

Sleep HealthCenters Expands to Arizona!

Sleep HealthCenters and REM Medical are pleased to announce they have joined forces to become the leading national comprehensive sleep services company.

REM Medical has locations in Mesa, Phoenix, Scottsdale and Tucson, Arizona.



Sleep HealthCenters is a network of sleep medicine centers staffed by experts in the field of sleep medicine. Our integrated care system provides all the services needed to diagnose and treat patients with the entire array of sleep disorders including obstructive sleep apnea, insomnia, narcolepsy and restless legs syndrome.

In this issue of the Sleep HealthCenters Newsletter...

- ▶ Future of Clinical Sleep Medicine Presentation Recap
 - New and Future Pharmacotherapies in Sleep Medicine
 - Evaluation and Management of Commercial Drivers for Sleep Apnea
 - Thinking Forward: The Promise of Genomics in Managing Sleep Apnea
 - A Health Plan Medical Director Perspective on Sleep Medicine
- ▶ CEO Corner
 - Future of Clinical Sleep Medicine Recap
 - Sleep HealthCenters' New Look
 - Sleep HealthCenters and REM Medical Merge
- ▶ Research Activities

Massachusetts Affiliations: Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Faulkner Hospital, Hallmark Health, Marlborough Hospital, Massachusetts Eye and Ear Infirmary, McLean Hospital, New England Sinai Hospital, Southcoast Hospitals Group; *New York Affiliations:* Beth Israel Medical Center

Massachusetts Locations: Bedford, Beverly, Boston, Brighton, Framingham, Jamaica Plain, Marlborough, Medford, North Dartmouth, Stoughton, Weymouth, Worcester; *New York Locations:* Manhattan; *Rhode Island Locations:* Cumberland; *Arizona Locations:* Mesa, Phoenix, Scottsdale, Tucson

For more information, please contact us at: 1-877-SLEEPHC (1-877-753-3742) or visit our website at www.sleephealth.com.

Requisition forms are available on our website.

Sleep HealthCenters® Newsletter

Lawrence J. Epstein, MD, Editor

Fall 2009

Dear Colleague:

This September, we held our 3rd Annual Future of Clinical Sleep Medicine forum. Our four distinguished guest speakers included John W. Winkelman, MD, PhD, Brigham and Women's Hospital and Harvard Medical School; Nancy A. Collop, MD, Johns Hopkins University; Susan Redline, MD, MPH, Case Western Reserve University; and Harold A. Picken, MD, MPH, Blue Cross Blue Shield of Rhode Island.

Dr. Winkelman's presentation discussed new pharmacotherapies for treating sleep disorders. In particular, he explored potential new treatments for disorders resulting in difficulty initiating and maintaining sleep or excessive daytime sleepiness. Dr. Collop's talk explored how a sleep disorder can affect the safety of the general public as well as the health of individuals. She looked at recent efforts to improve health and performance of commercial truck drivers by evaluating and treating those with obstructive sleep apnea. Dr. Redline spoke on the application of the new and expanding field of genetics to sleep medicine. She has been a leader in research on the genomics of obstructive sleep apnea and discussed recent innovations and possible applications from this work. Dr. Picken is one of the leaders of the largest health management organization in Rhode Island, Blue Cross Blue Shield, and is involved in shaping the response of insurance organizations to changes in the healthcare system. He shared his view on how sleep medicine fits into the larger picture of healthcare and how the sleep medicine field can influence the direction the field takes.

In the CEO Corner, Paul Valentine announces our merger with REM Medical of Arizona. With this merger and other ongoing activities, Sleep HealthCenters moves from a regional to a national organization. This opens new and exciting opportunities for us.

If you have any questions about sleep disorders, our services, our affiliations or our locations, please feel free to contact us.



Sincerely,
Lawrence J. Epstein, MD
Chief Medical Officer
Sleep HealthCenters LLC


Sleep HealthCenters®
Better Sleep. Better Health.

