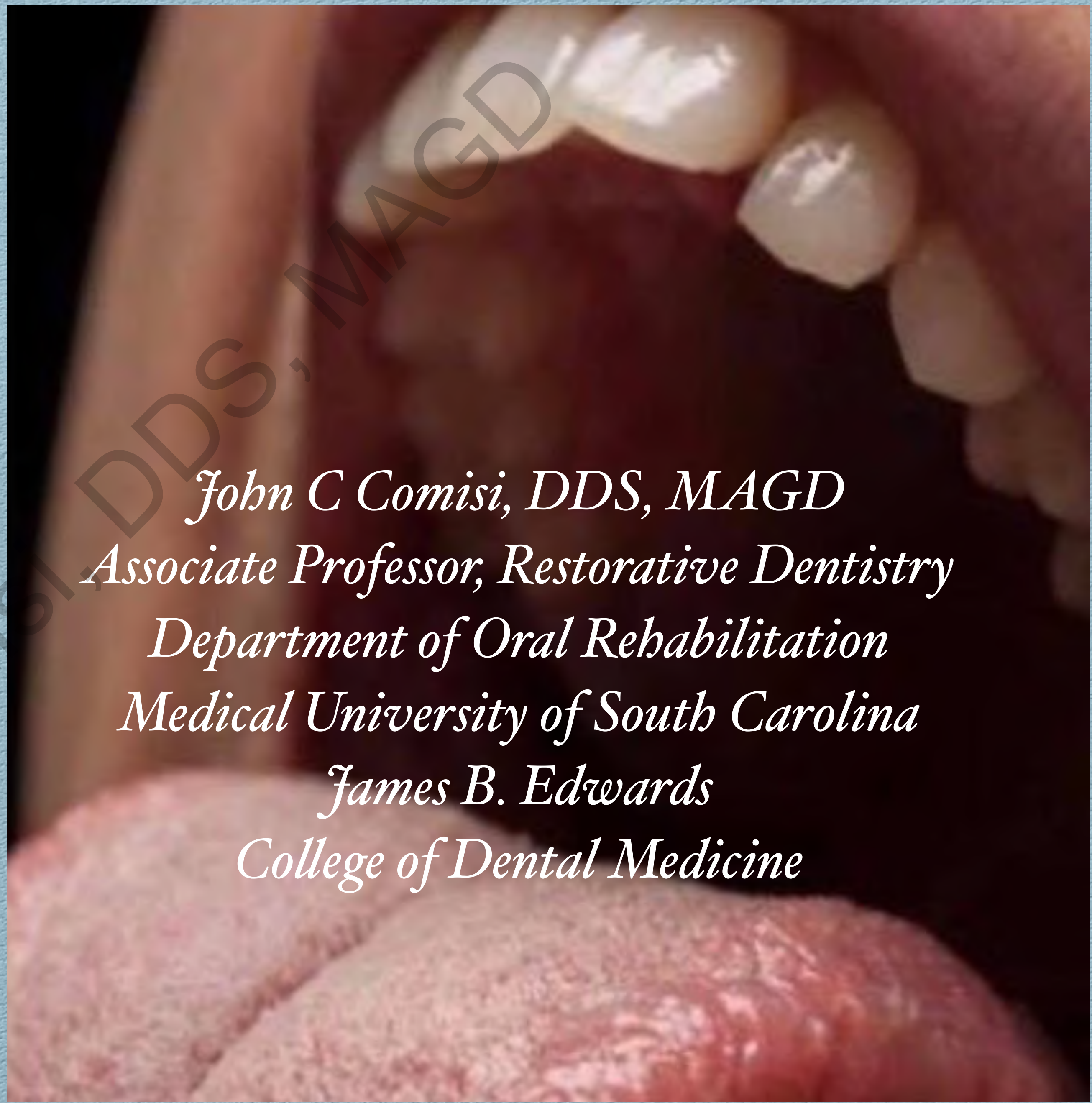
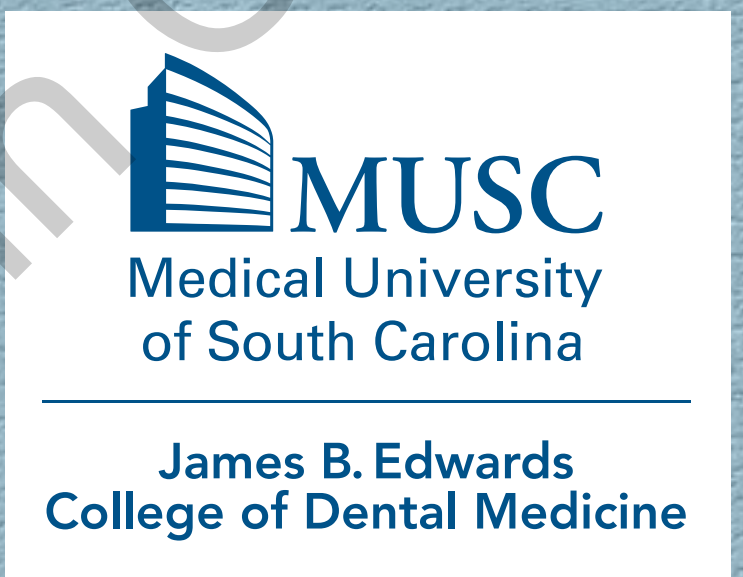


# **The Adult Airway - Sleep and the Oral Microbiome**

**OCTOBER 6, 2022**



*John C Comisi, DDS, MAGD  
Associate Professor, Restorative Dentistry  
Department of Oral Rehabilitation  
Medical University of South Carolina  
James B. Edwards  
College of Dental Medicine*



Continuing Dental Education  
Affidavit of Image Authenticity

I declare that all photographic and radiographic images used by me, or any associate, are original and unaltered. Furthermore, I declare that all treatment outcomes depicted are being represented accurately.

Conflict of Interest

I declare that neither I or any member of my family has any financial interest/arrangement or financial affiliation with any commercial organization providing financial support or grant monies for this continuing education program.

I am a member of the ProBiora Health Dental Professional Advisory Council and a customer.



*Dum spiro, spero*

is a Latin phrase of indeterminate origin. It is the motto of various places and organizations, including the U.S. state of South Carolina.







**James B. Edwards**  
College of Dental Medicine

Course Syllabus

Course **GENDT\*813\*01**  
Dental Sleep Medicine - Elective Course

**General Information:**

Director: John C Comisi, DDS  
Department: Oral Rehabilitation  
Division: Restorative Dentistry  
Designation: Associate Professor  
Credit Hours: 1.5 Credit Hours  
Academic Year: 2022  
Semester: Fall  
Course URL: [brightspace.musc.edu/](https://brightspace.musc.edu/)

**Contact Hours:**

Lecture 12 hours  
Simulation Laboratory: 0  
Other (Study): 12  
Total: 24 hours

**Course Bulletin Description:**

This multi and Interdisciplinary course will introduce the participants to the important field of Dental Sleep Medicine. This course will provide an understanding of Sleep Related Breathing Disorders (SRBD), the necessity for a medical diagnosis and the types of treatments available. The role of the dental professional will be presented, and importance of the team approach across the medical and dental disciplines to improve outcomes for our patients

Successful completion of this elective class, covering both the medical and dental science of sleep disorder breathing and its comorbidities, will provide the participant competencies and knowledge to be eligible to apply for an Academic Certificate in Dental Sleep Medicine (C.DSM) from the Academy of Clinical Sleep Disorder Disciplines (ACSDD).

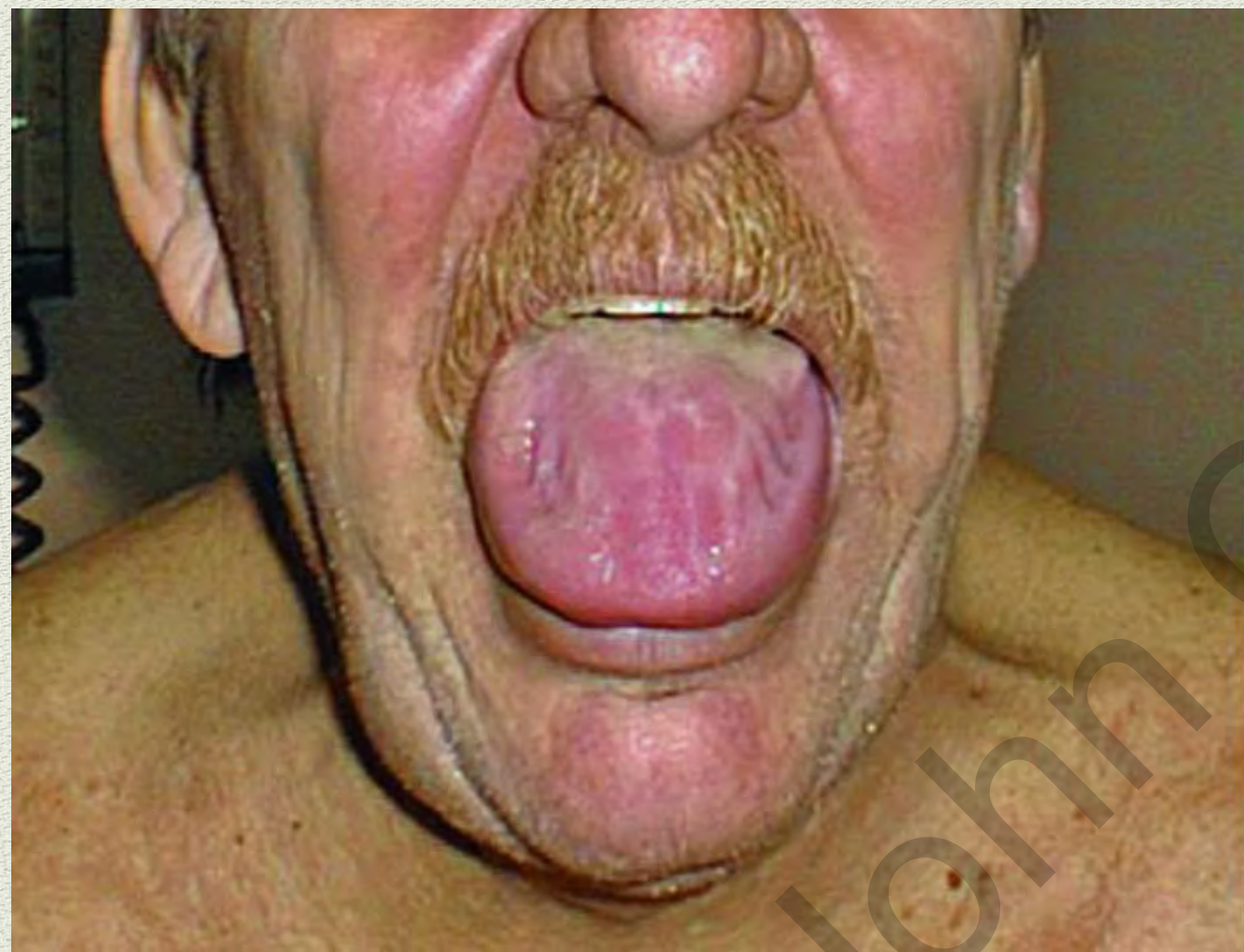
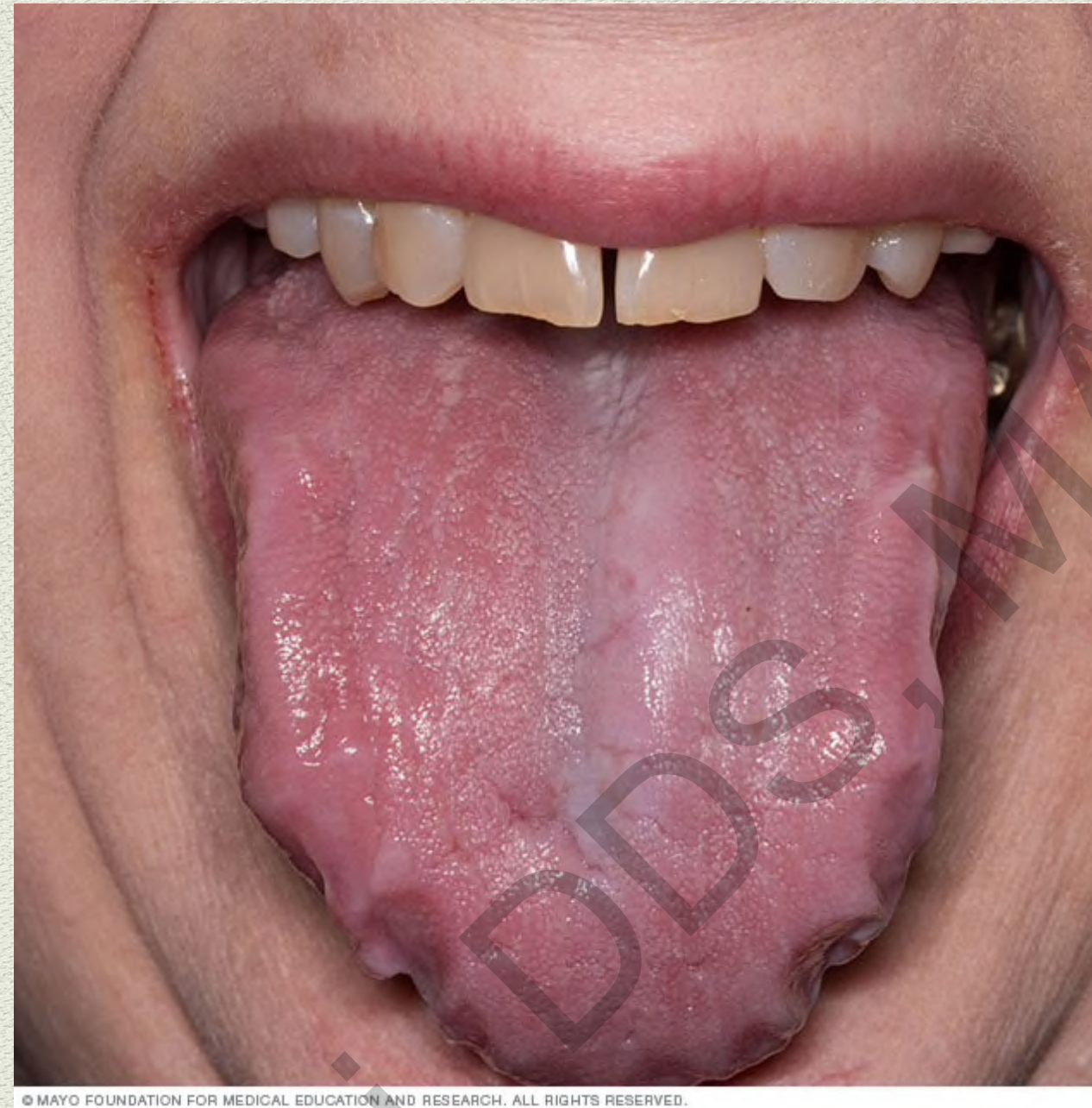


# Disease

*A disorder of structure or function in a human, animal or plant, especially one that produces specific signs or symptoms or affect a specific location and is not simply a direct result of physical injury.*

*Oxford languages dictionary.*







# A GOOD NIGHT'S SLEEP FOR A BETTER TOMORROW

Use products only as directed.

