated with opioids and benzodiazepines, did not demonstrate day-night organization of sleep and had diminished untradian variability in EEG power (Kudchadkar S, et al 2015).
Sleep Duration: Consensus Statement of AASM, AAP, NIH

- Panel of 13 experts reviewed 864 relevant articles
  - Paruthi S et al 2016
- Recommended sleep durations (include naps)
  - 4 months to 12 months: 12 to 16 hours
  - 1 to 2 years: 11 to 14 hours
  - 3 to 5 years: 10 to 13 hours
  - 6 to 12 years: 9 to 12 hours
  - 13 to 18 years: 8 to 10 hours
Sleep Duration: Consensus Statement of AASM, AAP, NIH

Sleeping the recommended hours on a regular basis is associated with better health outcomes including improved attention, behavior, learning, memory, emotional regulation, quality of life, and mental/physical health.

Regularly sleeping fewer than the recommended hours is associated with problems in attention, behavior, and learning. Insufficient sleep also increases risk of accidents, injuries, hypertension, obesity, diabetes, and depression.

Insufficient sleep in teenagers is associated with increased risk of self-harm, suicidal thoughts, and suicide attempts.

Sleeping more than the recommended hours may be associated with adverse health outcomes such as hypertension, diabetes, obesity, and mental health problems.

Sleeping too little or too much may be associated with the presence of a sleep disorder.
General Development

• Older age is associated with lower percentage of N3, higher N2, and higher REM sleep. EEG power in higher frequency bands was lower in older vs. younger adolescents, with equal effects across electrodes. Older boys (but not girls) had more frequent awakenings and WASO (Baker et al 2016).

• Sigma frequencies become linearly faster with age and sigma power declines with a complex trajectory, most likely due to synaptic elimination (Campbell I et al 2016).

• Both adolescents and preadolescents with a circadian preference for eveningness have impaired sleep quality. Preadolescents were more involved in gaming and television, and adolescents were more involved in internet, phone, and social network activities when they were not sleeping (Bruin O, et al 2015).

• Preterm children have shorter sleep duration than term children even at age 5-12 measured by actigraphy. Parental estimates of sleep were about 45 minutes longer than actigraphic estimates (Biggs S et al 2016).
Cognition

• A daytime nap was associated with more effective learning of word meanings, including forgetting of irrelevant information, in toddlers (Horvath K et al 2016).

• A week of partial sleep deprivation (5 hrs/night) impairs a wide range of cognitive functions, alertness, and mood even in high-performing high school adolescents. Even after 2 nights of recovery sleep (9 hours/night), sleepiness and sustained attention did not return to baseline (Lo J, Ong J et al 2016).
Sleep Education

• Systematic review evaluated “lessons learned” from 13 studies, to identify factors contributing to success and to make recommendations for improvement.

• Recommendations:
  • Teacher participation is essential
  • Parent and family involvement must happen
  • Sleep education should begin earlier than high school
  • Motivational components should be included
  • Consider online delivery and interactive engagement
  • Including sleep diaries is helpful
  • Consider cultural impact

Blunden S, et al
Scoring Sleep in Infants

• Score in 30 second epochs as Wake (W), REM (R), NREM (N), and transitional (T).
• Minimum EEG montage is F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1; C3-Cz, Cz-C4 help to detect early and asynchronous spindles.
• Sleep onset is most often R until 2-3 months postterm
• Drowsiness is best scored by visual observation
• Wide open eyes is crucial determinant of W
• Regular/irregular respiration is very useful for scoring sleep stages
• Presence of spindles = N
• Score R with any 4 or more of the following: low chin EMG, eyes closed with at least 1 REM and low chin EMG, irregular respiration, mouthing/sucking/twitchin, no spindles
Scoring Sleep in Infants

• Score R with any 4 or more of the following:
  • low chin EMG
  • eyes closed with at least 1 REM and low chin EMG
  • irregular respiration
  • mouthing/sucking/twitching
  • continuous EEG pattern no spindles

• Score N with any 4 or more of the following:
  • regular respiration
  • EEG pattern of trace alternans, high voltage slow activity, or spindles
  • eyes closed with no eye movement
  • chin tone present

• Score T if epoch contains 2 or more discordant PSG states

Grigg-Damberger M 2016.


Reference List


Reference List


Year in Review: Insomnia

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Insomnia Update

- Pharmacologic: Suvorexant
- Non-Pharmacologic:
  - Thermal Cooling
  - Web-based CBT-I
Suvorexant

• Belsomra
  • Approved in the U.S. in Aug 2014
  • Schedule C-IV controlled substance
• Mechanism of action: orexin receptor antagonist
  • Orexin pathway originates in the lateral hypothalamus and projects widely throughout the brain to mediate transitions between wakefulness and sleep
  • Antagonism of orexin receptors selectively dampens unwanted wakefulness interfering with sleep
• Half life: 12 hours
• Time to peak: 2 hours
• Metabolism: primarily hepatic by CYP3A
• Excretion: primarily in feces
Suvorexant

- Efficacy: shown to improve sleep efficiency
  - Michelson et al. 2014:
    - 781 patients with primary insomnia were randomly assigned to receive nightly suvorexant or placebo for one year, followed by a two-month randomized discontinuation phase. The dose of suvorexant used was 40 mg for patients <65 yo and 30 mg for patients ≥65 yo.
    - At one month, patients treated with suvorexant had increased subjective total sleep time (39 versus 16 minutes; difference 23 minutes, 95% CI 16-29) and decreased subjective time to sleep onset (-18 versus -8 minutes, 95% CI -15 to -5) compared with placebo.
    - Improvements in subjective sleep persisted at one year.
  - Herring et al. 2012: 254 subjects received doses ranging from 10 to 80 mg nightly for 4 weeks
    - Compared to placebo, suvorexant showed improved sleep efficiency of about 5-10%. Increase is TST was seen due to increase in N2 and REM.
Suvorexant

• Efficacy: shown to improve sleep efficiency
  • Herring et al. 2016:
    • Analysis of pooled data from two identical randomized, double-blind, placebo-controlled, parallel-group, 3-month trials in non-elderly (18–64 years) and elderly (≥ 65 years) patients with insomnia. Patients were randomized to suvorexant 20/15 mg (non-elderly/elderly, N= 493), suvorexant 40/30 mg (not reported in this article), or placebo (N=767). Efficacy was assessed by self-reported and polysomnography sleep maintenance and onset endpoints.
Difference between placebo and suvorexant between mean change from baseline:

<table>
<thead>
<tr>
<th>Measure</th>
<th>Week 1 / night 1</th>
<th>1 mo</th>
<th>3 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTST</td>
<td>15 min</td>
<td>18.4 min</td>
<td>16.0 min</td>
</tr>
<tr>
<td>sTSO</td>
<td>-6.1 min</td>
<td>-5.6 min</td>
<td>-5.9 min</td>
</tr>
<tr>
<td>sWASO</td>
<td>-5.3 min</td>
<td>-6.6 min</td>
<td>-4.7 min</td>
</tr>
<tr>
<td>TST</td>
<td>44.8 min</td>
<td>34.7 min</td>
<td>27.5 min</td>
</tr>
<tr>
<td>WASO</td>
<td>-34.6 min</td>
<td>-25.4 min</td>
<td>-23.1 min</td>
</tr>
<tr>
<td>LPS</td>
<td>-11.2 min</td>
<td>-9.1 min</td>
<td>-4.6 min</td>
</tr>
<tr>
<td>SE</td>
<td>9.3</td>
<td>7.2</td>
<td>5.7</td>
</tr>
<tr>
<td>ISI</td>
<td>--</td>
<td>-1.4</td>
<td>-1.3</td>
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</table>
Suvorexant

• Side effects:
  • Somnolence (2-12%), more common in females and with higher doses
  • Rebound insomnia can be seen with discontinuation of suvorexant (in studies of 1 year but not 1 or 3 months)
  • Minimal potential to worsen respirations during sleep
  • Driving is minimally impaired
  • Headache (7%), dizziness (3%), abnormal dreams (2%), abnormal thinking/behavior changes, cough/URI (2%), sleep paralysis. No reported cases of parasomnias or cataplexy.
  • No evidence for abuse.

• Interactions:
  • Suvorexant is metabolized by cytochrome P450 3A4 (CYP3A4), and there is potential for increased toxicity when used in combination with CYP3A4 inhibitors.

• Dosing:
  • Start at 5 mg and titrate as needed up to 20 mg once daily, taken within 30 minute of going to bed, allow at least 7 hrs in bed.
Thermal System for Insomnia

• In May 2016, FDA approved a “thermal system for insomnia” – “a prescription device for use in patients with insomnia that is used to apply a specified temperature [14-16°C] to the skin surface”.

• CERÊVE SLEEP SYSTEM

De Novo Summary (DEN140032)
Thermal System for Insomnia

• “Our novel technology is designed to work differently than other products and pills, by addressing the source of the problem – calming the overactive mind that is thought to be responsible for preventing us from falling asleep at night. By calming this mental “hyperarousal”, we can turn off our minds and get to sleep faster.”


• Frontal cortical hyperarousal in insomnia
  • There is growing evidence showing hyper-metabolism during sleep in the frontal regions.
  • Multiple studies show increased beta EEG power during sleep and wakefulness in the frontal regions.
Thermal System for Insomnia

- Efficacy: decreased latency to stage 1 and stage 2 sleep
  - Randomized, multi-center trial, 116 primary insomnia adults, treated for 2 nights: no differences for primary endpoint (sustained sleep, sleep efficiency) but showed decreased sleep latency to stage 1 and stage 2 sleep
  - Cross-over trial of 145 subjects testing 2 temperature modes, treated for 5-7 nights, no difference to persistent sleep or sleep efficiency
  - 32 subjects used treatment at home for 30 days, reported improved self-reported sleep quality, no serious adverse events were reported

- Labeling: “Other than reduction of sleep latency to Stage 1 and Stage 2 sleep, the efficacy of other sleep measures associated with insomnia has not been established by the Cerêve Sleep System in controlled clinical trials. ”

- Listed adverse events: adverse skin reactions, electrical safety, thermal injury

- Adverse events noted in studies: headache
Web-based Cognitive Behavioral Therapy for Insomnia (CBT-I)

- Cognitive Behavioral Therapy received a Standard level of recommendation by the AASM (2006 Practice Parameter) and is recommended as the initial intervention when appropriate and when conditions permit (2008 clinical guideline).
- However, there are few trained providers and therapy may be costly and not available for many patients.
- Several trials show effectiveness of web-based delivery of CBT-I:
  - Ritterband et al. 2009: 22 internet and 22 control subjects
    - Mean ISI decreased from 15.7 to 6.5, WASO decreased from 66 to 29 min, SE increased from 77% to 89%. At 6 months, ISI remained low at 7.3 in the internet group.
  - Espite et al. 2012: 164 subjects assigned to web-based CBT-I, web-based control (IRT) or treatment as usual
    - SE improved from 63% to 82%, SOL decreased from 47 to 21 min, WASO decreased from 76 to 48 min. Improvements were sustained at 6 months.
Web-based CBT-I

• Randomized trials show web-based CBT-I is effective, but may be less effective compared to in-person therapy

• Lancee et al. 2016: guided online (with e-mail feedback) and individual face-to-face CBT-I were compared to a wait-list condition
  • At post-assessment, face-to-face and online intervention groups showed significantly larger treatment effects than the wait-list group on insomnia severity and sleep efficiency
  • Larger treatment effect was seen in the face-to-face group, especially on depression and anxiety outcomes

| Table 2—Pretest and posttest means with corresponding Cohen d scores for the online, face-to-face (F2f), and wait-list (WL) condition. |
|-------------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|
|                     | Pretest, mean (SD) | Posttest, mean (SD) | Cohen d |
|                     | F2f   | Online | WL    | F2f   | Online | WL    | F2f x Online | F2f x WL | Online x WL |
| ISI                 | 17.3  | 18.2   | 17.5  | 7.1   | 12.4   | 16.5  | 0.9***        | 2.3***    | 1.0***     |
| CES-D               | 15.7  | 17.5   | 21.5  | 8.0   | 14.5   | 21.3  | 0.7***        | 1.2**     | 0.4**      |
| HADS-A              | 5.9   | 6.3    | 7.2   | 3.6   | 5.3    | 8.7   | 0.4***        | 1.2***    | 0.8**      |
| TST                 | 336.7 | 322.3  | 325.7 | 395.3 | 382.6  | 361.8 | 0.0***        | 0.3***    | 0.4**      |
| SE                  | 67.1  | 64.1   | 67.4  | 84.3  | 78.1   | 74.1  | 0.2**         | 0.8**     | 0.6*       |
| TWT                 | 162.0 | 179.1  | 157.6 | 72.8  | 102.7  | 126.1 | 0.2**         | 0.9***    | 0.8**      |

*P < 0.05; **P < 0.01; ***P < 0.001. Missing posttest scores are imputed with predictive mean matching. Total wake time is SOL + WASO + TWAK. See Table S1 for means and corresponding Cohens d’s for SOL, WASO, TWAK, NWA, SOL and for the ISI score with the first item left out. See Table S5 for the multilevel regression coefficients. CES-D, depressive symptoms; HADS-A, anxiety symptoms; ISI, insomnia severity index; SD, standard deviation; SE, sleep efficiency; TST, total sleep time; TWT, total wake time.
Web-based CBT-I