1-877-SLEEPHC
1-877-753-3742

3rd Annual Future of Clinical Sleep Medicine Forum

Our goal with this forum is to explore new trends affecting the practice of sleep medicine, from new therapies to new understanding of the nature and workings of sleep to changes in the health care environment.

This year's program reflected this diversity of ideas. In this edition of the newsletter we have summarized each of the presentations to give you a feel for some of the exciting innovations in sleep medicine.

New and Future Pharmacotherapies in Sleep Medicine

Presented by John W. Winkelman, MD, PhD

*Medical Director, Sleep HealthCenter associated with Brigham and Women's Hospital
Assistant Professor of Psychiatry, Harvard Medical School*

Pharmacotherapies in sleep medicine are slowly moving from the use of agents discovered through serendipity to those developed in a translational approach based upon an understanding of processes involved in the regulation of sleep and the pathophysiology of sleep disorders. In this way, arousal pathways using cholinergic, adrenergic, histaminergic, orexinergic and serotonergic neurotransmission, as well as GABA inhibitory pathways, become targets of novel pharmacotherapies.

Due to their efficacy, safety, and price, the majority of prescriptions for the treatment of insomnia continue to be for GABA-A acting agents, the most prominent being the selective (zolpidem) and non-selective (temazepam, eszopiclone) benzodiazepine receptor agonists. However, non-GABA acting agents, directed at amine arousal pathways, such as trazodone and quetiapine, continue to rise in popularity, even though they are off-label and have only modest empirical (as opposed to clinical experience) support for their use.

New agents in the pipeline for insomnia include eplivanserin (a serotonergic 2A receptor antagonist) and almorexant (an orexin antagonist). In addition, generic medications being repackaged as potentially branded drugs for insomnia include a low dose of the antidepressant doxepin and sublingual zolpidem. Phase II and III studies demonstrate efficacy of eplivanserin and doxepin as compared to placebo for sleep maintenance insomnia, though neither is consistently effective in reducing sleep onset. Of note, eplivanserin enhances slow wave sleep, though the clinical benefits of this are unknown. Neither of these agents acts as the GABA receptor, and should avoid the concerns for the benzodiazepine hypnotics, including psychomotor impairment, amnesia, complex sleep-related behaviors, and non-medical diversion. The sublingual administration of zolpidem allows for more rapid absorption and thus increased rapidity of return to sleep at mid-night awakenings. Although little data is available on the use of almorexant as a hypnotic, its development is of substantial interest. Orexin is a hypothalamic peptide that regulates wakefulness and is dramatically reduced in those with narcolepsy with cataplexy. In theory, an orexin antagonist might treat insomnia.

A number of promising agents in development for the treatment for restless legs syndrome (RLS) may avoid the concerns associated with dopaminergic medications. Approved medications ropinirole and pramipexole, though extremely effective for RLS acutely, can produce a worsening of symptoms over longer-term use, characterized by earlier onset and anatomical extension of symptoms. A controlled release prodrug formulation of gabapentin has demonstrated substantial efficacy for RLS in Phase II and III trials and is under review by the FDA. As a prodrug, it avoids the non-linear absorption of gabapentin. Similar benefits for RLS have been observed in Phase II studies for another alpha 2 delta calcium channel blocker, pregabalin. Given that the pathophysiology of RLS is related to a reduction in brain iron, another promising approach involves the use of IV iron. Parenteral administration avoids the limitations of absorbing oral iron. Early studies have been promising.

A number of medications to treat sleepiness in patients with narcolepsy, shift-work sleep disorder and treated sleep apnea are currently available. Most appear to work through enhancement of dopamine activity in the CNS. One agent recently approved by the FDA for these disorders is an isomer of modafinil, armodafinil. This new isomer has a longer half-life so it may produce longer-lasting benefit than its soon-to-be-generic parent compound.

Sleep HealthCenters® Newsletter

In summary, we have many effective pharmacotherapies for sleep disorders. New compounds feature lower doses, isomers, prodrugs, or controlled release formulations of existing agents, with varying benefits over the parent compounds. In addition, some truly new approaches have appeared on the horizon that are promising alternatives to our current approaches.