Check the ingredients in your medicine. Use only 1 product that contains acetaminophen at a time.

SIMPLY SLEEP\* contains a nighttime sleep aid only and does not contain a pain reliever. TYLENOL® PM contains a pain reliever and nighttime sleep aid.

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## LOGO sweet dreams

Cu meliore noluisse percipitur eam splendide rationibus usu dolore inermis ea nam viris aeterno fabellas no vel ne mei dico rationibus Adipiscing ad pro habeo viris, nam aliquam fabellas amquam scribentur reprehendunt omnium capere et ea

Odio facilis eleifend ne nam partem populo consequat in

Cu praesent vituperatoribus ad commodo labores legimus mea

Affert salutaris liberavisse ius ea, est brute graecis maluiset ad

1134910494

## 6 Nightly Techniques to Help You Fall Asleep Fast, According to Sleep Experts

REALSIMPLE

## Sleep·eze

EXTRA STRENGTH gelcaps

50 mg Diphenhydramine Hydrochloride Capsule

EXTRA FORT 50 mg Diphenhydramine Chlorhydrate En Capsule

sleep well tonight... feel alert tomorrow  
dormez bien cette nuit... soyez en pleine forme demain

20 soft gel capsules / gelules  
safety sealed / emballage à l'épreuve

Use as directed.

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The surprising (and serious) links  
between sleep, snoring, and  
stroke



REVIEW

Open Access

# Obstructive sleep apnea and comorbidities: a dangerous liaison



Maria R. Bonsignore<sup>1,2\*</sup> , Pierpaolo Baiamonte<sup>1</sup>, Emilia Mazzuca<sup>1</sup>, Alessandra Castrogiovanni<sup>3</sup> and Oreste Marrone<sup>2</sup>

## Abstract

Obstructive sleep apnea (OSA) is a highly prevalent disease, and is traditionally associated with increased cardiovascular risk. The role of comorbidities in OSA patients has emerged recently, and new conditions significantly associated with OSA are increasingly reported. A high comorbidity burden worsens prognosis, but some data suggest that CPAP might be protective especially in patients with comorbidities. Aim of this narrative review is to provide an update on recent studies, with special attention to cardiovascular and cerebrovascular comorbidities, the metabolic syndrome and type 2 diabetes, asthma, COPD and cancer. Better phenotypic characterization of OSA patients, including comorbidities, will help to provide better individualized care. The unsatisfactory adherence to CPAP in patients without daytime sleepiness should prompt clinicians to examine the overall risk profile of each patient in order to identify subjects at high risk for worse prognosis and provide the optimal treatment not only for OSA, but also for comorbidities.

**Keywords:** Mortality, prognosis, cardiovascular disease, diabetes, asthma, COPD, cancer



# Common Comorbidities of OSA Patients

Bonsignore et al. *Multidisciplinary Respiratory Medicine* (2019) 14:8  
<https://doi.org/10.1186/s40248-019-0172-9>

Multidisciplinary  
Respiratory Medicine

REVIEW

Open Access

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- Cerebrovascular Diseases
- Systemic Hypertension
- Cardiovascular Events and /or Death
- Arrhythmias
- Metabolic Diseases
- Diabetes
- Obesity
- Renal Disease
- COPD
- Asthma
- Cancer



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Multidisciplinary  
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## • Metabolic Diseases -

### OSA and the Metabolic Syndrome

- The metabolic syndrome (MetS), a pre-diabetic state associated with central obesity and increased cardiovascular risk
- Highly prevalent in OSA patients and, according to some authors, OSA should be considered as an additional manifestation of MetS.



# Insufficient or poor-quality sleep

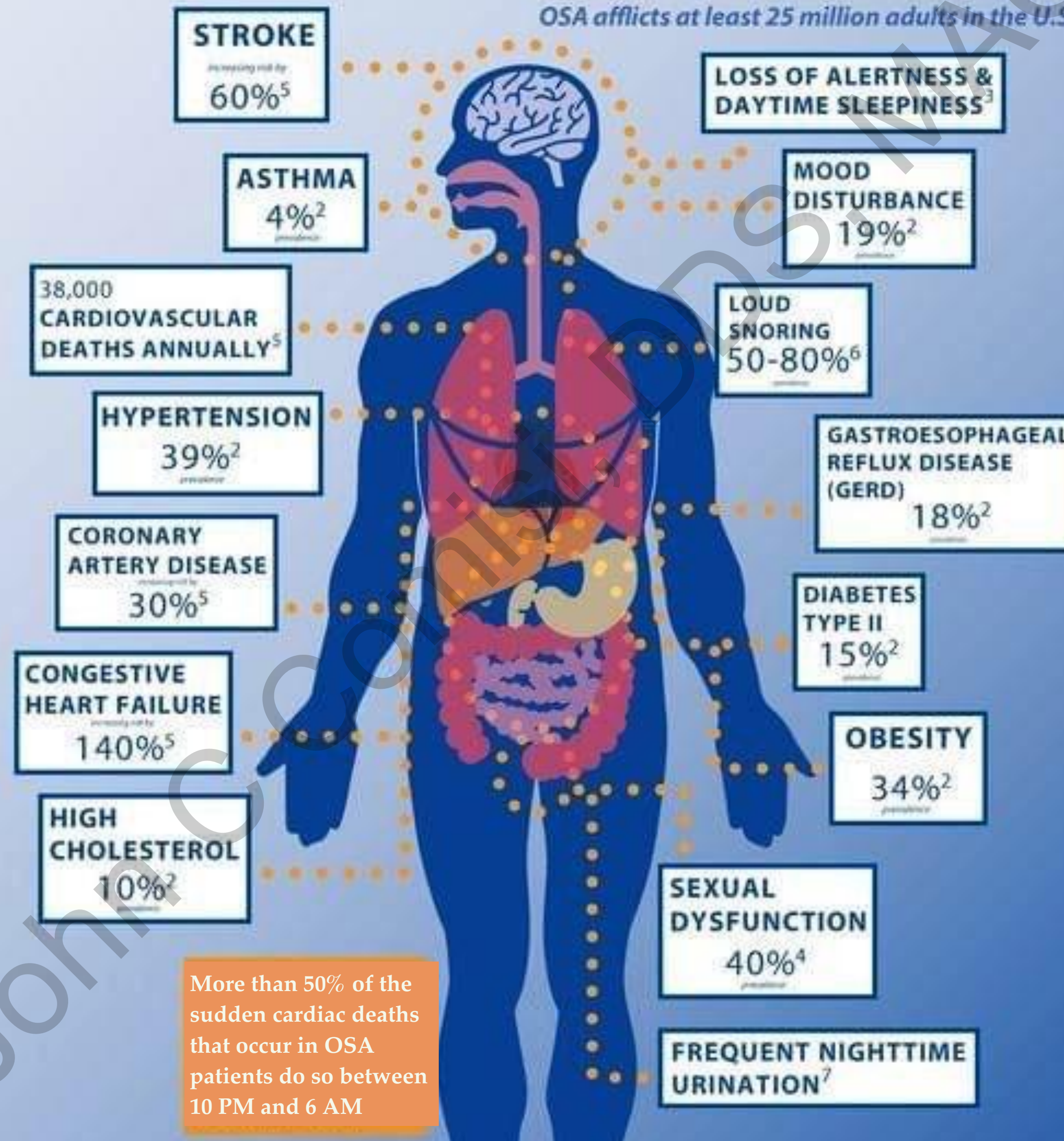
- ◆ Immune System
- ◆ Weight management
- ◆ Glucose metabolism
- ◆ Cardiovascular / cerebral health
- ◆ Cognition
- ◆ Work productivity
- ◆ Psychological well-being
- ◆ Public safety

Gosselin N, Baril AA, Osorio R, Kaminska M, Carrier J. Am J Respir Crit Care Med 199. 142-148. 2019



# The Consequences of Untreated **OBSTRUCTIVE SLEEP APNEA**

OSA afflicts at least 25 million adults in the U.S.<sup>1</sup>



More than 50% of the sudden cardiac deaths that occur in OSA patients do so between 10 PM and 6 AM





SLEEP

is the most blessed  
and blessing of all  
natural graces.

— ALDOUS HUXLEY —



Sleep

*Can't Live without it!!*



# Why Do We Sleep?

- ▶ Rest & recovery.
- ▶ Sleep serves important immune system functions and memory.
- ▶ Various hormones (HGH) are secreted into the body during sleep.
- ▶ Lack of “deep” (non-REM) sleep results in a person feeling physically tired.
- ▶ Lack of REM sleep can cause you to feel anxious & irritable.
- ▶ The more exercise performed, the more sleep is needed.



“If I didn’t wake up, I’d still be sleeping”  
Yogi Berra





# GROWTH & DEVELOPMENT



John C. Combs



# Does your child have?

*What happens if we just say, "See you again in 6 months!"*  
*Slide Courtesy Barry Raphael, DMD*

Besides crooked or crowded teeth, also look for....

Open mouth posture



Frequent stuffy nose, colds, allergies



Long and recessive chin profile



No space between baby teeth



Dry, chapped lips



Snoring and loud breathing



Lips purse when swallowing



Forward head posture





# What happens next?

- ▶ Fast forward 40 years and many patients still have, or develop, Obstructive Sleep Apnea
- ▶ Hundreds of breathing obstructions throughout the night lead to life threatening complications!