- Treatment effects remained greater for the face-to-face group at 3 and 6 month follow up
Web-based CBT-I

- Web-based CBT-I is more cost-effective than in-person CBT-I
- De Bruin et al. 2016: 62 participants, aged 12-19 yo, randomized to web-based CBT-I with personal feedback (IT) compared to group CBT-I (GT)
  - At each measurement occasion, parents filled out retrospective cost questionnaires that reported on resource usage over the past 2 months (e.g., doctors’ visits, use of medication, mental health care visits, additional help at school/home, etc.)
  - IT had a smaller cost posttreatment at 1 year, mostly due to the differences in cost of the therapy
  - There was no significant difference in proportions of participants in IT and GT who had SE ≥ 85%: at posttreatment, 87% for IT and 74% for GT and at 1 year 90% for IT and 94% for GT
Let's build your sleep improvement program

$300, 1 year

$135, 16-weeks
Take home points

• Suvorexant is an effective pharmacologic treatment of insomnia, with minimal residual sleepiness.
• Thermal system for insomnia is well tolerated but provides minimal improvement in insomnia with decreased latency to stage 1 and stage 2 sleep.
• Web-based CBT-I is an effective alternative method of delivering CBT-I at a smaller cost.
References: Insomnia

• Suvorexant
References: Insomnia

- **Thermal cooling device**

- **Frontal activation in insomnia**
References: Insomnia

• CBT-I

• Web-based CBT-I delivery
  • Espie CA; Kyle SD; Williams C; Ong JC; Douglas NJ; Hames P; Brown JSL. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. SLEEP 2012;35(6):769-781.
References: Insomnia

• **Web-based CBT-I**
  • https://www.sleepio.com/
  • http://shuti.me/
  • http://t2health.dcoe.mil/apps/CBT-i: adjunct for face-to-face care; a collaborative effort between VA’s National Center for PTSD, Stanford School of Medicine and DoD’s National Center for Telehealth & Technology.
  • http://cobalitx.com/cbt-online-insomnia-treatment.html
  • http://www.sleeptutor.com/
  • http://www.cbtforinsomnia.com/

Websites accessed 7/31/2016 and 8/31/2016
Year in Review:
Sleep & Medical Disorders

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Assistant Professor, University of Michigan
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Sleep & Kidney Disease

Sleep Apnea and the Risk of Chronic Kidney Disease: A Nationwide Population-Based Cohort Study

Yi-Che Lee, MD, MS,1,6 Shih-Yuan Hung, MD,1 Hao-Kuang Wang, MD,2,6 Chi-Wei Lin, MD, MS,3 Hsi-Hao Wang, MD, MS,1 Shih-Wei Chen, MD, MS,5 Min-Yu Chang, MD, MS,1 Li-Chun Ho, MD,1,6 Yi-Ting Chen, MD,1 Hung-Hsiang Liou, MD,7 Tsuen-Chiuan Tsai, MD, PhD,4 Shih-Hann Tseng, MD,10 Wei-Ming Wang, MS,8 Sheng-Hsiang Lin, PhD,6,* and Yuan-Yow Chiou, MD, PhD6,9,*

### Table: Multivariable-Adjusted Cox Regression Models and Multivariable-Adjusted Competing-Risk Regression Models Hazard Ratios of Chronic Kidney Disease Among the Cohort of Sampled Patients During the Follow-Up Years

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 28,044)</th>
<th>Male (n = 18,552)</th>
<th>Female (n = 9,492)</th>
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<tbody>
<tr>
<td></td>
<td>SA (n = 4,674)</td>
<td>Non-SA (n = 23,370)</td>
<td>SA (n = 3,092)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Yes</td>
<td>119 (2.6)</td>
<td>270 (1.2)</td>
<td>73 (2.4)</td>
</tr>
<tr>
<td>Crude HR</td>
<td>2.16 (1.70, 2.73)a</td>
<td>1</td>
<td>1.87 (1.39, 2.52)a</td>
</tr>
<tr>
<td>Cox model</td>
<td>1.94 (1.52, 2.46)a</td>
<td>1</td>
<td>1.70 (1.25, 2.30)a</td>
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<tr>
<td>CRR model</td>
<td>1.90 (1.47, 2.47)a</td>
<td>1</td>
<td>1.80 (1.32, 2.54)a</td>
</tr>
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</table>

Adjustments were made for age group, geographic location, enrollee category, income, urbanization level, and comorbidities, including hypertension, diabetes mellitus, atherosclerotic vascular disease, hyperlipidemia, nephrolithiasis, chronic hepatitis, diseases of the musculoskeletal system and connective tissue, gout, obesity, and chronic obstructive pulmonary disease. Values given as adjusted HR (95% CI). aP < 0.001. CI, confidence interval; CRR, Fine and Gray competing-risk regression; HR, hazard ratio; SA, sleep apnea.
Subjects with lower estimated glomerular filtration rate were older, more obese, more often female, had worse obstructive sleep apnea and more co-morbidities