Evaluation and Management of Commercial Drivers For Sleep Apnea

Presented by Nancy A. Collop, MD

*Medical Director, Johns Hopkins Sleep Disorders Center
Johns Hopkins Hospital, East Baltimore Campus
Professor of Medicine, Johns Hopkins University*

Obstructive sleep apnea (OSA) increases the risk of a motor vehicle crash (MVC) 2 to 7 fold in commercial truck drivers. Studies show a high prevalence of OSA in commercial drivers, with upwards of 10 % having moderate to severe OSA.

The Federal Motor Carrier Safety Administration (FMCSA) holds truck drivers to a higher standard than the general driving public because they operate larger vehicles, may transport hazardous chemicals and have a greater risk of a crash being fatal to other motorists. They estimate that 30-40% of major crashes are due to sleepiness.

Drivers have medical qualification exams every two years to detect the presence of conditions that affect the driver's ability to operate a vehicle safely. OSA is listed as one of several respiratory disorders that can interfere with oxygen exchange and affect alertness. Commercial Driver Medical Examiners must ask whether the driver has a sleep disorder, pauses in breathing while asleep, daytime sleepiness or loud snoring. If answering yes, the driver is referred to a specialist for further evaluation and therapy. There is concern that this process leads to under-reporting of symptoms because of a fear that drivers might be removed from work. The recommendations regarding OSA were last updated in 1991.

Multiple methods of quantifying sleepiness and alertness have been developed including the Multiple Sleep Latency Test, Maintenance of Wakefulness Test (MWT), Oxford Sleep Resistance Test, Psychomotor Vigilance Test and driving simulator tests. None of these tests has been shown to predict MVCs.

Two recent taskforces have recommended updating the regulations regarding drivers. The 2006 Joint Task Force recommended detailed evaluations for OSA during qualification exams. Continued driving status would be determined by the likelihood of having OSA. They recommended diagnostic in-lab polysomnography. If OSA is present, demonstration of effective therapy and monitoring of compliance was recommended for continued driving.

In 2008, a Medical Expert Panel presented recommendations to the FMCSA Medical Review Board. They similarly recommended an increase in surveillance for OSA. Drivers with OSA symptoms or a BMI > 33 should undergo sleep testing. If OSA is present, the driver must obtain effective therapy and demonstrate improvement and compliance with therapy.

Other transportation regulatory agencies under-evaluate for OSA. There are no requirements by the Federal Aviation Administration that questions about OSA be asked during pilots' regular medical exams. If OSA is suspected, a pilot must have a sleep study and treatment, if indicated. A MWT may be requested to evaluate response to CPAP and is required following surgery for OSA. The Federal Railroad Administration has no standards that address OSA.

In summary, commercial drivers have a high prevalence of OSA but there are currently no good predictors of MVCs in OSA patients. Recommendations have been made to improve OSA screening in this population, but these have not been implemented.

Summarized by Lawrence Epstein, MD

Thinking Forward: The Promise of Genomics in Managing Sleep Apnea

Presented by Susan Redline, MD, MPH

*Director, University Hospital Comprehensive Sleep Center
Professor of Medicine and Pediatrics, Case Western Reserve
Academic Program Director, Case Center for Clinical Investigation*

Obstructive sleep apnea (OSA) is a very common condition with prevalence rates reported between 5-25%. Efficient screening tests or biomarkers have not yet been identified as they have in other conditions, such as fasting blood glucose for diabetes. Familial aggregation studies suggest a strong genetic basis for OSA with the odds of an individual having OSA increasing with the number of family members affected. However, heritability is substantial (30-40%); with 60% of the genetic basis for AHI arising through pathways independent of obesity.

The etiology for OSA is therefore complex, related to anatomic factors (i.e., craniofacial features and weight), neuromuscular factors (i.e., ventilatory stability and airway collapsibility) and environmental factors (i.e., tobacco, alcohol use, and medications). Better understanding of the intermediate pathways that lead to OSA may allow for better screening, risk stratification, and more targeted intervention. In this effort, genomics research is attempting to better characterize the genetic variability of the OSA population.