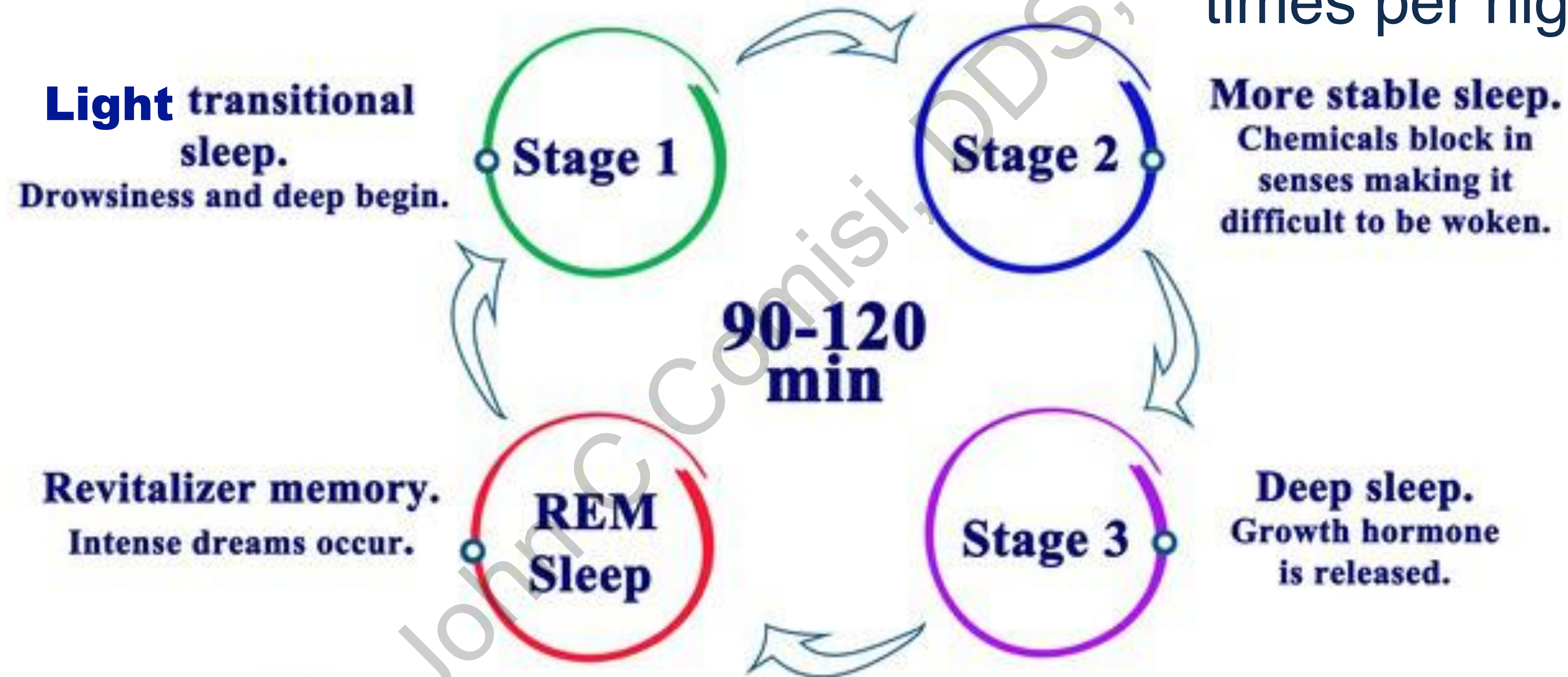




# Sleep Cycle Stages

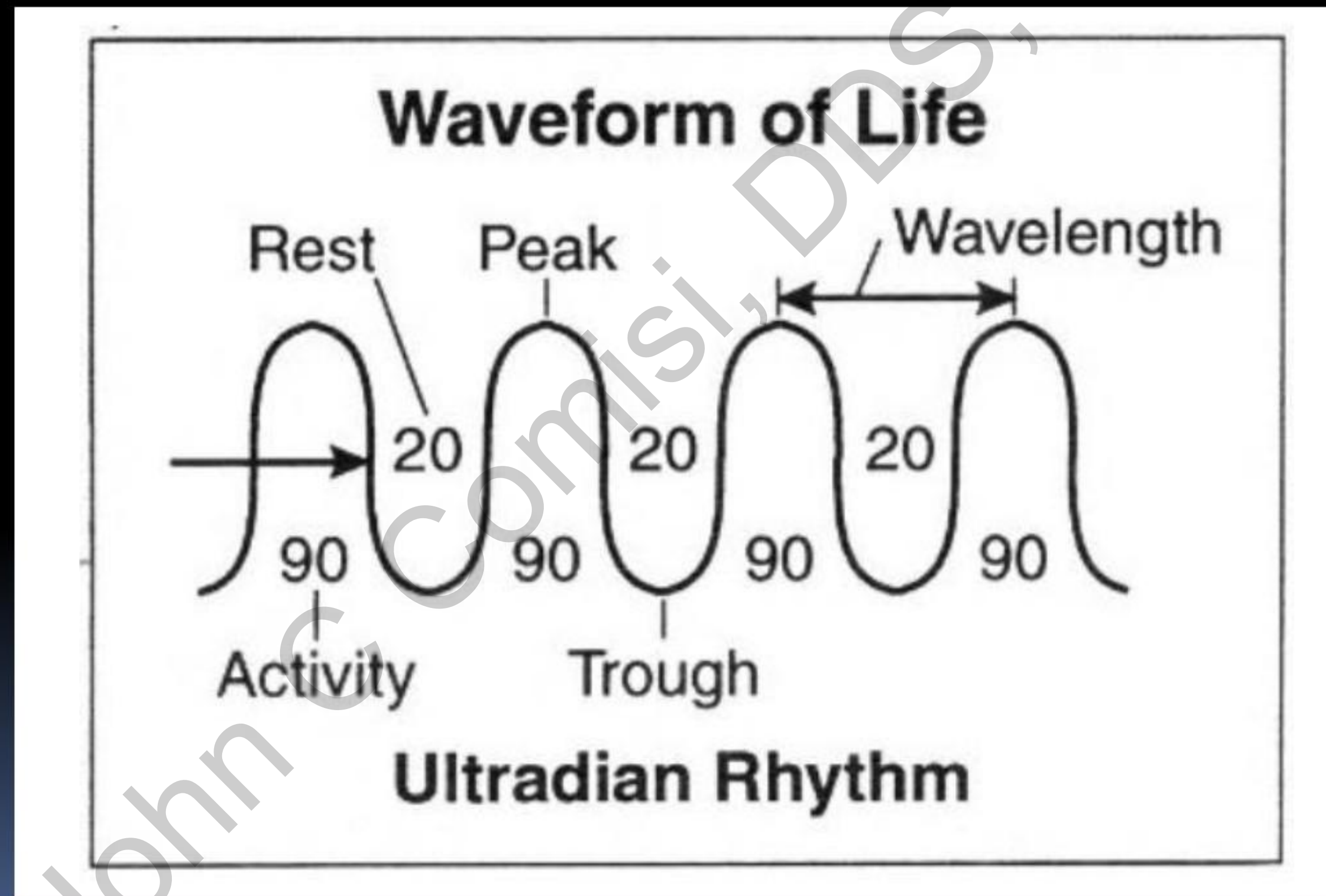
ideal pattern of sleep

repeated four to six times per night.



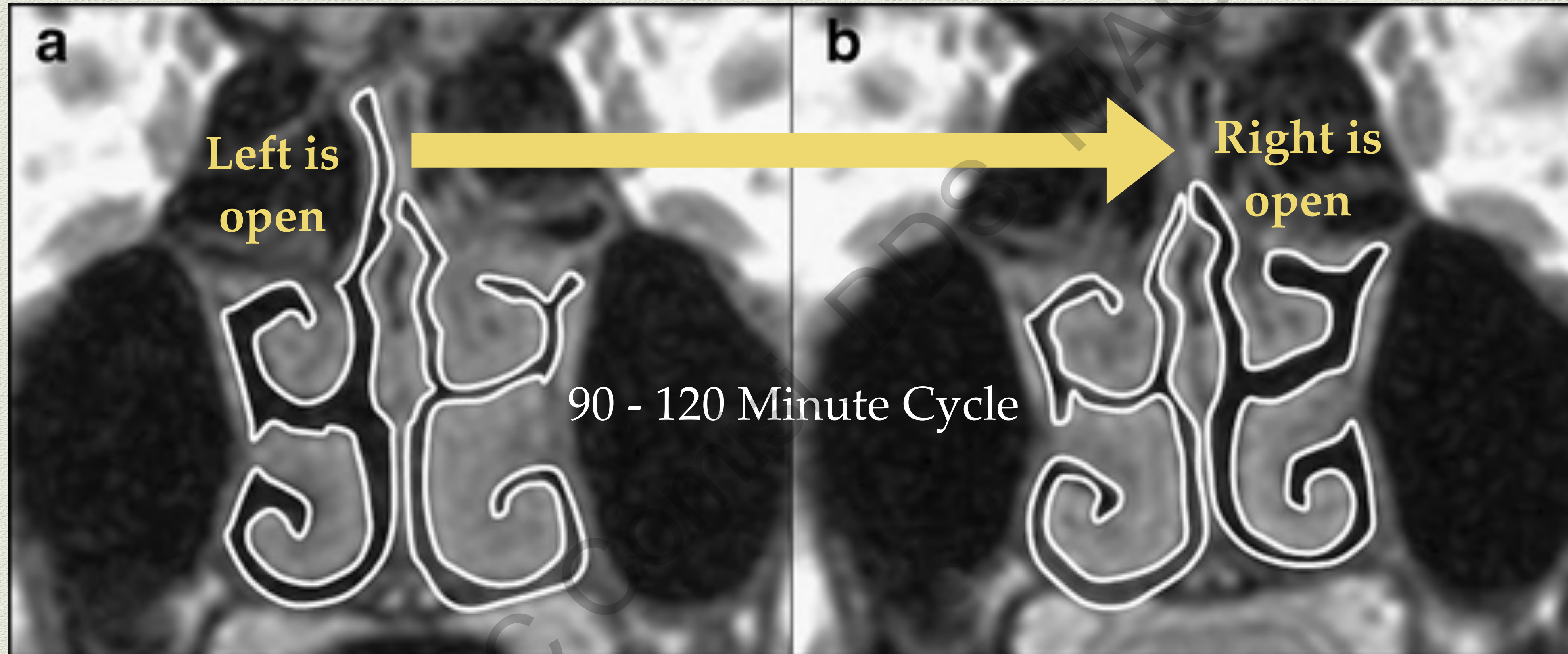


# Nighttime 2 Hour Nasal Cycle REM cycle





# Nasal Cycle: Function and Purpose



Open: Heats and Humidifies

Closed: Removes inhaled particles and mucus



# When Sleep Goes Wrong

When you're not getting enough sleep, or if your quality of sleep is poor, all of the positive things that happen in sleep—decrease.

Your body is unable to repair effectively, biological processes are disturbed, and there are significant effects on brain function and cognition.



# OSA Facts



- ▶ **Obstructive Sleep Apnea (OSA)**
- ▶ One of the most common sleep disorders.
- ▶ Breathing is impaired (hypopnea) or completely stopped (apnea) due to an obstruction in the upper airway.
- ▶ A single event lasts at least 10 seconds.
- ▶ A typical sufferer has hundreds of events per night.

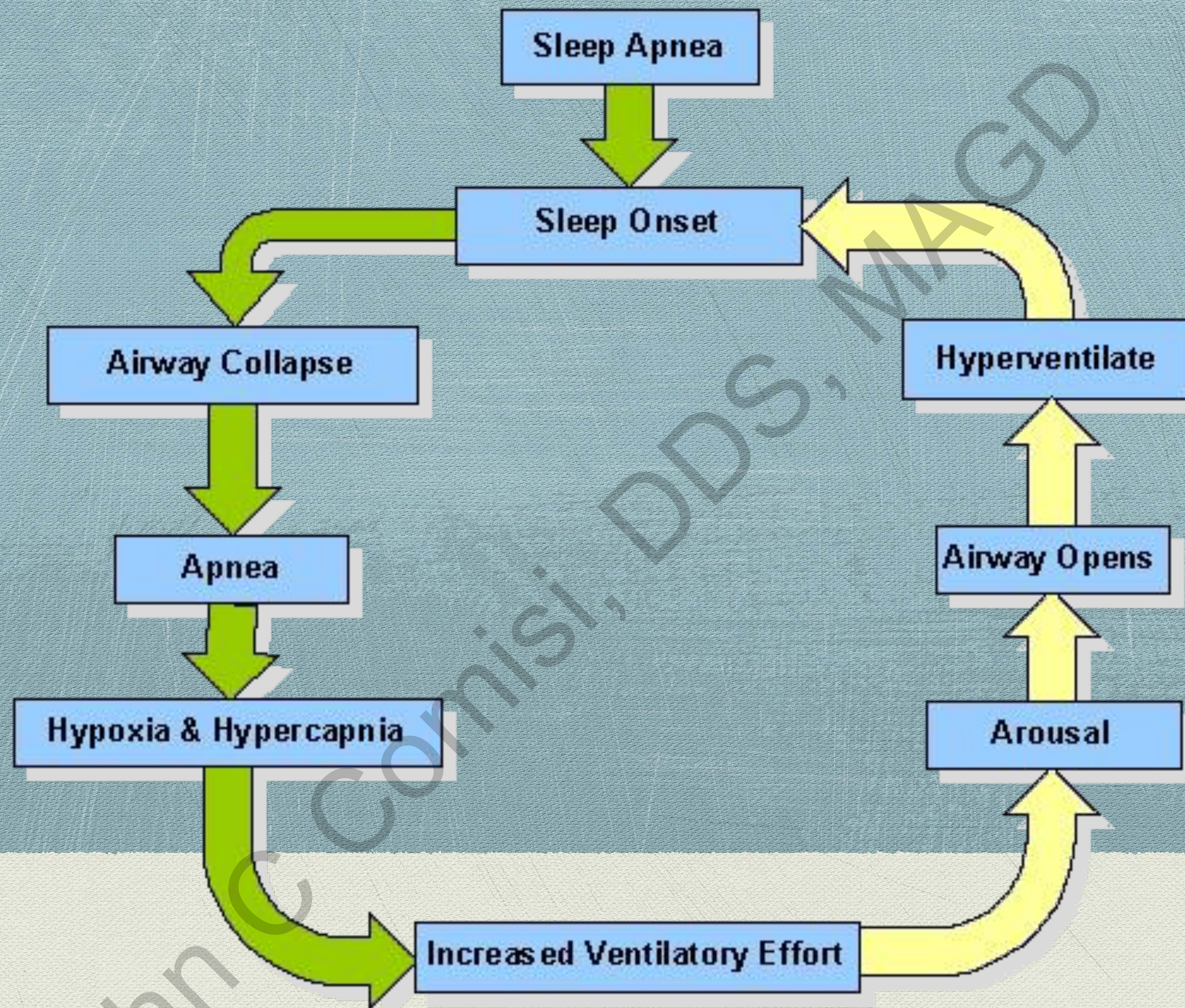
**FACT:** Untreated OSA can take up to 12-15 years off your life.