### OSA & Psoriasis

**Table 2** Stratified analysis of the association between psoriasis and obstructive sleep apnea (n = 36,346)

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>n</th>
<th>OSA in psoriasis cases (n = 12,336)</th>
<th>OSA in controls (n = 24,008)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>36,344</td>
<td>327 (2.7%)</td>
<td>369 (1.5%)</td>
<td>1.74 (1.50-2.03)**</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>18,537</td>
<td>226 (3.5%)</td>
<td>279 (2.3%)</td>
<td>1.55 (1.30-1.86)**</td>
</tr>
<tr>
<td>Females</td>
<td>17,807</td>
<td>99 (1.7%)</td>
<td>90 (0.8%)</td>
<td>2.24 (1.68-2.99)**</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21–39</td>
<td>7,813</td>
<td>14 (0.6%)</td>
<td>19 (0.3%)</td>
<td>1.72 (0.86-3.44)</td>
</tr>
<tr>
<td>40–59</td>
<td>14,252</td>
<td>154 (3.2%)</td>
<td>173 (1.8%)</td>
<td>1.73 (1.39-2.16)**</td>
</tr>
<tr>
<td>60–69</td>
<td>14,279</td>
<td>159 (3.1%)</td>
<td>177 (1.9%)</td>
<td>1.63 (1.31-2.03)**</td>
</tr>
<tr>
<td>Body mass index categories (n = 30,567)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt; 20 kg/m²)</td>
<td>1,042</td>
<td>2 (0.6%)</td>
<td>2 (0.3%)</td>
<td>2.36 (0.33-16.9)</td>
</tr>
<tr>
<td>Normal (20–24.9 kg/m²)</td>
<td>6,806</td>
<td>16 (0.8%)</td>
<td>27 (0.6%)</td>
<td>1.32 (0.70-2.45)</td>
</tr>
<tr>
<td>Overweight (25–29.9 kg/m²)</td>
<td>10,288</td>
<td>56 (1.6%)</td>
<td>107 (1.6%)</td>
<td>1.03 (0.74-1.43)</td>
</tr>
<tr>
<td>Obesity (30–39.9 kg/m²)</td>
<td>10,234</td>
<td>179 (4.4%)</td>
<td>175 (2.8%)</td>
<td>1.60 (1.29-1.98)**</td>
</tr>
<tr>
<td>Severe obesity (&gt; 40 kg/m²)</td>
<td>2168</td>
<td>61 (6.9%)</td>
<td>45 (3.5%)</td>
<td>2.04 (1.37-3.03)**</td>
</tr>
<tr>
<td>Peptic disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without peptic disease</td>
<td>33,635</td>
<td>265 (7.8%)</td>
<td>304 (1.4%)</td>
<td>1.77 (1.50-2.01)**</td>
</tr>
<tr>
<td>With peptic disease</td>
<td>2709</td>
<td>62 (5.3%)</td>
<td>65 (4.2%)</td>
<td>1.28 (0.89-1.83)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without hyperlipidemia</td>
<td>21,217</td>
<td>110 (1.7%)</td>
<td>148 (1.0%)</td>
<td>1.77 (1.37-2.27)**</td>
</tr>
<tr>
<td>With hyperlipidemia</td>
<td>15,127</td>
<td>217 (3.6%)</td>
<td>221 (2.4%)</td>
<td>1.51 (1.24-1.83)**</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without COPD</td>
<td>34,798</td>
<td>278 (2.4%)</td>
<td>340 (1.5%)</td>
<td>1.64 (1.40-1.93)**</td>
</tr>
<tr>
<td>With COPD</td>
<td>1,546</td>
<td>49 (7.0%)</td>
<td>29 (3.4%)</td>
<td>2.10 (1.31-3.36)**</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without hypothyroidism</td>
<td>33,878</td>
<td>290 (8.6%)</td>
<td>340 (1.5%)</td>
<td>1.72 (1.46-2.02)**</td>
</tr>
<tr>
<td>With hypothyroidism</td>
<td>2,466</td>
<td>37 (3.7%)</td>
<td>29 (2.0%)</td>
<td>1.87 (1.13-3.06)*</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jewish</td>
<td>31,440</td>
<td>306 (2.7%)</td>
<td>340 (1.3%)</td>
<td>1.65 (1.41-1.93)**</td>
</tr>
<tr>
<td>Arab</td>
<td>4,904</td>
<td>19 (1.7%)</td>
<td>29 (0.8%)</td>
<td>2.28 (1.26-4.05)**</td>
</tr>
</tbody>
</table>

N = 12,336  N = 24,008

CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio; OSA, obstructive sleep apnea; PH, pulmonary hypertension.

*P < 0.05.

**P ≤ 0.01.

***P ≤ 0.001.

Odds ratio = 1.27 (95% CI 1.08–1.49, p < 0.001) when adjusted for age, sex, ethnicity, BMI, COPD, hypothyroidism, hyperlipidemia, and peptic disease.

Patients with non-apnea sleep disorders are associated with a higher risk for developing autoimmune diseases.

Table 3—Incidence and hazard ratios of autoimmune diseases in patients with different types of non-apnea sleep disorders.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of Events</th>
<th>Person-Years</th>
<th>Incidence Rate*</th>
<th>Crude HR (95% CI)</th>
<th>P Value</th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sleep disorders</td>
<td>4,753</td>
<td>664,413</td>
<td>71.54</td>
<td>1.64 (1.56-1.73)</td>
<td>&lt; 0.001</td>
<td>1.51 (1.46-1.57)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NSD</td>
<td>7,731</td>
<td>656,668</td>
<td>117.70</td>
<td>1.71 (1.64-1.79)</td>
<td>&lt; 0.001</td>
<td>1.43 (1.40-1.57)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3,892</td>
<td>300,313</td>
<td>122.94</td>
<td>1.89 (1.76-2.02)</td>
<td>&lt; 0.001</td>
<td>1.42 (1.39-1.56)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chronic①</td>
<td>936</td>
<td>69,109</td>
<td>135.26</td>
<td>1.96 (1.91-1.99)</td>
<td>&lt; 0.001</td>
<td>1.46 (1.42-1.50)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Acute</td>
<td>2,756</td>
<td>231,114</td>
<td>119.25</td>
<td>1.56 (1.50-1.64)</td>
<td>&lt; 0.001</td>
<td>1.48 (1.42-1.57)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>3,861</td>
<td>339,292</td>
<td>112.10</td>
<td>1.57 (1.50-1.64)</td>
<td>&lt; 0.001</td>
<td>1.46 (1.40-1.59)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Others</td>
<td>378</td>
<td>29,683</td>
<td>126.07</td>
<td>1.75 (1.68-1.90)</td>
<td>&lt; 0.001</td>
<td>1.47 (1.41-1.55)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Per 10⁶ person-years. ①Adjusted for age, sex, urbanization, income, Charlson comorbidity index score, coronary artery disease, cerebrovascular disease, hypertension, diabetes mellitus, chronic kidney disease, dyslipidemia, and medication for non-apnea sleep disorders. ②According to the International Classification of Sleep Disorders, 3rd edition (ICSD-3) definition as insomnia lasts more than three months. ICD-9-CM codes: Insomnia: 780.52, 307.41, 307.42; Sleep disturbance: 780.3, 780.50; Others: 780.35, 780.50, 780.95, 307.4. HR: hazard ratio; CI, confidence interval; NSD, non-apnea sleep disorders.