Trends in medicine have been moving away from the traditional symptoms-based approach toward a more systems-based approach. The effort in systems-based medicine is to better understand intermediary

pathways to disease and to better characterize patients through genomics and molecular diagnostics so as to "personalize" medicine – to stratify patient groups to target those at high risk of disease and to identify those more likely to benefit from therapy.

The role of genomics in sleep medicine is still in its infancy but advances, particularly in sleep neurobiology and restless legs syndrome, have been notable. Linkage studies done in OSA patients have identified the hypocretin 2 receptor gene on chromosome 6 as a candidate gene. Other candidate genes that have been implicated to be associated with OSA include ApoE, angiotensin converting enzyme, TNF α , IL-6, and serotonergic pathway genes. In an effort to identify potential biomarkers for screening, Dr. Redline reported a pilot study in which a urinary protein was able to discriminate between OSA subjects and controls. Although her results are preliminary and need to be replicated with a larger sample, they offer the promise of a simple screening protein for OSA.

New studies are seeking to establish methodologies and resources to expand the study of genomics in sleep medicine. In one effort, ten National Heart, Lung and Blood Institute cohorts are creating a large bank of genetic and phenotypic data for study. Researchers are also working on a sleep and circadian rhythm single nucleotide polymorphism chip to screen for gene associations for sleep disorders.

To fully realize the promise of genomics, sleep medicine must follow a new road. This requires the development of large samples for gene discovery, well defined experiments and translational research opportunities.

Summarized by Anjali Ahn, MD

A Health Plan Medical Director Perspective on Sleep Medicine

Presented by Harold A. Picken, MD, MPH

*Vice President of Health Operations
Associate Chief Medical Officer
Blue Cross Blue Shield of Rhode Island, Inc.*

The early portion of his discussion centered on the quality standards in Rhode Island for sleep medicine. Beginning April 1, 2010, sleep medicine physicians need to be board certified in sleep medicine in order to interpret sleep studies billed to BCBS and sleep centers and laboratories must be AASM-accredited in order to run studies billed to BCBS. These standards were drawn from similar standards issued by Medicare following their review of sleep medicine in 2008. Dr. Picken polled some of his BCBS colleagues in other states regarding their standards for sleep medicine and it was clear that Sleep Medicine is not being closely examined in some states. As of yet, many insurance organizations have

not had discussions about physician board certification, lab accreditation, or payment for home monitoring, much less changed their standards.

Insurance companies are looking at new models for payment. Current models of care management tend to involve complex and fragmented provider-patient interactions. One new model is the Patient-Centered Medical Home (PCMH). In this model the PCP or relevant specialist serves as the “quarterback”, coordinating and navigating care.

The insurance industry would also prefer to evaluate new models that don't just pay for testing, but would pay for “added value to a patient's life” with an increased focus on clinical outcomes. In the PCMH model, physicians would be rewarded for coordinating care and treatment compliance. Dr. Picken noted that this model increased the accountability of physicians, by rewarding change in outcome rather than just performing a billable action. Health insurance companies are continuing to re-think their products, he said, noting that one new model had a very high deductible, but members could generate credit back against their deductible for improving their health practices (having a colonoscopy at the right age, visiting their diabetic doctor, etc). This type of model generated a better health response from many of the patients involved in a small trial.

To make these changes, specialists and health care plans need to partner in recognition of mutual need and benefit. Care management models need to be evidence based and plans must demonstrate to their purchasers/consumers a tangible tie between clinical outcomes and reimbursement.

In closing, he suggested that sleep medicine as a field should improve its metrics in terms of the health outcomes associated with the diagnosis of, treatment of, and compliance with treatments for, sleep disorders. He recommended a focus on clinical outcomes efficacy and tying these outcomes to the reimbursement model. Sleep specialists need to take a broad view to understand how sleep medicine fits within a network of healthcare delivery and develop a clear vision of the specialist's role.