- Smoking takes only 7-10 (men)
- Type II Diabetes takes 5-10
- OSA increases risk of death by 46%









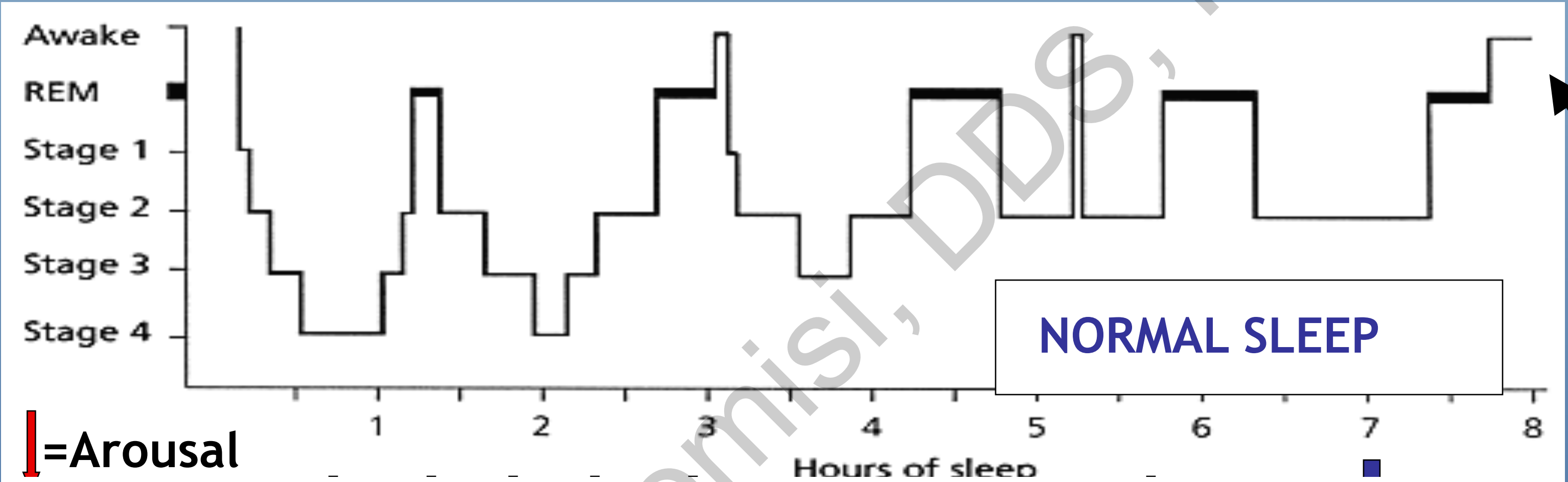
# The Pathophysiology of Sleep Apnea



# Sleep Studies: How A Diagnosis is rendered

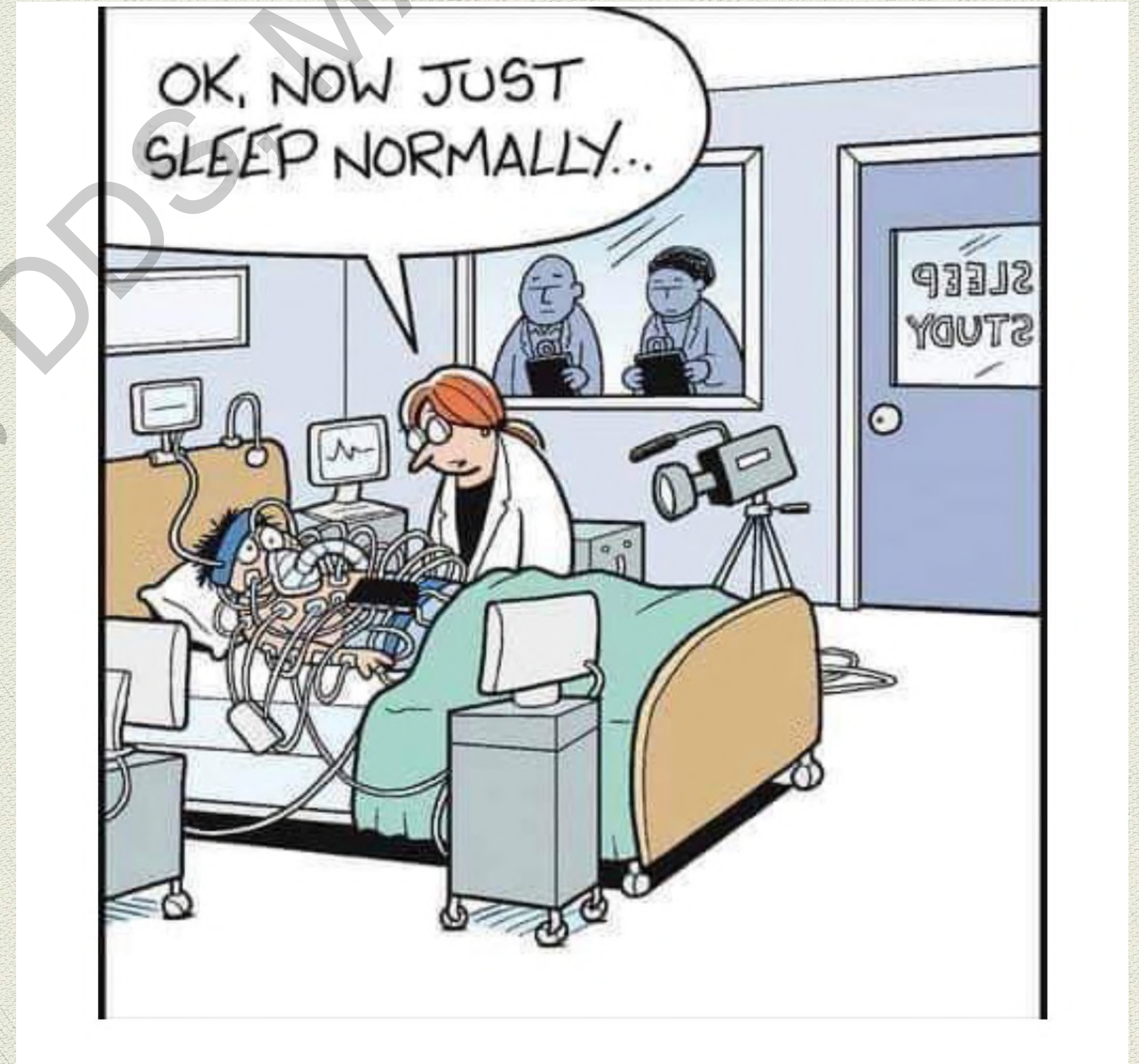
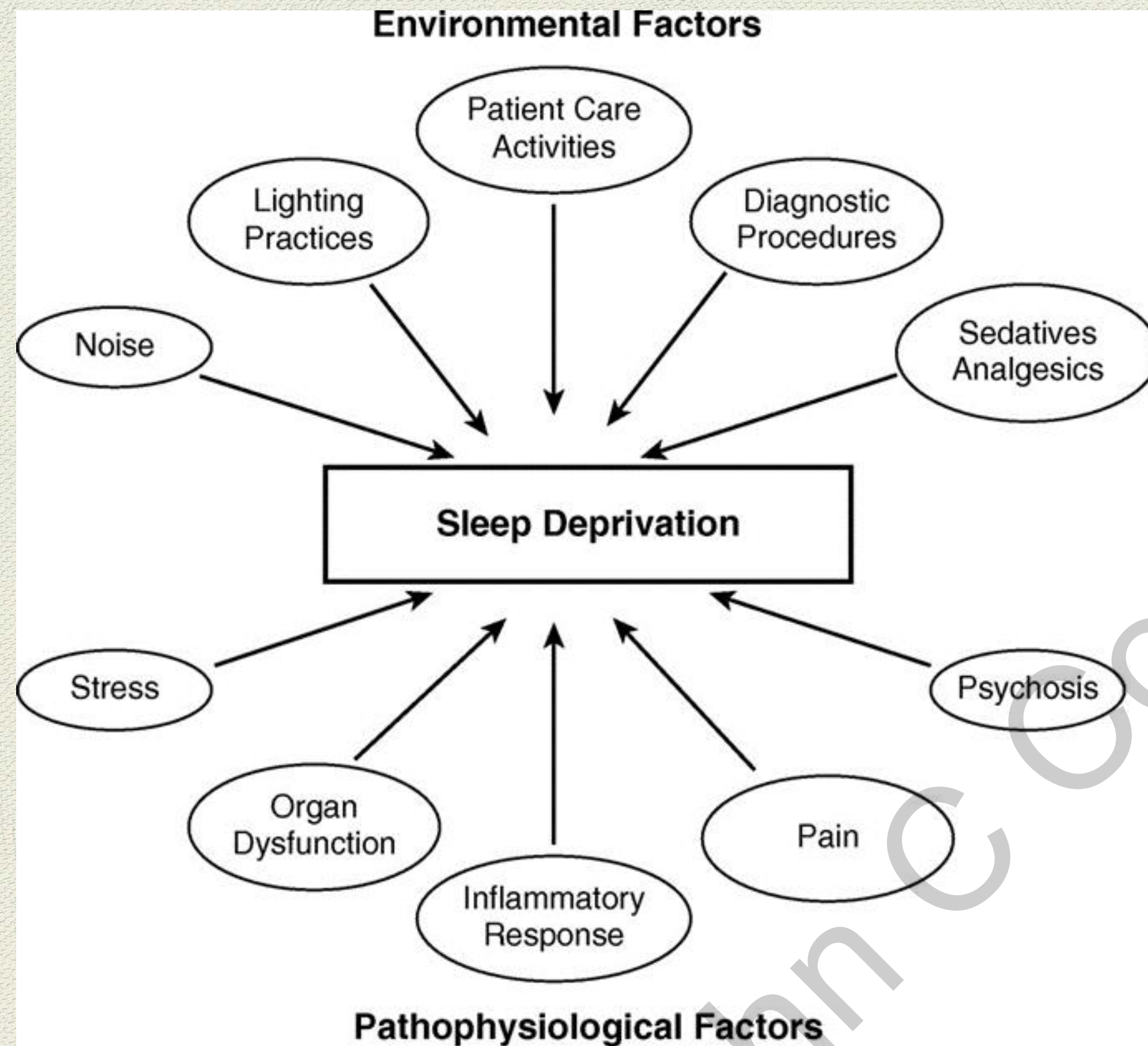


# Sleep Fragmentation Affects Sleep Quality





# Sleep in the Hospital



Pisani MA, Friese RS, Gehlbach BK, Schwab RJ, Weinhouse GL, Jones SF. Amer J Resp Crit Care Med 2015. 191(7).



# Why are Sleep Studies Needed?

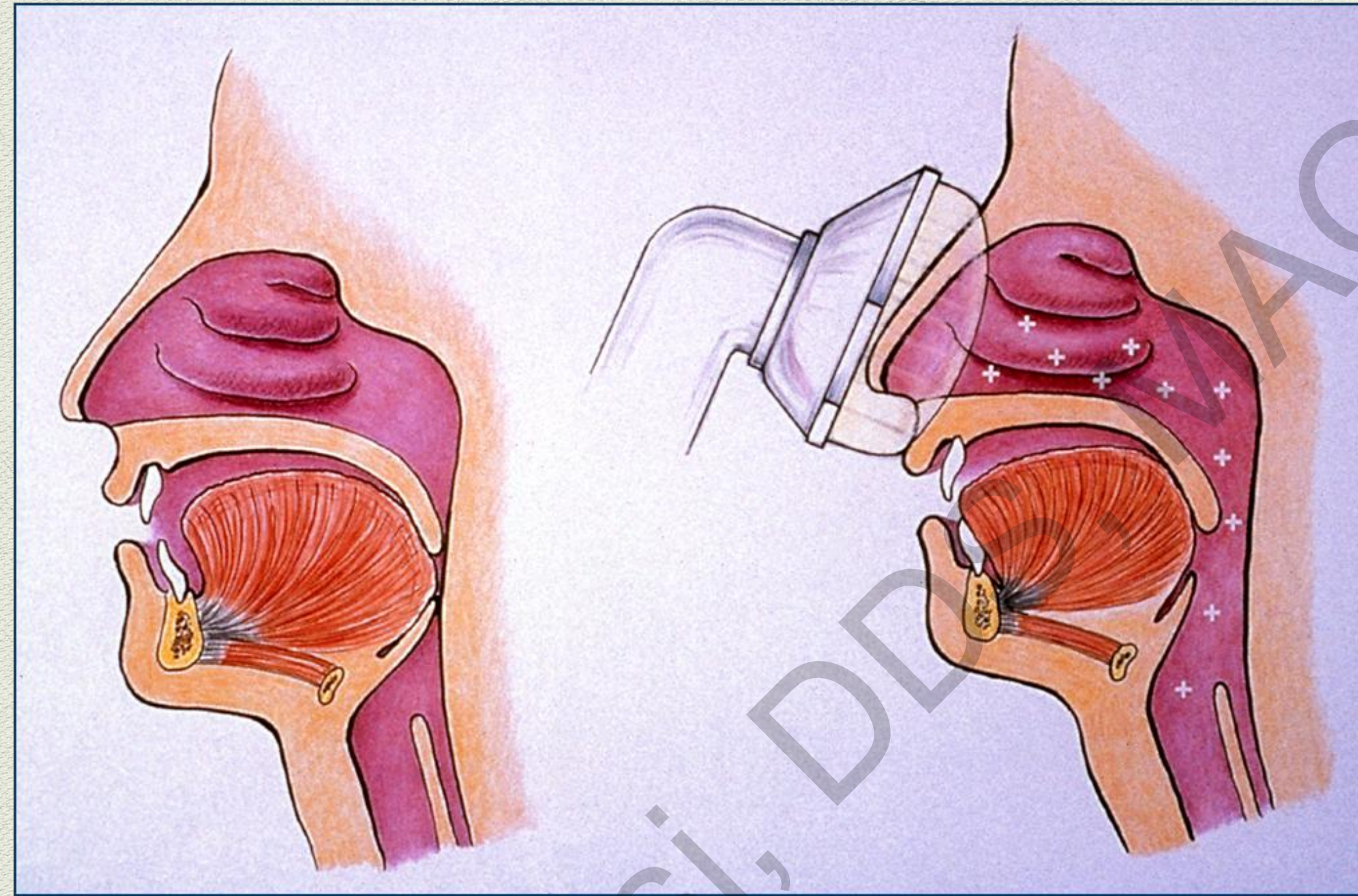
- ▶ You WILL uncover severe apnea that is considered imminently life threatening.
- ▶ One of the most rewarding parts of dental sleep medicine is “*solving the mystery*” and finding cases that may even ultimately be treated with CPAP but had caused much suffering over many years.
- ▶ Without treatment, these patients simply will not survive
- ▶ Be prepared for the bad result, you’ll find plenty.



So how is SRBD Treated?

John C. Comisar, DDS, MAGD





- ◆ The most common type of treatment is CPAP (continuous positive air pressure)
- ◆ Although highly effective, patients are frequently non-compliant with CPAP
- ◆ Other treatments include oral appliances, surgery and weight loss





CPAP works quite well... if its worn!



# Philips Recalls Specific CPAP, BiPAP Masks with Magnets

September 6, 2022



“The magnetic headgear clips are used to attach the headgear straps to the masks, which is a method that is commonly used in the sleep therapy devices industry,” states a release issued by Philips Respironics. “This is a voluntary notification to users of specific CPAP or Bi-Level PAP therapy masks containing such magnetic clips to inform them of the updated instructions and labeling. All users should read and follow Philips Respironics’ voluntarily updated warning and added contraindication described below. This represents a new and industry-leading practice.”