OSA & Cancer

**TABLE 2. ADJUSTED RELATIVE HAZARDS OF TOTAL AND CANCER MORTALITY ACCORDING TO SLEEP-DISORDERED BREATHING CATEGORIES**

<table>
<thead>
<tr>
<th>SDB (AHI Range)</th>
<th>All-Cause Mortality</th>
<th>Cancer Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent (&lt;5)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Mild SDB (5–14.9)</td>
<td>1.8 (1.1–2.8)</td>
<td>1.1 (0.5–2.7)</td>
</tr>
<tr>
<td>Moderate SDB (15–29.9)</td>
<td>1.1 (0.5–2.5)</td>
<td>2.0 (0.7–5.5)</td>
</tr>
<tr>
<td>Severe SDB (≥30)*</td>
<td>3.4 (1.7–6.7)</td>
<td>4.8 (1.7–13.2)</td>
</tr>
</tbody>
</table>

*N for trend 0.0014 0.0052


**Figure 2**—The univariate association between sleep apnea and cancer mortality.

**Figure 3**—The univariate association between sleep apnea and the incidence of cancer.


**Sleep apnea increased incidence of primary central nervous system cancers: a nationwide cohort study**

Jin-Cheng Chen a, b, Juen-Haur Hwang c, d, * Sleep Medicine 15 (2014) 749–754

**Association between sleep disordered breathing and aggressiveness markers of malignant cutaneous melanoma**

European Respiratory Journal 2014 43: 1661-1668; DOI: 10.1183/09031936.00115413

**Sleep apnea and the subsequent risk of breast cancer in women: a nationwide population-based cohort study**

Sleep Medicine 15 (2014) 1016–1020
Sleep Apnea and Cancer: Analysis of a Nationwide Population Sample

David Gozal, MD, MBA; Sandra A. Ham, MS, MA; Babak Mokhlesi, MD, MSc

1Sections of Pediatric Sleep Medicine and Pulmonology, Department of Pediatrics, Pritzker School of Medicine, Biological Sciences Division, The University of Chicago, Chicago, IL; 2Center for Health and the Social Sciences, The University of Chicago, Chicago, IL; 3Sleep Disorders Center and the Section of Pulmonary and Critical Care Medicine, Department of Medicine, The University of Chicago, Chicago, IL

SLEEP 2016;39(8):1493–1500

Figure 1—Hazard ratios of incident cancer in OSA versus demographically matched and comorbidity matched cohort groups. Bar = 95% CI. Demographically matched control group-matched with OSA by age, gender, and state. Comorbidity-matched control group-matched with OSA by age, gender, and all comorbidities.
Sleep, Stroke, & Stroke Recovery

Sleep Disordered Breathing
• SDB is an independent predictor of stroke
• Stroke risk increases with increasing AHI
• SDB most severe in acute stroke & improved during recovery
• 53% of patients had AHI > 10 four weeks post stroke
• Stroke patients may have combination of OSA & CSA
• In patients with stroke, OSA (AHI > 15 or AHI > 20) predicts death or nonfatal cardiovascular events (namely recurrent stroke)

Hypersomnia
• Mostly found after subcortical and pontomesencephalic stroke
• Although hypersomnia improves during the first months poststroke, fatigue can persist for years.
• Fatigue 2 years poststroke associated with nursing home referral and predicted mortality in the following year
• Long sleep (8–9+ hours sleep/night in questionnaires), is an independent predictor of incident stroke
• EDS predicts stroke & impairs stroke recovery

Sleep, Stroke, & Stroke Recovery

• 12 - 13% of Stroke patients had RLS 15-30 days after stroke.
  • Those with RLS had a higher neck circumference, poorer sleep quality, and higher diabetes prevalence than patients without RLS.

• RBD prevalence in ischemic stroke patients ~11%.
  • 46% of patients with RBD had brainstem infarcts.

• During the first months poststroke, insomnia prevalence may be as high as 50%.

• Short sleep (< 5–6 hours sleep/night in questionnaires) and physician-diagnosed insomnia are independent predictors of incident stroke

• Short sleep (</ = 5 hours sleep/night) predicted cardiovascular events only when symptomatic (i.e., associated with difficulty falling asleep, difficulty maintaining sleep, early morning awakening, or nonrestorative sleep), but not when asymptomatic

The Association Between Insomnia and Increased Future Cardiovascular Events: A Nationwide Population-Based Study

Chien-Yi Hsu, MD, Yung-Tai Chen, MD, Mu-Hong Chen, MD, Chin-Chou Huang, MD, Chia-Hung Chiang, MD, Po-Hsun Huang, MD, PhD, Jaw-Wen Chen, MD, Tzeng-Ii Chen, MD, PhD, Shing-Jong Lin, MD, PhD, Hsin-Bang Leu, MD, PhD, and Wan-Leong Chan, MD

TABLE 2. Association Between Insomnia and CV Events

<table>
<thead>
<tr>
<th></th>
<th>Crude</th>
<th>Adjusted⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Events</td>
<td>Person-Years</td>
</tr>
<tr>
<td>AML</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia(*)</td>
<td>212</td>
<td>94,387</td>
</tr>
<tr>
<td>Insomnia(*)</td>
<td>90</td>
<td>83,329</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia(*)</td>
<td>743</td>
<td>92,754</td>
</tr>
<tr>
<td>Insomnia(*)</td>
<td>306</td>
<td>82,860</td>
</tr>
<tr>
<td>Total CV events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia(*)</td>
<td>917</td>
<td>92,299</td>
</tr>
<tr>
<td>Insomnia(*)</td>
<td>387</td>
<td>82,738</td>
</tr>
</tbody>
</table>

CI = confidence interval; AML = acute myocardial infarction; CV = cardiovascular.

⁴Per 10⁵ person-years.

⁶Adjusted for age, sex, history of hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, chronic kidney disease, congestive heart failure, peripheral artery disease, and chronic pulmonary disease.
Meta-analysis of all-cause and cardiovascular mortality in obstructive sleep apnea with or without continuous positive airway pressure treatment

N = 3,162,083
27 cohort studies

Figure S1. OSA and risk of all-cause mortality

S1a. All-cause mortality in patients with OSA vs control

HR 1.86; 95% CI, 1.81–1.91

S1b. All-cause mortality in patients with mild OSA vs control

HR 1.19; 95% CI 0.86 – 1.65

S1c. All-cause mortality in patients with moderate OSA vs control

HR 1.28; 95% CI 0.96 – 1.69

S1d. All-cause mortality in patients with severe OSA vs control

HR 2.13; 95% CI 1.94 – 3.85
Meta-analysis of all-cause and cardiovascular mortality in obstructive sleep apnea with or without continuous positive airway pressure treatment

Figure S2. OSA and risk of cardiovascular mortality

S2a. Cardiovascular mortality in patients with OSA vs control

HR 2.36; 95% CI, 1.22–4.57

S2b. Cardiovascular mortality in patients with mild OSA vs control

1.24 (0.53–2.55)

S2c. Cardiovascular mortality in patients with moderate OSA vs control

2.05 (0.57–5.47)

S2d. Cardiovascular mortality in patients with severe OSA vs control

2.73 (1.94–3.85)
Meta-analysis of all-cause and cardiovascular mortality in obstructive sleep apnea with or without continuous positive airway pressure treatment

Figure S3. CPAP treatment and risk of all-cause and cardiovascular mortality

S3a. All-cause mortality of CPAP treatment vs untreated OSA

S3b. All-cause mortality of CPAP treatment vs control

S3c. Cardiovascular mortality of CPAP treatment vs untreated OSA

S3d. Cardiovascular mortality of CPAP treatment vs control

Sleep Breath 2016; DOI 10.1007/s11325-016-1393-1
CSA & HF (SERVE-HF)