Summarized by Douglas Kirsch, MD



CEO CORNER

Paul S.Valentine
President and
Chief Executive Officer

This past September, Sleep HealthCenters hosted its 3rd Annual Future of Clinical Sleep Medicine. Larry Epstein, Chief Medical Officer for Sleep HealthCenters, led a group of distinguished sleep clinicians and scientists from medical campuses including Harvard, Tufts, Johns Hopkins and Case Western to discuss how recent developments in sleep medicine impact and affect healthcare today. Topics ranged from recent sleep-related transportation accidents to the gene researchers have newly identified as controlling the amount of sleep a person needs. We have recapped the four key presentations in this newsletter. If you are interested in joining us next September for the 4th Annual Future of Clinical Sleep Medicine forum, drop us a line and we will be sure you receive an invitation to this important and well-attended event.

Sleep HealthCenters will be getting a new look – starting with a new logo. You will begin to see that and many additional changes incorporating our new look in the coming months.

In other big Sleep HealthCenters news, we are pleased to announce we have joined forces with REM Medical of Arizona. As part of a focused strategy to provide a national network of high-quality, comprehensive

sleep medicine centers, we are bringing together two sleep companies dedicated to elevating the quality of care in sleep medicine and pursuing a path of innovation to meet the growing sleep needs of the population.

Both companies have nationally-recognized sleep physician leadership offering the highest standards in sleep medicine. Each organization participates in clinical research with nationally-recognized principal investigative teams supporting pharmaceutical and device sponsors on next-generation sleep disorder treatments. The two organizations also bring significant innovation to the newly-merged company through their respective offerings of sleep wellness programs for employers and payers.

As a result of the merger, we are pleased to welcome new members to our senior management team. Russell Benaroya has assumed the position of Chief Development Officer and Eric Page is our new Chief Operating Officer. Larry Epstein continues as our senior clinical leader in his role as Chief Medical Officer. Steve Harvey remains our Chief Financial Officer.

We are happy to continue to provide sleep medicine services to your patients. Please do not hesitate to contact us if you have any questions. For more information about Sleep HealthCenters, please visit www.sleephealth.com.

We hope you have a terrific holiday season!

Research Activities

Sleep HealthCenters is proud to work with some of the premier sleep researchers in the country. The following research studies are currently underway in conjunction with our partners. To take part in a study or for more information, please contact us toll free at 877-SLEEPHC (877-753-3742). For a full listing of our research activities, please visit www.sleephealth.com/research-studies.

Are You On CPAP?

Have you been diagnosed with Central Sleep Apnea? If so, we would like you to participate in our research study. Subjects will be asked to sleep one night in our sleep lab located at 1505 Commonwealth Avenue in Brighton, Massachusetts, and will receive up to \$300 in compensation.

Please call Barbara for more information at 877-476-6732 x5.

Are You Having Surgery to Treat Your Sleep Apnea?

If so, researchers at Brigham and Women's Hospital Division of Sleep Medicine would like to measure how much the surgery opens your airway. This will help us better understand the role of surgery in sleep apnea management. To participate you must:

- be between the ages of 21 and 65
- have no lung problems and not take any medication which affects breathing or sleep (including birth control)
- be planning to have upper airway surgery

Receive up to \$750 for participation. For information on participating in this study, call Lauren Hess at 617-732-8976.

Do You have Insomnia?

Are you between the ages of 21 and 65? Brigham and Women's Hospital is looking for people who have been diagnosed with insomnia to participate in a research study. The study involves approximately two weeks of at-home assessments and one 9-hour visit in our laboratory. Up to four screening visits may be required prior to beginning the study. Receive up to \$300 at the completion of the study.

For more information, please contact Julia at 617-732-6460 or email jshekeleton@partners.org.

Do You Suffer from Restless Legs Syndrome?

Achy. Tingly. Twitchy. Fidgety. That's how your legs may feel if you have Restless Legs Syndrome (RLS). The Sleep HealthCenter associated with Brigham and Women's Hospital in Brighton is enrolling patients in a research study for people who are currently being treated for RLS. Compensation will be provided for your time.

If interested, please call Kate at 617-783-1496 x115 or email SleepResearch@sleephealth.com.