ORIGINAL ARTICLE

Bedaquiline–Pretomanid–  
Linezolid Regimens for Drug-  
Resistant Tuberculosis

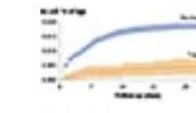


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Nirmatrelvir Use and Severe  
Covid-19 Outcomes during the  
Omicron Surge

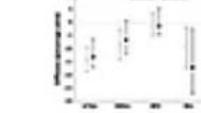


MEDICINE AND SOCIETY

Building Black Wealth — The  
Role of Health Systems in  
Closing the Gap

ORIGINAL ARTICLE

Dolutegravir in Pregnancy as  
Compared with Current HIV  
Regimens in the United St...



PERSPECTIVE

Science, Com  
Trade-offs in  
The Example

ORIGINAL ARTICLE

## CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea

R. Doug McEvoy, M.D., Nick A. Antic, M.D., Ph.D., Emma Heeley, Ph.D., Yuanming Luo, M.D., Qiong Ou, M.D., Xilong Zhang, M.D., Olga Mediano, M.D., Rui Chen, M.D., Luciano F. Drager, M.D., Ph.D., Zhihong Liu, M.D., Ph.D., Guofang Chen, M.D., Baoliang Du, M.D., *et al.*, for the SAVE Investigators and Coordinators\*

This secondary prevention trial in adults with cardiovascular disease and obstructive sleep apnea showed that the risk of serious cardiovascular events was not lower among patients who received treatment with CPAP in addition to usual care than among those who received usual care alone. Treatment with CPAP was associated with a greater reduction in symptoms of daytime sleepiness and with improved health-related quality of life, mood, and attendance at work. This study was not powered to provide definitive answers regarding the effects of CPAP on secondary cardiovascular end points, but there was no indication of a significant benefit with respect to any cause-specific cardiovascular outcome.

Three other randomized trials have investigated the effect of CPAP on cardiovascular end points in patients with obstructive sleep apnea.<sup>26-28</sup> Two studies — a multicenter study conducted in Spain that compared CPAP with usual care in 725 patients with obstructive sleep apnea who did not have prior cardiovascular disease<sup>26</sup> and a single-center study involving 224 patients with obstructive sleep apnea and coronary artery disease who had just undergone revascularization<sup>28</sup> — showed no difference in composite cardiovascular end points over several years of follow-up, although in adjusted analyses, both studies reported better outcomes among patients who were adherent to CPAP therapy (≥4 hours per night) than among patients who did not receive CPAP or who used CPAP less than 4 hours per night. The third study involving 140 patients with recent ischemic stroke showed no effect of CPAP on event-free survival over 2 years.<sup>27</sup>

September 8, 2016

N Engl J Med 2016; 375:919-931

DOI: 10.1056/NEJMoa1606599

Chinese Translation 中文翻译



How does Dentistry come into play  
here??

John C Comisi, DDS, MAGD



When you lean the patient back a touch more...



(SCREAMING)



# 2015 American Academy of Sleep Medicine Practice Parameters

Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015

- ◆ **Recommend sleep physicians prescribe oral appliances, rather than no therapy, for adult patients who request treatment of primary snoring (without obstructive sleep apnea). (STANDARD)**
- ◆ **Recommend sleep physicians consider prescription of oral appliances, rather than no treatment, for adult patients with obstructive sleep apnea who are intolerant of CPAP therapy or prefer alternate therapy. (STANDARD)**
- ◆ **When oral appliance therapy is prescribed by a sleep physician for an adult patient with obstructive sleep apnea, a qualified dentist use a custom, titratable appliance over non-custom oral devices. (GUIDELINE)**
- ◆ **Suggest qualified dentists provide oversight—rather than no follow-up—of oral appliance therapy in adult patients with obstructive sleep apnea, to survey for dental-related side effects or occlusal changes and reduce their incidence. (GUIDELINE)**



# Dentistry's Role

## **ADA Adopts Policy on Dentistry's Role in Treating Obstructive Sleep Apnea, Similar Disorders**

*House of Delegates adopts official policy statement at ADA 2017 – America's Dental Meeting*

October 23, 2017

CHICAGO, October 23, 2017 — The House of Delegates approved an American Dental Association (ADA) policy statement addressing dentistry's role in sleep-related breathing disorders (SRBD), developed as a result of a 2015 resolution calling for the action.

The adopted policy emphasizes that "dentists are the only health care provider with the knowledge and expertise to provide oral appliance therapy (OAT)."

SRBDs are a set of potentially serious medical conditions – snoring, upper airway resistance syndrome (UARS), obstructive sleep apnea (OSA) and others – characterized by disruptions in normal breathing patterns. Metabolic, cardiovascular, respiratory, dental and other diseases have been associated with OSA.

The adopted policy statement outlines the role of dentists in treating SRBD. Key components include assessing a patient's risk for SRBD as part of a comprehensive medical and dental history and referring affected patients to appropriate physicians; evaluating the appropriateness of OAT as prescribed by a physician and providing OAT for mild and moderate sleep apnea when a patient does not tolerate a continuous positive airway pressure (CPAP) device; recognizing and managing OAT side effects; continually updating dental sleep medicine knowledge and training; and communicating patients' treatment progress with the referring physician and other healthcare providers.



## Study Shows Dental Appliance Successful in Treating Patients with Severe Sleep Apnea

The University of Texas Health Science Center at San Antonio  
Monday, February 23, 2009

SAN ANTONIO (Jan. 14, 2009) - Imagine choking and gasping for air every time you fall asleep. Between 18 million and 20 million people in the United States suffer from these frightening symptoms because of a common disorder called sleep apnea. Because of a lack of awareness among both health professionals and the public, up to 90 percent of sufferers aren't diagnosed or treated, and that could prove deadly.

When left untreated, sleep apnea may lead to more serious health problems. According to national health statistics, nearly 38,000 cardiovascular deaths annually are in some way related to sleep apnea.

Although treatment is available, many don't comply with standard therapies. Researchers in the Dental School at The University of Texas Health Science Center at San Antonio are offering another treatment option that is more appealing, more affordable and easier to use than standard therapies.

Paul McLornan, B.D.S., assistant professor in the Department of Prosthodontics, is the lead investigator of an 18-month study involving sleep apnea patients at the South Texas Veterans Health Care System, Audie Murphy Division. Researchers used an oral appliance called the Thornton Adjustable Positioner (TAP) to treat those suffering from moderate to severe sleep apnea.

"What we found was that many of our patients with moderate to severe sleep apnea were not adhering to standard treatment with a Continuous Positive Airway Pressure (CPAP) machine," Dr. McLornan said. Although the CPAP is considered to be the gold standard in treating sleep apnea and is very effective, Dr. McLornan said compliance by patients is well below 50 percent.



We Need to Screen  
for Sleep Related  
Breathing Disorders, (SRBD),  
in Our Practices on  
Every Patient!





# Snoring - a sign of a problem





# How To Stop Snoring:

-Place pillow  
tightly over  
partner's face

-Hold til snoring  
stops



# Can't I just treat Snoring?

- ◆ Problem with “just treating snoring”
- ◆ How do you know they just snore?
- ◆ Over 70% of the time loud snoring is indicative of some form of OSA
- ◆ How do you follow up?
- ◆ Risk of creating “silent apnea”





# Treating Snoring without a Sleep Test



Treating snoring alone is like turning off the alarm, but not putting out the fire.



**WE MUST THINK MEDICALLY!!!!**

John C Comisi, DDS, MAGD



# Healthcare Utilization

- ◆ ***“Sleep apnea patients use healthcare resources at approximately twice the rate of controls as far back as ten years before their diagnosis...”***

***Source: Ronald, Kryger et al, 1997 APSS***

- ◆ ***Hospitalization stays for patients with OSA in days is 2.8 times higher than those without OSA.***



# Sleep Apnea – the not-so-silent killer

## Sleep apnea raises death risk 46 percent: study

WASHINGTON (Reuters, Aug. 18, 2009) – Severe sleep apnea raises the risk of dying early by 46 percent, U.S. researchers reported Monday, but said people with milder sleep-breathing problems do not share that risk.

They said people with severe breathing disorders during sleep were more likely to die from a variety of causes than similar people without such sleep disorders. The risks are most obvious in men aged 40 to 70, Naresh Punjabi of Johns Hopkins University in Baltimore and colleagues found.

Punjabi's team studied 6,400 men and women for an average of eight years. Those who started with major sleep apnea were 46 percent more likely to die from any cause, regardless of age, sex, race, weight or smoking, they reported in the Public Library of Science journal PLOS Medicine.

Men aged 40 to 70 with severe sleep-disordered breathing were twice as likely to die from any cause as healthy men the same age, they reported in the study. available online at:

<http://medicine.plosjournals.org/perlserv/?request=get-document&doi=1000132>





**Look for the warning signs**

John C Comisi, DDS, MAGD



# Signs & Symptoms of OSA

## ▶ **Most Common Symptoms**

- ▶ SNORING
- ▶ Excessive Daytime Sleepiness
- ▶ Hypertension (High Blood Pressure)

## ▶ **Other Symptoms**

- ▶ Acid Reflux (GERD – Gastro Esophageal Reflux Disease)
- ▶ Morning Headaches
- ▶ Diabetes
- ▶ Sexual Dysfunction
- ▶ Social Problems
- ▶ Memory Problems – Alzheimer's / Dementia
- ▶ Dental Symptoms (Abfractions from nocturnal bruxism)
- ▶ Nocturia

## ▶ **Contributing Factors**

- ▶ Obesity & Large Neck Circumference
- ▶ Menopause
- ▶ Mouth Breathing
- ▶ Family History



# What Your Dentist Looks For In **SCREENING** Sleep Apnea

**Uvula**  
Enlarged and elongated uvula contacting or touching the tongue.

**Tonsils**  
The larger the tonsils, the smaller the airway, the easier to obstruct airflow.

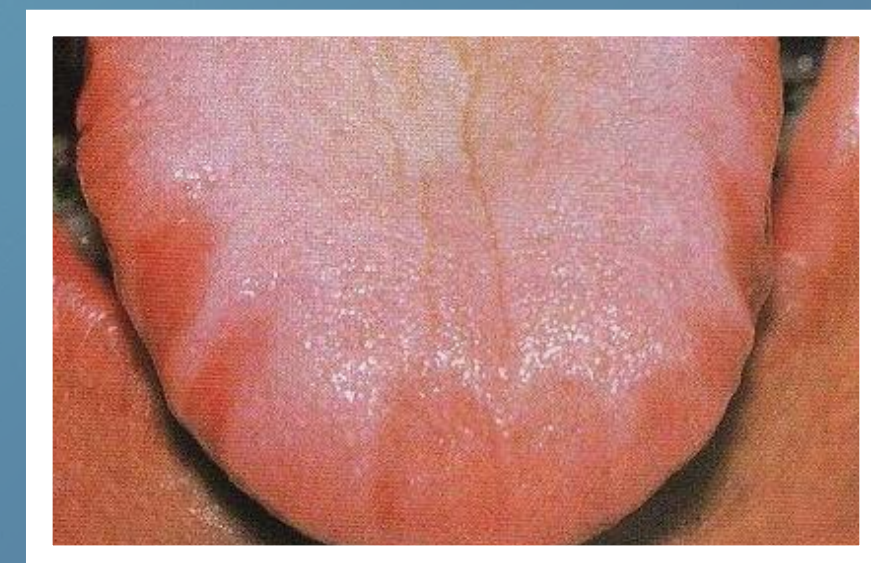
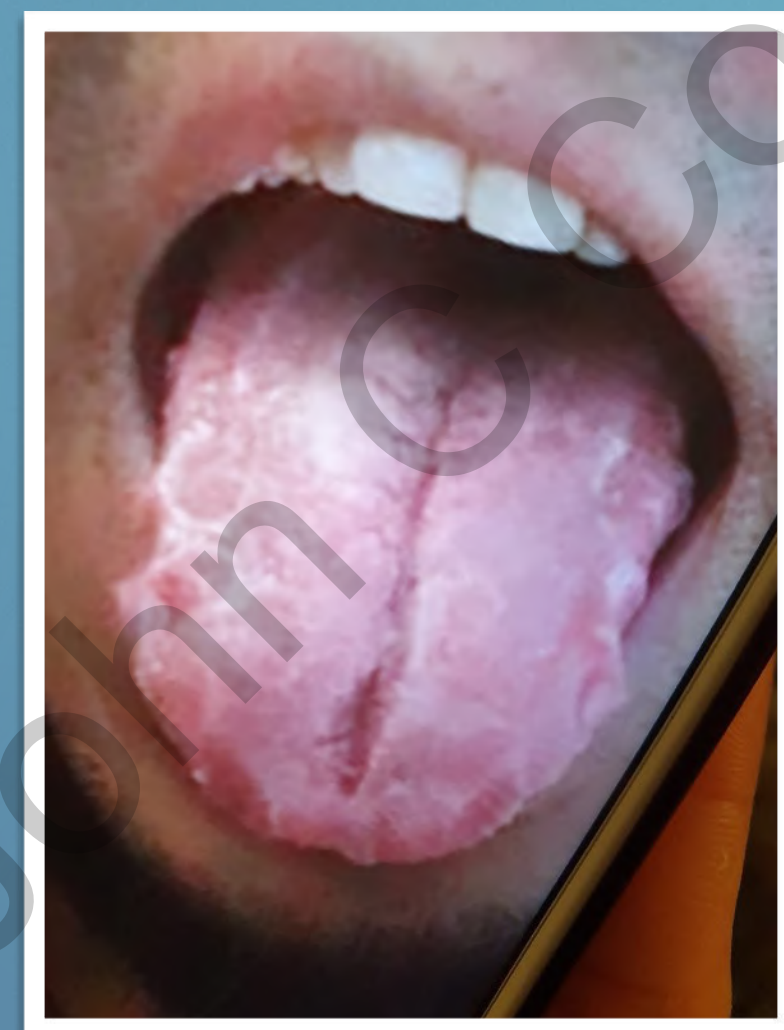
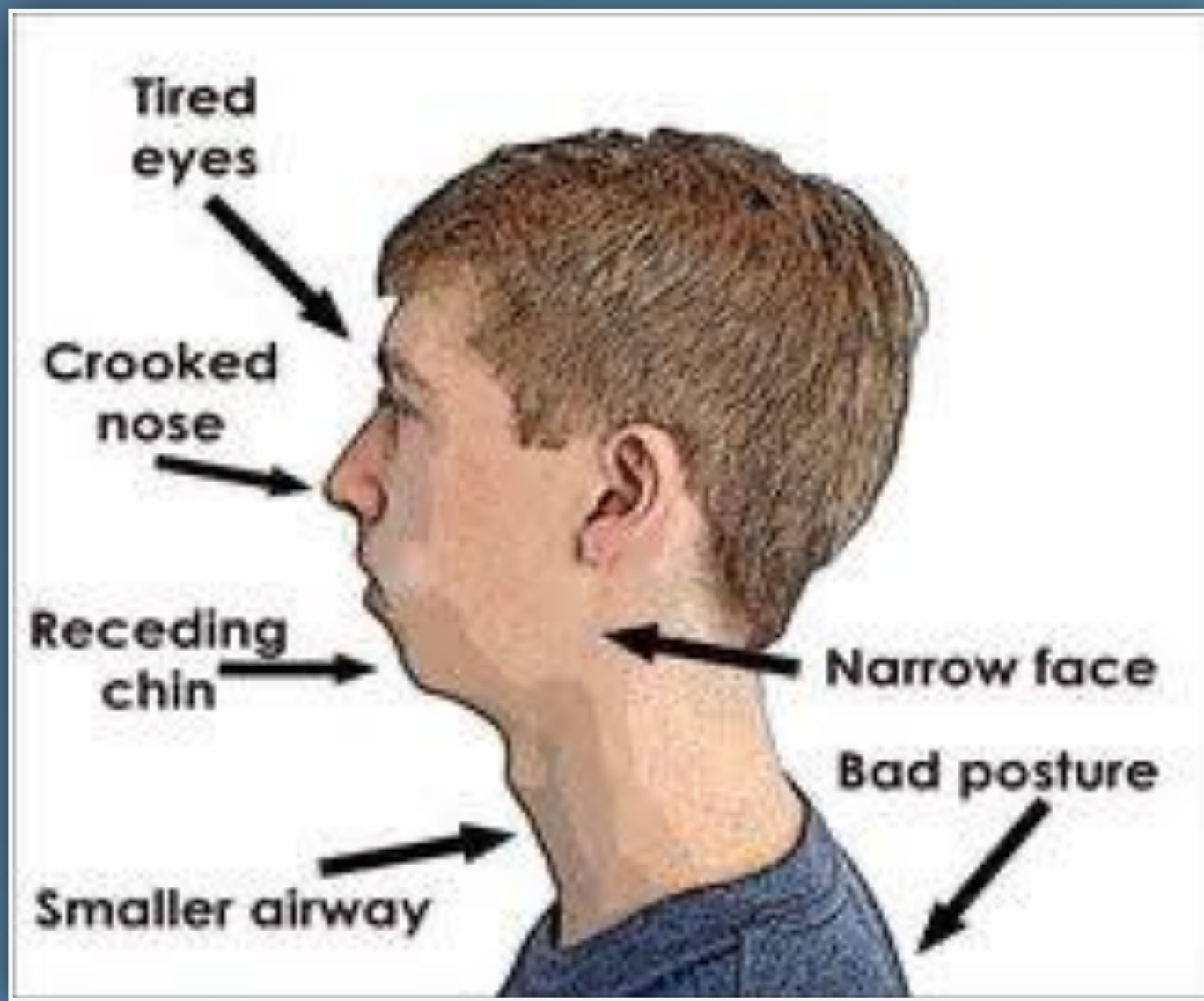
**Tongue**  
A large tongue rests on top of or above your lower teeth causes airflow obstruction by falling back into the throat area during sleep.