- International, multicenter, randomized, parallel-group, event-driven study

- Investigate effects of adding ASV to guideline-based medical treatment on survival and CV outcomes in patients with HFrEF and predominantly CSA (with AHI > 15)

- Primary endpoint = 1st of unplanned hospitalization worsening HF, lifesaving CV intervention, or death

- Recruited over 5 years + 2 year follow up. Target 651 events
SERVE – HF Baseline Characteristics

<table>
<thead>
<tr>
<th>Respiratory Characteristics at Baseline.†</th>
<th>Control (N = 659)</th>
<th>Adaptive Servo-Ventilation (N = 666)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epworth Sleepiness Scale score‡</td>
<td>7.1±4.6</td>
<td>7.0±4.3</td>
</tr>
<tr>
<td>AHI — no. of events/hr</td>
<td>31.7±13.2</td>
<td>31.2±12.7</td>
</tr>
<tr>
<td>Central apnea index/total AHI — %</td>
<td>46.5±30.0</td>
<td>44.6±28.9</td>
</tr>
<tr>
<td>Central AHI/total AHI — %</td>
<td>81.8±15.7</td>
<td>80.8±15.5</td>
</tr>
<tr>
<td>Oxygen desaturation index — no. of events/hr‡</td>
<td>32.8±19.0</td>
<td>32.1±17.7</td>
</tr>
<tr>
<td>Oxygen saturation — %</td>
<td>92.8±2.5</td>
<td>92.8±2.3</td>
</tr>
<tr>
<td>Mean</td>
<td>80.3±7.5</td>
<td>80.7±7.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>55.7±73.9</td>
<td>50.5±68.2</td>
</tr>
</tbody>
</table>

Demographic and Clinical Characteristics of the Patients at Baseline.†

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (N = 659)</th>
<th>Adaptive Servo-Ventilation (N = 666)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>69.3±10.4</td>
<td>69.6±9.5</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>599 (90.9)</td>
<td>599 (89.9)</td>
</tr>
<tr>
<td>Body weight — kg</td>
<td>86.1±17.5</td>
<td>85.6±15.8</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>28.6±5.1</td>
<td>28.4±4.7</td>
</tr>
<tr>
<td>NYHA class — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>194/654 (29.7)</td>
<td>195/662 (29.5)</td>
</tr>
<tr>
<td>III</td>
<td>454/654 (69.4)</td>
<td>456/662 (68.9)</td>
</tr>
<tr>
<td>IV</td>
<td>6/654 (0.9)</td>
<td>11/662 (1.7)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction — %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>32.5±8.0</td>
<td>32.2±7.9</td>
</tr>
<tr>
<td>Range</td>
<td>9.0–71.0</td>
<td>10.0–54.0</td>
</tr>
<tr>
<td>Diabetes mellitus — no./total no. (%)</td>
<td>252/653 (38.6)</td>
<td>254/660 (38.5)</td>
</tr>
<tr>
<td>Cause of heart failure — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>366/642 (57.0)</td>
<td>390/653 (59.7)</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>276/642 (43.0)</td>
<td>263/653 (40.3)</td>
</tr>
</tbody>
</table>
Early Discontinuation of Study

<table>
<thead>
<tr>
<th>Event</th>
<th>Control (N = 659)</th>
<th>Adaptive Servo-Ventilation (N = 666)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients (%)</td>
<td>No. of Events/Yr (95% CI)</td>
<td>No. of Patients (%)</td>
<td>No. of Events/Yr (95% CI)</td>
</tr>
<tr>
<td>Primary end point‡</td>
<td>335 (50.8)</td>
<td>0.212 (0.190–0.236)</td>
<td>360 (54.1)</td>
<td>0.245 (0.220–0.272)</td>
</tr>
<tr>
<td>First secondary end point‡</td>
<td>317 (48.1)</td>
<td>0.200 (0.179–0.224)</td>
<td>345 (51.8)</td>
<td>0.235 (0.211–0.261)</td>
</tr>
<tr>
<td>Second secondary end point‡</td>
<td>465 (70.6)</td>
<td>0.405 (0.369–0.444)</td>
<td>482 (72.4)</td>
<td>0.441 (0.403–0.483)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>193 (29.3)</td>
<td>0.093 (0.081–0.107)</td>
<td>232 (34.8)</td>
<td>0.119 (0.104–0.135)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>158 (24.0)</td>
<td>0.076 (0.065–0.089)</td>
<td>199 (29.9)</td>
<td>0.102 (0.088–0.117)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>448 (68.0)</td>
<td>0.384 (0.349–0.421)</td>
<td>452 (67.9)</td>
<td>0.411 (0.374–0.451)</td>
</tr>
<tr>
<td>Unplanned hospitalization for worsening heart failure</td>
<td>272 (41.3)</td>
<td>0.164 (0.145–0.185)</td>
<td>287 (43.1)</td>
<td>0.190 (0.169–0.214)</td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>35 (5.3)</td>
<td>0.017 (0.012–0.024)</td>
<td>33 (5.0)</td>
<td>0.017 (0.012–0.024)</td>
</tr>
</tbody>
</table>

R. Nisha Aurora, MD, MHS; Sabin R. Bista, MD; Kenneth R. Casey, MD, MPH; Susmita Chowdhuri, MD; David A. Kristo, MD; Jorge M. Mallea, MD; Kannan Ramar, MD; James A. Rowley, MD; Rochelle S. Zak, MD; Jonathan L. Heald, MA

• Adaptive servo-ventilation (ASV) targeted to normalize the apnea-hypopnea index (AHI) should not be used for the treatment of CSAS related to CHF in adults with an **ejection fraction ≤ 45%** and moderate or severe CSA predominant, sleep-disordered breathing. (**STANDARD AGAINST**)

• Adaptive servo-ventilation (ASV) targeted to normalize the apnea-hypopnea index (AHI) can be used for the treatment of CSAS related to CHF in adults with an **ejection fraction > 45%** or mild CHF-related CSAS. (**OPTION**)

Summary

• Patients with sleep apnea are at increased risk for CKD and ESRD compared with the general population.
• Those with lower eGFR tend to be older, more obese, more often female, and have worse obstructive sleep apnea and more co-morbidities
• Insomnia is associated with an increased risk of future cardiovascular events (MI & Stroke)
• Patients with sleep apnea and non-apnea sleep disorders are increased at risk for auto-immune disorders
• Associations between sleep apnea and cancer appear to be selective and affect certain types of solid malignancies such as melanoma and those of the kidney and pancreas
• ASV should NOT be used for treatment of CSA in patients with HFrEF.
Year in Review:
Updates on Non PAP Rx for OSA