© Dear Doctor, Inc.



# Dental Red Flags





**When you Screen a Patient  
Check the Medical History**



# Medications

**No. 10 Hydrochlorothiazide (high blood pressure)**

**No. 9 Amoxicillin (antibiotic)**

**No. 8 Amlodipine (high blood pressure)**

**No. 7 Lipitor (high cholesterol)**

**No. 6 Metformin (diabetes)**

**No. 5 Azithromycin (antibiotic)**

**No. 4 Levothyroxine sodium (thyroid disorders)**

**No. 3 Lisinopril (high blood pressure)**

**No. 2 Simvastatin (high cholesterol)**

**No. 1 Hydrocodone/acetaminophen (painkiller)**

**7 out of 10 top drugs prescribed in the US are related to signs/symptoms or co-morbid factors of Obstructive Sleep Apnea**

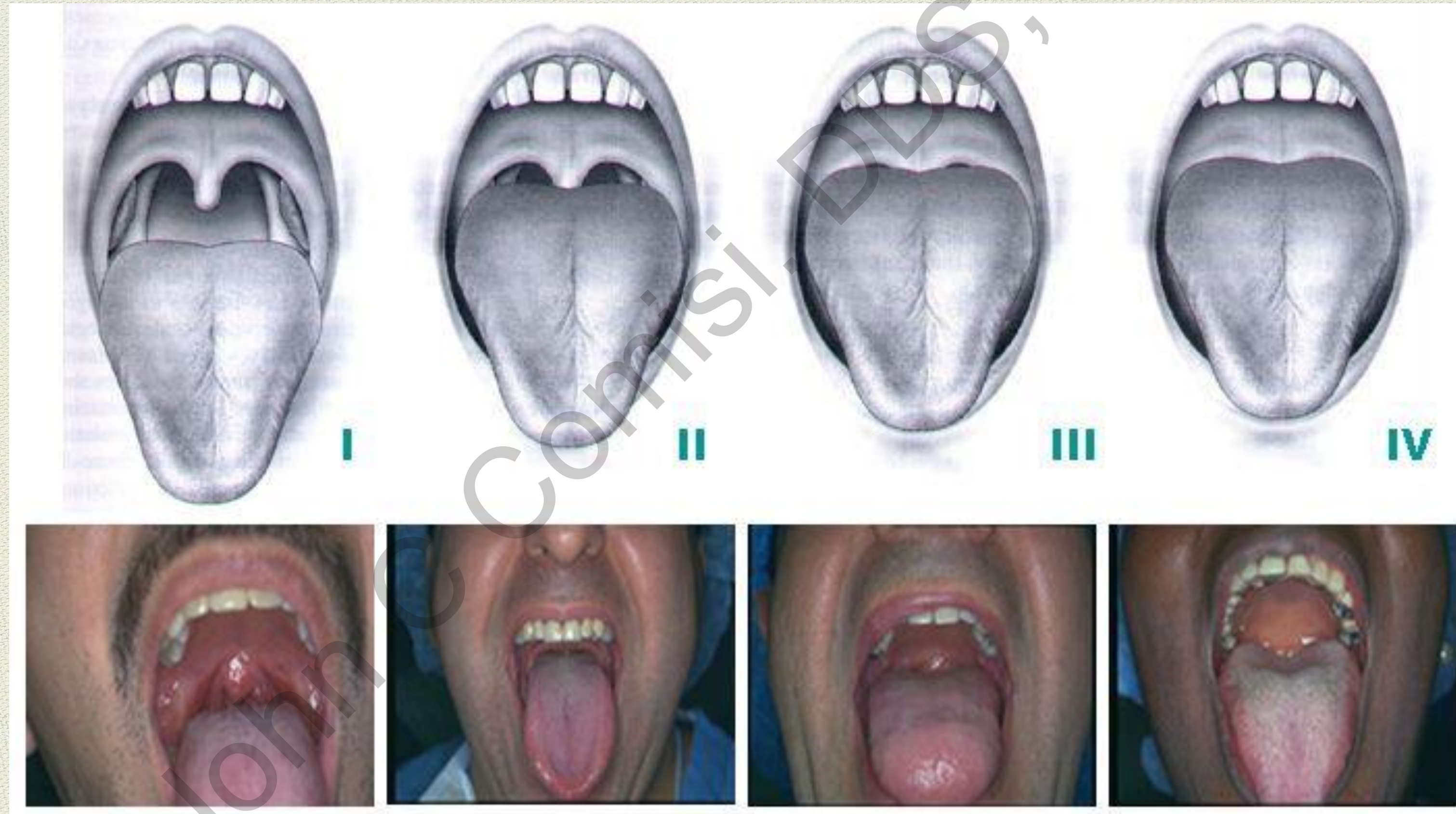


# Oral Screening for SRBD

John C Comisi, DDS, MAGD

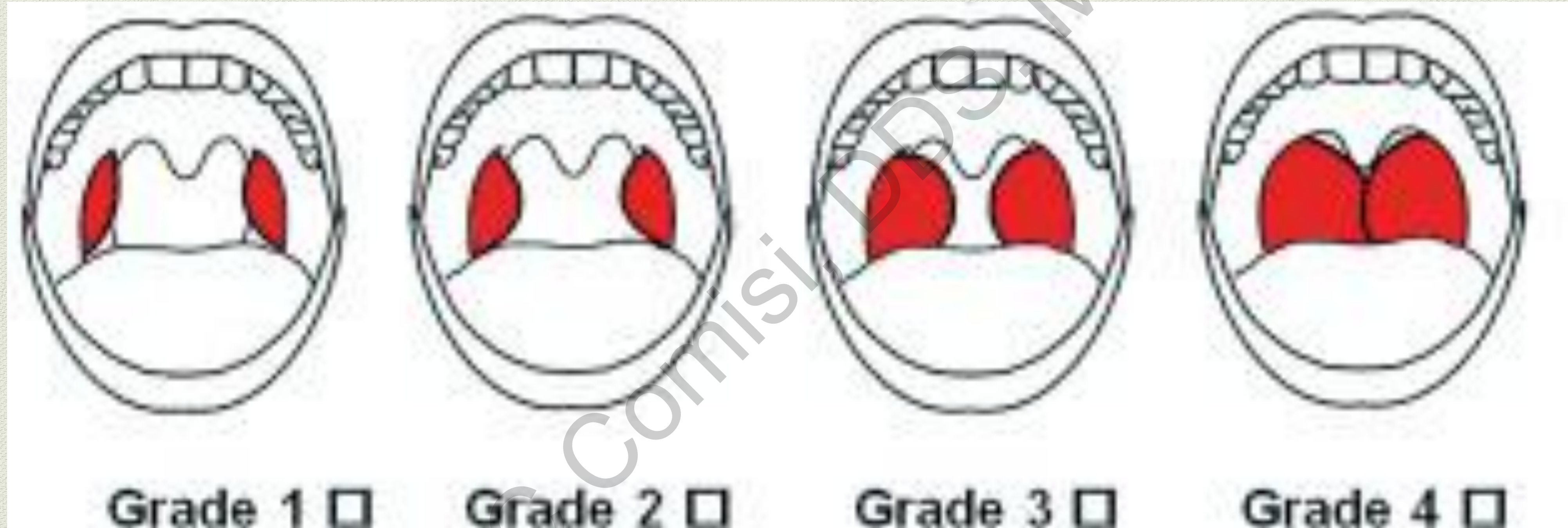


# Exams done as part of OSA screening: Mallampati Classification



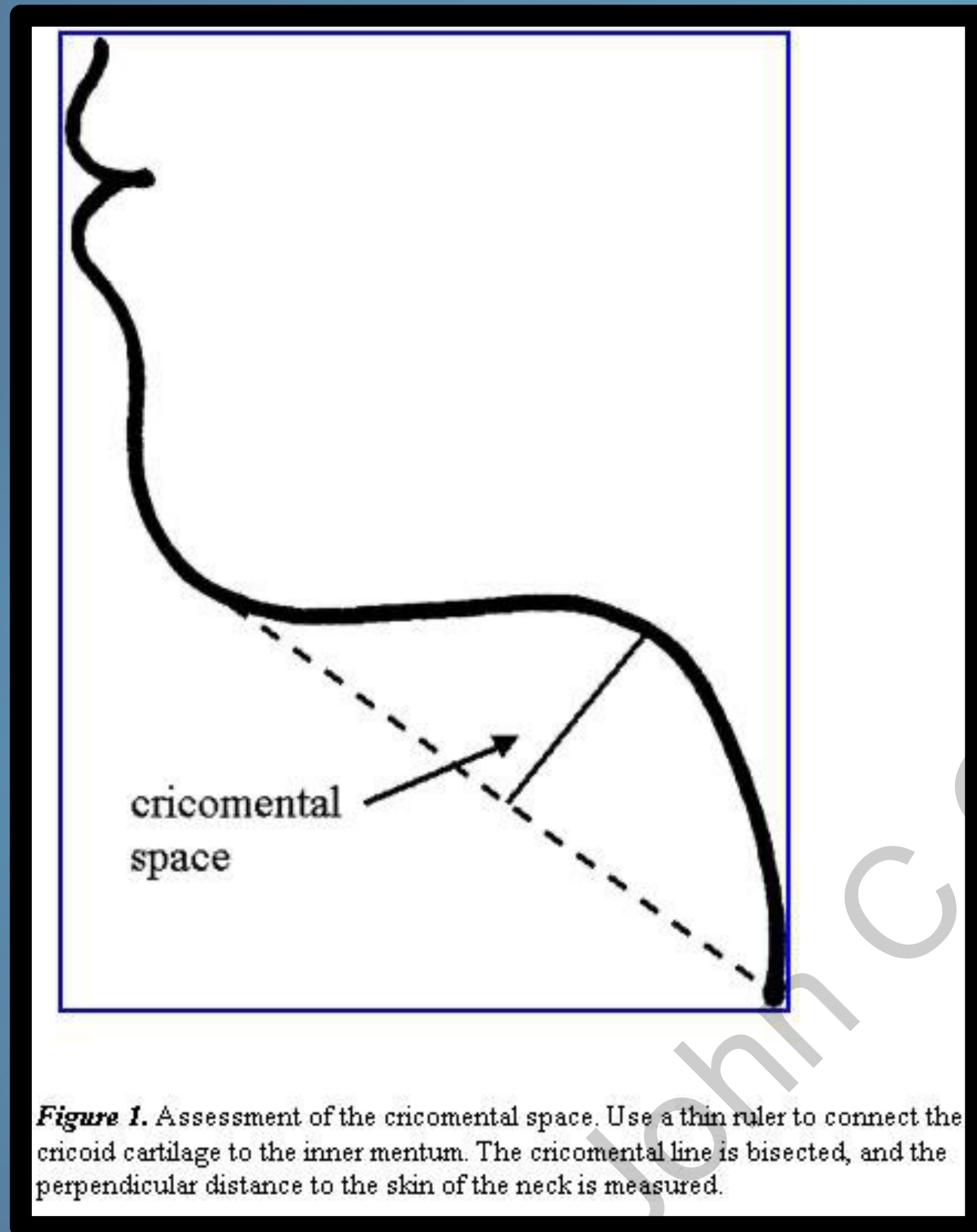


## ▶ Sampsoon-Young Pharyngeal Grade





# The “Turkey Waddle” (Crico-mental space)





- ▶ Overbite (greater than 4 mm or 50%)
- ▶ Crico-mental space (Turkey Waddle) < 1.5 cm
- ▶ Pharyngeal grade > II

**With all 3, there is a positive predictive value of 95%**

2002 publication of New England Journal of Medicine; 2003 study by American Thoracic Society  
<http://ajrccm.atsjournals.org/cgi/content/full/167/10/1427>



# Think About it....

- The dental health of patients who suffer from Sleep Related Breathing Disorders can be greatly reduced because of mouth breathing.
- Patients that have been diagnosed (by a Sleep Physician via a Sleep Study (lab or home), can be at greater risk because of the drying effect of the therapeutics used (CPAP, Oral Device).
- Those who have all the signs and symptoms we have discussed here and are yet to be diagnosed.