Neeraj Kaplish, M.D.
President, MASM
Medical Director, U of M Sleep Lab
Assistant Professor, Dept. of Neurology
Conflict of Interest Disclosures for Speakers

1. I do not have any relationships with any entities **producing, marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients, OR

2. I have the following relationships with entities **producing, marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients:

<table>
<thead>
<tr>
<th>Type of Potential Conflict</th>
<th>Details of Potential Conflict</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td></td>
</tr>
<tr>
<td>Consultant</td>
<td></td>
</tr>
<tr>
<td>Speakers’ Bureaus</td>
<td></td>
</tr>
<tr>
<td>Financial support</td>
<td></td>
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<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

3. The material presented in this lecture has no relationship with any of these potential conflicts, OR

4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

   1.
   2.
   3.
We Have Options. Do We?
Life Style Modifications: Wt. Loss - OSA

- Randomized controlled trial compared Chinese OSA patients (with AHI>15) to receive dietician led LMP vs usual care.

- Follow up - 12 months

- LMP was more effective in reducing
  - AHI from baseline (P = 0.011)
  - BMI from baseline (P < 0.001)

- Mental health and healthier eating habits were noted at 4 months and sustained at 12 months

Susanna S.S. Ng et al, CHEST 2015; 148(5): 1193-1203
Medications-Weight Loss and OSA

- 32 weeks of randomized, double-blind trial in OSA pts (AHI>15) of Liraglutide vs. Placebo, both as adjunct to diet and exercise.
  - Mean Age - 49.2
  - Males - 71.5%
  - Mean AHI - 49.2
  - Severe OSA - 67.1%
  - BMI of 39.1

- Liraglutide arm showed a greater reduction in
  - AHI (12.2 vs 6.1)  P=0.015
  - Weight (5.7% vs 1.6%)  P<0.0001
  - HbgA1c
  - Systolic BP

Weight Loss Surgery and Sleep Apnea

- 205 OSA patients (AHI>15) who underwent Roux-en-Y gastric bypass which underwent pre and post operative PSG
  - Mean AHI - 32.3
  - Mean BMI - 46
  - Mean age - 48.8 years
  - Women – 63%

- Follow Up (mean 8.6 months) showed
  - Mean BMI decrease of 12.2
  - Excess weight loss of 61.1%
  - Mean AHI was 8.5

- About 25.9% still had AHI >15

Christel A.L. deRaff et al, Surg Obes Relat Dis 2016 Mar
PAP Compliance After Weight Loss Surgery

• Retrospective controlled cohort study studied compliance in severe OSA pts (s/p bariatric surgery) vs matched controls. Follow up- 2 yrs.

• A single center study at a Tertiary Center in France.

• Predictors of non-compliance on univariate analysis included
  • Female Gender
  • Absence of co-morbidites
  • Greater Weight Loss
  • Lower OSA severity

• No factors were predictive on multivariate analysis

C Agosta et al., Obes Surg 2016 26: 2082-2088
STAR Trial - 3 Year Follow Up

Diagram:
- Baseline: 126 received implant
  - 1 death due to unrelated cause; 1 elective explant
- 12-mo: 124 completed 12-mo follow-up
  - 46 completed RCT withdrawal study
- 18-mo: 124 completed 18-mo follow-up
  - 1 explant due to septic arthritis
- 24-mo: 123 completed 24-mo follow-up
- 30-mo: 123 completed 30-mo follow-up
  - 2 deaths due to unrelated causes; 1 elective explant; 4 lost to follow-up
- 36-mo: 116 completed 36-mo follow-up
  - 98 completed voluntary PSG study

Graphs:
- AH1: Baseline, Month 12, Month 18, Month 36
- QD1: Baseline, Month 12, Month 18, Month 36
- FOSQ: Baseline, Month 12, Month 18, Month 36
- ESS: Baseline, Month 12, Month 18, Month 36
## Table 2. PSG Outcome Measures for Participants Completed PSG at 36 months (N = 98).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 mo</th>
<th>36 mo</th>
<th>Baseline to 12 mo</th>
<th>Baseline to 36 mo</th>
<th>12 to 36 mo</th>
<th>Change (95% CI; P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AHI, even breath</strong></td>
<td>30.4 ± 10.4</td>
<td>13.5 ± 14.3</td>
<td>11.5 ± 13.9</td>
<td>16.9 (13.9, 19.9; &lt;.001)</td>
<td>18.8 (16.1, 21.6; &lt;.001)</td>
<td>1.95 (~10.4, 9.2, 20)</td>
<td></td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>28.2</td>
<td>8.7</td>
<td>6.2</td>
<td>17.4</td>
<td>19.4</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td><strong>ODI, even breath</strong></td>
<td>27.1 ± 10.8</td>
<td>12.0 ± 13.6</td>
<td>9.1 ± 11.7</td>
<td>15.1 (12.3, 17.9; &lt;.001)</td>
<td>18.0 (15.5, 20.4; &lt;.001)</td>
<td>2.86 (0.4, 5.3, 0.02)</td>
<td></td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>24.3</td>
<td>7.1</td>
<td>4.8</td>
<td>15.5</td>
<td>17.2</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td><strong>SaO₂ &lt;90%</strong></td>
<td>7.9 ± 9.7</td>
<td>5.0 ± 11.2</td>
<td>5.7 ± 10.2</td>
<td>2.9 (1.0, 4.8; 0.01)</td>
<td>2.2 (~0.1, 4.5; 0.06)</td>
<td>-0.73 (~2.7, 1.2; 46)</td>
<td></td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>4.8</td>
<td>0.7</td>
<td>1.0</td>
<td>2.1</td>
<td>1.5</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AHI, apneas-hypopneas index; CI, confidence interval; ODI, oxygen desaturations index; PSG, polysomnography; SaO₂, oxygen saturation.

*Baseline and 12-month values are from the cohort that completed PSG at 36 months (n = 98). Results in mean ± SD or median as noted. Statistical significance, P < .05.