# What does a healthy oral microbiome look like?

- A balanced oral microbiome consists of bacteria that form a thin, protective, clear, and odorless film.
- Teeth feel clean and your gums appear pink and well oxygenated in this balanced state.
- When imbalanced, this biofilm transforms into a thick, sticky, and smelly film, which is commonly observed as the off-white plaque film on your teeth in the morning .



## RESEARCH ARTICLE

# Impact of sleep on the microbiome of oral biofilms

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## Abstract

Dysbiosis of the oral microbiome is associated with diseases such as periodontitis and dental caries. Because the bacterial counts in saliva increase markedly during sleep, it is broadly accepted that the mouth should be cleaned before sleep to help prevent these diseases. However, this practice does not consider oral biofilms, including the dental biofilm. This study aimed to investigate sleep-related changes in the microbiome of oral biofilms by using 16S rRNA gene sequence analysis. Two experimental schedules—post-sleep and pre-sleep biofilm collection—were applied to 10 healthy subjects. Subjects had their teeth and oral mucosa professionally cleaned 7 days and 24 h before sample collection. Samples were collected from several locations in the oral cavity: the buccal mucosa, hard palate, tongue dorsum, gingival mucosa, tooth surface, and saliva. *Prevotella* and *Corynebacterium* had higher relative abundance on awakening than before sleep in all locations of the oral cavity, whereas fluctuations in *Rothia* levels differed depending on location. The microbiome in different locations in the oral cavity is affected by sleep, and changes in the microbiome composition depend on characteristics of the surfaces on which oral biofilms form.

## OPEN ACCESS

**Citation:** Sotozono M, Kuriki N, Asahi Y, Noiri Y, Hayashi M, Motooka D, et al. (2021) Impact of sleep on the microbiome of oral biofilms. PLoS ONE 16(12): e0259850. <https://doi.org/10.1371/journal.pone.0259850>

**Editor:** Yiping Han, Columbia University, UNITED STATES

**Received:** May 17, 2021

**Accepted:** October 27, 2021

**Published:** December 9, 2021



## ORIGINAL ARTICLE

### Severe Obstructive Sleep Apnea Is Associated with Alterations in the Nasal Microbiome and an Increase in Inflammation

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#### Abstract

**Rationale:** Obstructive sleep apnea (OSA) is associated with recurrent obstruction, subepithelial edema, and airway inflammation. The resultant inflammation may influence or be influenced by the nasal microbiome.

**Objectives:** To evaluate whether the composition of the nasal microbiota is associated with obstructive sleep apnea and inflammatory biomarkers.

**Methods:** Two large cohorts were used: 1) a discovery cohort of 472 subjects from the WTCSNORE (Seated, Supine and Post-Decongestion Nasal Resistance in World Trade Center Rescue and Recovery Workers) cohort, and 2) a validation cohort of 93 subjects from the Zaragoza Sleep cohort. Sleep apnea was diagnosed using home sleep tests. Nasal lavages were obtained from cohort subjects to measure: 1) microbiome composition (based on 16S rRNA gene sequencing), and 2) biomarkers for inflammation (inflammatory cells, IL-8, and IL-6). Longitudinal 3-month samples were obtained in the validation cohort, including after continuous positive airway pressure treatment when indicated.

**Measurements and Main Results:** In both cohorts, we identified that: 1) severity of OSA correlated with differences in microbiome diversity and composition; 2) the nasal microbiome of subjects with severe OSA were enriched with *Streptococcus*, *Prevotella*, and *Veillonella*; and 3) the nasal microbiome differences were associated with inflammatory biomarkers. Network analysis identified clusters of cooccurring microbes that defined communities. Several common oral commensals (e.g., *Streptococcus*, *Rothia*, *Veillonella*, and *Fusobacterium*) correlated with apnea-hypopnea index. Three months of treatment with continuous positive airway pressure did not change the composition of the nasal microbiota.

**Conclusions:** We demonstrate that the presence of an altered microbiome in severe OSA is associated with inflammatory markers. Further experimental approaches to explore causal links are needed.

**Keywords:** microbiome; inflammation; chronic rhinosinusitis; biomarkers

Am J Respir Crit Care Med Vol 199, Iss 1, pp 99–109, Jan 1, 2019

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Originally Published in Press as DOI: 10.1164/rccm.201801-0119OC on July 3, 2018

Internet address: www.atsjournals.org



Sleep  
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SLEEPJ, 2021, 1–17

doi: 10.1093/sleep/zsab061

Advance Access Publication Date: 11 March 2021

Review

#### REVIEW

### The microbiome in obstructive sleep apnea

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#### Abstract

Recent evidence has highlighted important associations between obstructive sleep apnea and the microbiome. Although the intricacies of the pathophysiologic mechanisms are not well understood, available evidence suggests a bidirectional relationship between obstructive sleep apnea and microbiota composition. Sleep fragmentation, intermittent hypoxia, and intermittent hypercapnia all play significant roles in altering the microbiome, and initial evidence has shown that alterations of the microbiota affect sleep patterns. Animal model evidence strongly supports the idea that the microbiome mediates disease states associated with obstructive sleep apnea including hypertension, atherosclerosis, and obesity. While evidence is limited, several studies suggest there may be a role for treatment of obstructive sleep apnea and obstructive sleep apnea-related comorbidities through alteration of the microbiome with probiotics, prebiotics, and microbiota transplantation.

**Key words:** obstructive sleep apnea; microbiome; microbiota; dysbiosis; hypertension; cardiovascular disease; probiotic



## SCIENTIFIC INVESTIGATIONS

## Pediatric Obstructive Sleep Apnea is Associated With Changes in the Oral Microbiome and Urinary Metabolomics Profile: A Pilot Study

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**Study Objectives:** Several cross-sectional studies have reported associations between oral diseases and obstructive sleep apnea (OSA). However, there have been no reports regarding the structure and composition of the oral microbiota with simultaneous evaluation of potential associations with perturbed metabolic profiles in pediatric OSA.

**Methods:** An integrated approach, combining metagenomics based on high-throughput 16S rRNA gene sequencing, and metabolomics based on ultra-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry and gas chromatography coupled with time-of-flight mass spectrometry, was used to evaluate the oral microbiome and the urinary metabolome.

**Results:** 16S rRNA gene sequencing indicated that the oral microbiome composition was significantly perturbed in pediatric OSA compared with normal controls, especially with regard to Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, and Actinobacteria. Moreover, metabolomics profiling indicated that 57 metabolites, 5 of which were metabolites related to the microflora of the digestive tract, were differentially present in the urine of pediatric patients with OSA and controls. Co-inertia and correlation analyses revealed that several oral microbiome changes were correlated with urinary metabolite perturbations in pediatric OSA. However, this correlation relationship does not imply causality.

**Conclusions:** High-throughput sequencing revealed that the oral microbiome composition and function were significantly altered in pediatric OSA. Further studies are needed to confirm and determine the mechanisms underlying these findings.

Xu H, Li X, Zheng X, Xia Y, Fu Y, Li X, Qian Y, Zou J, Zhao A, Guan J, Gu M, Yi H, Jia W, Yin S. Pediatric Obstructive Sleep Apnea is Associated With Changes in the Oral Microbiome and Urinary Metabolomics Profile: A Pilot Study. *J Clin Sleep Med*. 2018 Sep 15;14(9):1559-1567. doi: 10.5664/jcsm.7336. PMID: 30176961; PMCID: PMC6134247

## ARTICLE



## Analysis of oral microbiota in patients with obstructive sleep apnea-associated hypertension

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Received: 20 December 2018 / Revised: 28 February 2019 / Accepted: 9 March 2019 / Published online: 11 April 2019

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### Abstract

Obstructive sleep apnea–hypopnea syndrome (OSAHS) is an independent risk factor for hypertension (HTN). The oral microbiota plays a pathophysiological role in cardiovascular diseases; however, there are few reports directly investigating and identifying the organisms involved in OSAHS-related HTN. Therefore, this study aimed to identify those organisms. We obtained 139 oral samples and determined the microbiome composition using pyrosequencing and bioinformatic analyses of the 16S rRNA. We examined the fasting levels of cytokines and homocysteine in all participants and analyzed the correlations between the oral microbiota and homocysteine levels. We determined the molecular mechanism underlying HTN by investigating the genetic composition of the strains in the blood. We detected higher relative abundances of *Porphyromonas* and *Aggregatibacter* and elevated proinflammatory cytokines in patients with OSAHS of varying severity compared with individuals without OSAHS; however, the two organisms were not measured in the blood samples from all participants. High levels of specific *Porphyromonas* bacteria were detected in patients with OSAHS with and without HTN, whereas the relative abundance of *Aggregatibacter* was negatively correlated with the homocysteine level. The receiver operating characteristic curve analysis of controls and patients with OSAHS resulted in area under the curve values of 0.759 and 0.641 for patients with OSAHS with or without HTN, respectively. We found that the predictive function of oral microbiota was different in patients with OSAHS with and without HTN. However, there was no direct invasion by the two organisms causing endothelial cell injury, leading to speculation regarding the other mechanisms that may lead to HTN. Elucidating the differences in the oral microbiome will help us understand the pathogenesis of OSAHS-related HTN.

**Keywords** homocysteine · hypertension · oral microbiota · obstructive sleep apnea-hypopnea syndrome · periodontopathic bacteria



# Gut Microbiome and Hypertension

## Role of the Gut Microbiome in Obstructive Sleep Apnea-Induced Hypertension

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**Abstract**—Individuals suffering from obstructive sleep apnea (OSA) are at increased risk for systemic hypertension. The importance of a healthy gut microbiota, and detriment of a dysbiotic microbiota, on host physiology is becoming increasingly evident. We tested the hypothesis that gut dysbiosis contributes to hypertension observed with OSA. OSA was modeled in rats by inflating a tracheal balloon during the sleep cycle (10-s inflations, 60 per hour). On normal chow diet, OSA had no effect on blood pressure; however, in rats fed a high-fat diet, blood pressure increased 24 and 29 mmHg after 7 and 14 days of OSA, respectively ( $P<0.05$  each). Bacterial community characterization was performed on fecal pellets isolated before and after 14 days of OSA in chow and high-fat fed rats. High-fat diet and OSA led to significant alterations of the gut microbiota, including decreases in bacterial taxa known to produce the short chain fatty acid butyrate ( $P<0.05$ ). Finally, transplant of dysbiotic cecal contents from hypertensive OSA rats on high-fat diet into OSA recipient rats on normal chow diet (shown to be normotensive) resulted in hypertension similar to that of the donor (increased 14 and 32 mmHg after 7 and 14 days of OSA, respectively;  $P<0.05$ ). These studies demonstrate a causal relationship between gut dysbiosis and hypertension, and suggest that manipulation of the microbiota may be a viable treatment for OSA-induced, and possibly other forms of, hypertension. (*Hypertension*. 2016;67:469-474. DOI: 10.1161/HYPERTENSIONAHA.115.06672.) • [Online Data Supplement](#)



EUROPEAN RESPIRATORY REVIEW  
REVIEW  
X. ZHANG ET AL.

## Metabolomics and microbiome profiling as biomarkers in obstructive sleep apnoea: a comprehensive review

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Shareable abstract (@ERSpublications)

Unique alterations in metabolism and the microbiome play an integral role in the pathophysiology of OSA and OSA-induced cardiovascular complications <https://bit.ly/3mW2rD5>

Cite this article as: Zhang X, Wang S, Xu H, et al. Metabolomics and microbiome profiling as biomarkers in obstructive sleep apnoea: a comprehensive review. *Eur Respir Rev* 2021; 30: 200220 [DOI: 10.1183/16000617.0220-2020].

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Received: 8 July 2020  
Accepted: 3 Dec 2020

### Abstract

**Introduction** Obstructive sleep apnoea (OSA) is a common sleep disorder with a high social and economic burden. Thus, early prediction and diagnosis of OSA are important. Changes in metabolism and the microbiome may serve as biomarkers for OSA. Herein, we review the literature on the metabolomic and microbiome changes associated with OSA, and identify the metabolites and microorganisms involved.

**Methods** We searched the PUBMED and EMBASE electronic databases using the following terms: "obstructive sleep apnea", "OSA", "sleep disordered breathing", "SDB", "intermittent hypoxia", "sleep fragmentation", and either "metabolomics" or "microbiome". In total, 273 papers were identified, of which 28 were included in our study.

**Results** Changes in the levels of certain metabolites related to fatty acid, carbohydrate and amino acid metabolism were associated with the incidence of OSA. The diversity and abundance of microflora, particularly Firmicutes and Bacteroidetes, were altered in humans and rodents with OSA.

**Conclusions** Certain changes in metabolism and the microbiota play an integral role in the pathophysiology of OSA and OSA-induced cardiovascular complications. Metabolomic and microbiome biomarkers shed light on the pathogenesis of OSA, and facilitate early diagnosis and treatment.



# Altered Salivary Microbiota in Patients with Obstructive Sleep Apnea Comorbid Hypertension

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**Purpose:** Microorganisms contribute to the pathogenesis of obstructive sleep apnea (OSA)-associated hypertension (HTN), while more studies focus on intestinal microbiome. However, the relationship between oral microbiota and OSA-associated HTN has yet to be elucidated. This study aimed to identify differences in salivary microbiota between patients with OSA comorbid HTN compared with OSA patients, and furthermore evaluate the relationship between oral microbiome changes and increased blood pressure in patients with OSA.

**Patients and Methods:** This study collected salivary samples from 103 participants, including 27 healthy controls, 27 patients with OSA, 23 patients with HTN, and 25 patients with OSA comorbid HTN, to explore alterations of the oral microbiome using 16S rRNA gene V3-V4 high-throughput sequencing. And ultra-high-performance liquid chromatography was used for metabolomic analysis.

**Results:** Alpha- and beta-diversity analyses revealed a substantial difference in community structure and diversity in patients with OSA comorbid HTN compared with patients with OSA or HTN. The relative abundance of the genus *Actinomyces* was significantly decreased in patients with HTN compared with healthy controls, and those with OSA concomitant HTN compared with the patients in OSA, but was not significantly different between patients with OSA and healthy controls. Linear discriminant analysis effect size and variance analysis also indicated that the genera *Haemophilus*, *Neisseria*, and *Lactospira* were enriched in HTN. In addition, *Oribacterium* was an unique taxa in the OSA comorbid HTN group compared with the control group. Metabolomic analysis of saliva identified compounds associated with cardiovascular disease in patients with OSA comorbid HTN. 2-hydroxyadenine, was significantly increased in the group of patients with OSA compared with controls, and L-carnitine was significantly decreased in patients with OSA comorbid HTN compared with OSA patients.

**Conclusion:** This study highlighted noninvasive biomarkers for patients with OSA comorbid HTN. As the first study to find alterations of the salivary microbiome in patients with OSA comorbid HTN, it may provide a theoretical foundation for clinical diagnosis and treatment of this condition.

**Keywords:** OSA, hypertension, oral microbiome, 16S rRNA, metabolomics

## Introduction

Systemic hypertension, a very common chronic disease, is a leading risk factor for stroke, heart failure, atrial fibrillation, chronic kidney disease, and other life-threatening diseases.<sup>1</sup> It also coexists with obstructive sleep apnea (OSA), which is characterized by intermittent and repeated collapse of the upper airway, resulting in intermittent hypoxia (IH), hypercapnia, daytime sleepiness, and other consequences such as hypertension (HTN).<sup>2</sup> Approximately 50% of adult patients

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# Which came first....

- Did the OSA create the change in the oral microbiota?
- Did the change in the oral microbiota cause the OSA?

John C Comisi, DDS, MAGD



# What does a microbiome impacted by sleep apnea look like?

- Sleep fragmentation, intermittent hypoxia, and intermittent hypercapnia all play significant roles in altering the microbiome, and initial evidence has shown that alterations of the microbiota may affect sleep patterns.
- The upper airway microbiome may be associated with OSA and periodontitis-related oral cavity microbiome changes may have significance in OSA-related CVD

Cai Y, Juszczak HM, Cope EK, Goldberg AN. The microbiome in obstructive sleep apnea. *Sleep*. 2021 Aug 13;44(8):zsab061. doi: 10.1093/sleep/zsab061. PMID: 33705556.



# Perhaps...

- We should consider an Oral Probiotic supplement when managing Patients with OSA.
  - This can be both oral and gut probiotic treatment.



# Bad bacterial strains -> replaced with the good strains found oral-care probiotics.

- Patients with obstructive sleep apnea can favor the predisposing factors of periodontitis by the presence of *P. melaninogenica* and *C. albicans*, increasing the severity of the periodontal disease.
- It is critical for OSA patients to reestablish the good bacteria within their mouths so that the oral microbiome can properly rebalance
- The proprietary strains within a probiotic like, ProBioraPro® can do just that and help prevent the need for further treatment
- Other benefits include: fresher breath and whiter teeth

Cortés, M. E., & Otero, L. (2021). Patients with obstructive sleep apnea can favor the predisposing factors of periodontitis by the presence of *P. melaninogenica* and *C. albicans*, increasing the severity of the periodontal disease. *Frontiers in Cellular and Infection Microbiology*. <https://doi.org/10.3389/fcimb.2022.934298>



# Bad bacterial strains -> replaced with the good strains found oral-care probiotics.

- Dissolve in mouth nightly for 90 days or ongoing maintenance
- Replenishes the natural microbial balance in the mouth, supporting gum and tooth health
- These beneficial bacteria inhibit the growth of the harmful bacteria that cause gum disease and tooth decay which are common concerns in OSA patients
- ProBioraPro® species consist of *S. rattus*, *S. oralis*, *S. uberis* that crowds out harmful bacteria around teeth and gums

Cortés, M. E., & Otero, L. (2021). Patients with obstructive sleep apnea can favor the predisposing factors of periodontitis by the presence of *P. melaninogenica* and *C. albicans*, increasing the severity of the periodontal disease. *Frontiers in Cellular and Infection Microbiology*. <https://doi.org/10.3389/fcimb.2022.934298>

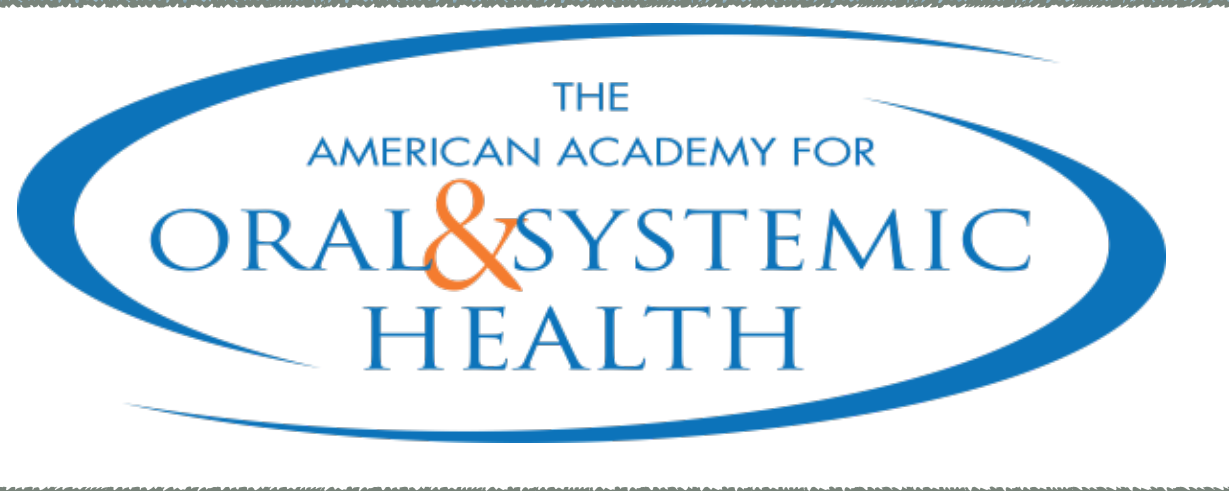


# Oral-care probiotics should be incorporated into proposed OSA treatment plans

- OSA patients tend to breathe through their mouths, the condition can promote tooth decay by causing their mouths to dry out.
- OSA patients typically also experience a change in the balance of their oral microbiota which can lead to the overgrowth of bad bacteria in the mouth passing into to the airway and resulting in further health problems.
- Probiotics for the mouth can help to balance out the bad bacteria by repopulating the patients mouth with native good bacterial strains to help them maintain a healthy mouth and upper airway, including support against tooth decay.

<https://www.dentistrytoday.com/combat-dental-problems-by-treating-sleep-apnea-patients/>

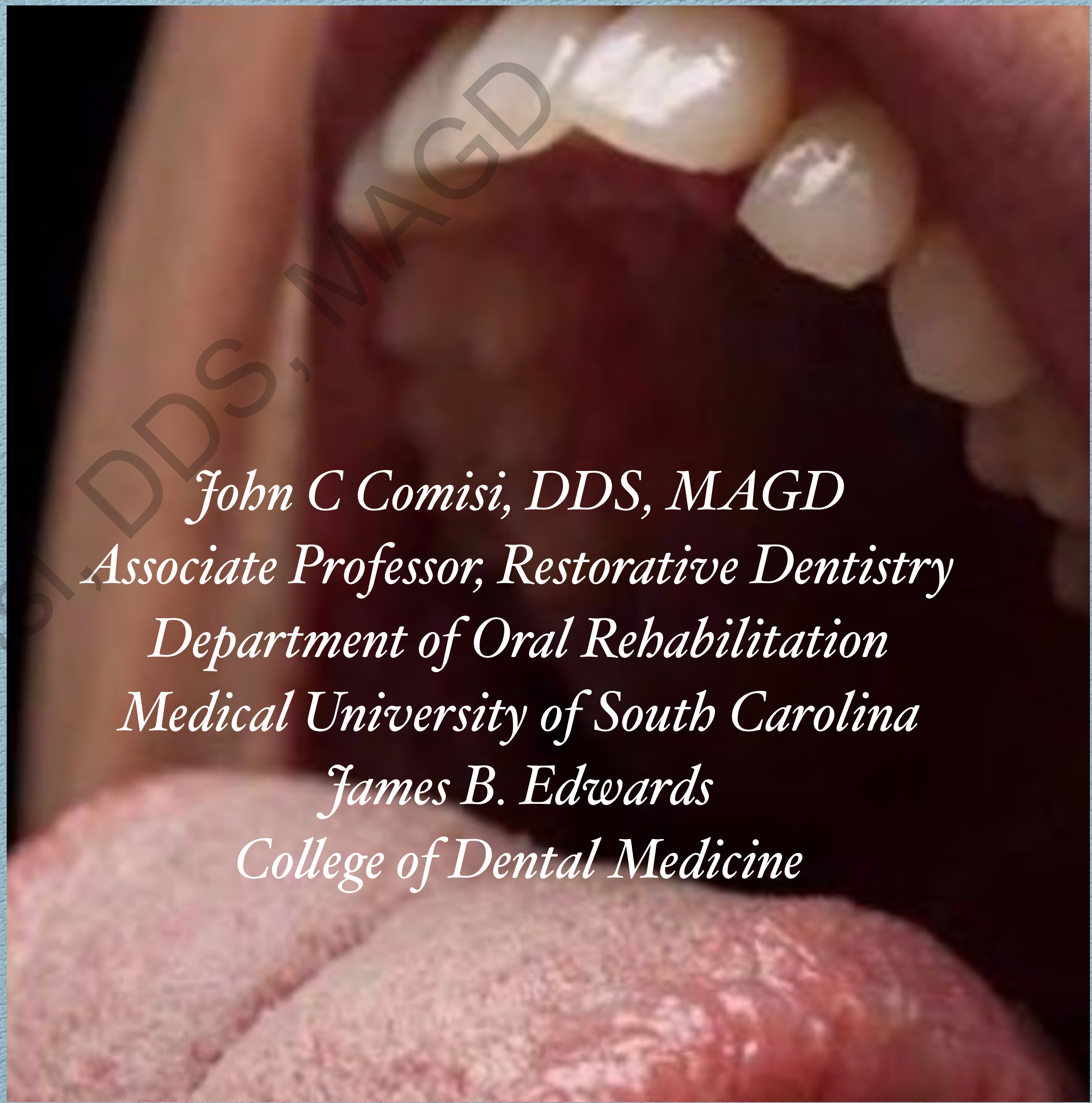
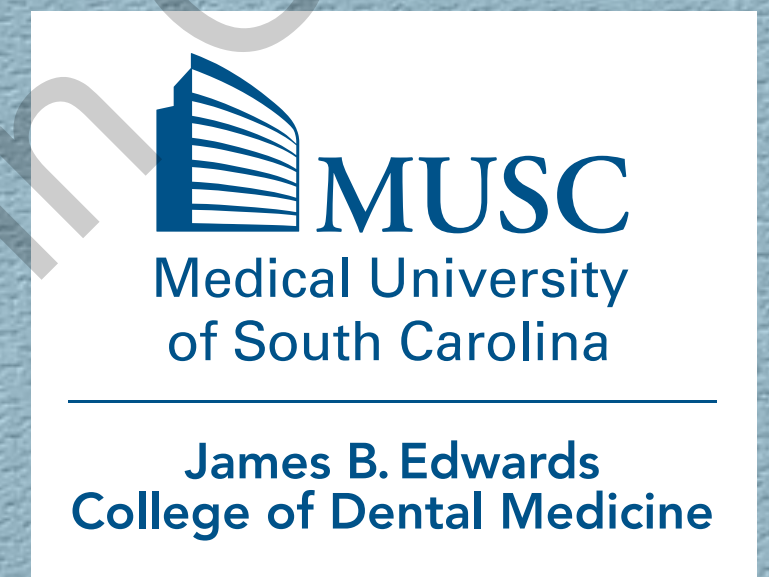




# **The Adult Airway - Sleep and the Oral Microbiome**

**THANK YOU!**

**OCTOBER 6, 2022**



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College of Dental Medicine*