## Table 3. Comparison of Baseline Characteristics between Responders and Nonresponders at 36 Months. *

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Responders (n = 73)</th>
<th>Nonresponders (n = 25)</th>
<th>Odds Ratio</th>
<th>95% CI (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.4 ± 10.4</td>
<td>51.6 ± 10.2</td>
<td>1.05</td>
<td>1.00, 1.10 (0.0496)</td>
</tr>
<tr>
<td>Male, %</td>
<td>82</td>
<td>92</td>
<td>0.37</td>
<td>0.08, 1.74 (0.21)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28.5 ± 2.0</td>
<td>29.2 ± 2.0</td>
<td>0.88</td>
<td>0.72, 1.08 (0.22)</td>
</tr>
<tr>
<td>Neck size</td>
<td>41.1 ± 3.5</td>
<td>41.6 ± 2.5</td>
<td>0.95</td>
<td>0.82, 1.10 (0.48)</td>
</tr>
<tr>
<td>Baseline AHI</td>
<td>28.8 ± 9.3</td>
<td>35.0 ± 12.4</td>
<td>0.95</td>
<td>0.91, 0.99 (0.01)</td>
</tr>
<tr>
<td>Baseline ODI</td>
<td>25.6 ± 9.5</td>
<td>31.5 ± 13.0</td>
<td>0.95</td>
<td>0.91, 0.99 (0.02)</td>
</tr>
<tr>
<td>Prior UPPP, %</td>
<td>25</td>
<td>4</td>
<td>0.13</td>
<td>0.02, 1.01 (0.05)</td>
</tr>
<tr>
<td>Baseline POSQ</td>
<td>14.6 ± 3.2</td>
<td>15.3 ± 2.6</td>
<td>0.92</td>
<td>0.79, 1.07 (0.28)</td>
</tr>
<tr>
<td>Baseline ESS</td>
<td>11.1 ± 4.8</td>
<td>11.1 ± 4.3</td>
<td>1.01</td>
<td>0.91, 1.11 (0.92)</td>
</tr>
</tbody>
</table>

Abbreviations: AHI, apneas-hypopneas index; CI, confidence interval; ESS, Epworth Sleepiness Scale; POSQ, Functional Outcomes of Sleep Questionnaire; ODI, oxygen desaturations index; UPPP, uvulopalatopharyngoplasty. Results in mean ± SD or percentage.

*Based on a step-wise logistic regression analysis with the 3 significant covariates, apneas-hypopneas index remained statistically significant (odds ratio, 0.95; 95% CI: 0.93, 0.99; P = .01).
THN Stimulation-6 Month F/U

Repeat PSG at 6 months
15 of 43 (35%) were AHI responders
   AHI= 35.7 to 8.5
28 of 43 (65%) were non AHI responders
   AHI= 34.5 remained at 34.5

Predictors of success
   AHI <65
   AI < 30
   BMI <35
   ODI <15 for desaturations >10%

N=46 patients implanted
Primary Outcomes
   ≥50% reduction in AHI+ AHI<20

Who's Got better OA Compliance?

• 1 year adherence with OA therapy
  • Arousers - 85%
  • Desaturators - 55% (P = 0.034)

• AHI was reduced in both
  • Arousers (14 to 3)
  • Desaturaters (18 to 7)

• Female gender was higher arousers.

• 77% reported side effects but majority still satisfied.

• Despite improvement in indices, daytime symptoms did not improve

OA vs CPAP in P-OSA

• Male OSA pts (AHI>15) who had P-OSA treated with OA and CPAP were compared.

• P-OSA was defined as
  • Supine ≥ 2x Lateral AHI
  • Lateral sleep > 60 min
  • Lateral REM > 10 min

• Primary endpoint being AHI

<table>
<thead>
<tr>
<th></th>
<th>P-OSA with MAD (n = 34)</th>
<th>P-OSA with nCPAP (n = 34)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.6 ± 7.6</td>
<td>47.2 ± 6.8</td>
<td>0.81</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.4 ± 2.7</td>
<td>25.4 ± 2.1</td>
<td>0.07</td>
</tr>
<tr>
<td>At baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total AHI (events/h)</td>
<td>20.6 ± 3.9</td>
<td>21.3 ± 1.7</td>
<td>0.35</td>
</tr>
<tr>
<td>Supine AHI (events/h)</td>
<td>32.5 ± 9.0</td>
<td>36.1 ± 10.9</td>
<td>0.14</td>
</tr>
<tr>
<td>Lateral AHI (events/h)</td>
<td>5.2 ± 4.0</td>
<td>6.5 ± 3.9</td>
<td>0.15</td>
</tr>
<tr>
<td>Nadir SpO₂ (%)</td>
<td>82.5 ± 7.9</td>
<td>81.0 ± 6.6</td>
<td>0.34</td>
</tr>
<tr>
<td>ESS</td>
<td>13.2 ± 5.9</td>
<td>10.9 ± 4.8</td>
<td>0.09</td>
</tr>
<tr>
<td>After treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total AHI (events/h)</td>
<td>4.7 ± 3.5</td>
<td>3.4 ± 3.7</td>
<td>0.12</td>
</tr>
<tr>
<td>Supine AHI (events/h)</td>
<td>6.1 ± 4.5</td>
<td>3.8 ± 3.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Lateral AHI (events/h)</td>
<td>1.6 ± 1.9</td>
<td>2.7 ± 6.5</td>
<td>0.35</td>
</tr>
<tr>
<td>Nadir SpO₂ (%)</td>
<td>90.4 ± 4.0</td>
<td>92.0 ± 3.6</td>
<td>0.09</td>
</tr>
<tr>
<td>ESS</td>
<td>9.9 ± 6.0</td>
<td>10.8 ± 4.7</td>
<td>0.49</td>
</tr>
</tbody>
</table>

OA Treatment Affects BP

- Reduction was seen in BP both SBP and DBP but only DBP reduction was significant.

- Reduction was much higher for both SBP an DBP if there was hypertension prior to OA therapy.

  - Mean SBP reduction was 11.3 mm Hg
  - Mean DBP was 6.4 mm Hg

Study population was Japanese
- Men 188
- Women 49
- Mean Age 54.7 years
- Mean BMI 24.6

BP was measured in clinic visits

Who should get a UPPP?

- Meta-analysis of 15 studies (trickle from search of 1257 studies) showed following as predictors of:
  - Success – Friedman Stage I
  - Failure - Friedman Stage III
  - Low Hyoid Suspension
  - Not Significant- Age
  - BMI
  - Pre-operative AHI
  - Cephalometrics
Multilevel Surgery Risks?

- Compared UPPP, UPPP+NC and UPPP+BOT for complications
  - Overall
  - Medical
  - Surgical
  - Readmission
  - Return to OR
  - Death
  - Hospital Stay Length

*Otolaryngol Head Neck Surg.*, 2016 Aug 23
What about MMA?

- Meta-analysis of 45 studies (518 patients) showed:
  - 78% (where data available) had gone prior surgery
  - AHI was reduced by 47.8
  - RDI was reduced by 44.4
  - PA went from 5.5 to 11.5 mm
  - ESS reduced from 13.5 to 3.3
  - Mean Maxillary Advance - 9 mm
  - Mean Mandibular Advance - 10.2 mm

QUESTIONS