# Best of Sleep Medicine 2012

## An Annual Collection of Scientific Literature

## TEOFILO LEE-CHIONG

# Best of
# Sleep
# Medicine
# 2012

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## What – when – how - who?

Another year; another edition of Best of. Nonetheless, same questions unanswered; same uncertainties; same challenges of incorporating evidence-based protocols in the field of Sleep Medicine. Five years ago, I listed several topics in the sleep sciences that needed (better) answers -

Insomnia
Clinical Features
1. What are the risk factors that predict the development of psychophysiologic insomnia? Insomnia in patients with depression?
2. What factors are predictive of relapse of insomnia following successful management of the condition?
Evaluation
1. How useful are sleep logs and diaries in the evaluation of insomnia?
2. What is the role of actigraphy in evaluation of patients with insomnia?
3. When is polysomnography indicated in the evaluation of insomnia?
Therapy
1. How useful is sleep hygiene education alone in the treatment of chronic primary insomnia? Chronic comorbid insomnia?
2. How effective is sleep restriction in the therapy of chronic insomnia? Chronic comorbid insomnia?
3. What are the best relaxation techniques for treating chronic insomnia?
4. When is paradoxical intention useful in treating patients with chronic insomnia?
5. Are there significant differences between individual sessions compared to group sessions for cognitive behavioral therapy of chronic insomnia?
6. What are the data regarding efficacy and safety of chronic regular use of benzodiazepines for insomnia?
7. What measures can be used to avoid relapse or rebound insomnia following discontinuation of chronic use of benzodiazepines?
8. Are sedating antidepressants effective and safe as therapy of chronic insomnia?
9. Are sedating antihistamines effective and safe when used for the treatment of acute and chronic insomnia?
10. Which sedating antipsychotic agents are effective and safe as therapy for chronic insomnia?
11. Are there efficacy and safety data on the use of melatonin for chronic insomnia?
12. Which of the various botanical compounds has proven efficacy and safety data for use in patients with acute or chronic insomnia?
13. What kind of follow-up is necessary following initiation of therapy for chronic insomnia?

Excessive Sleepiness
Clinical Features
1. What factors predict a higher risk of vehicular accidents in patients with complaints of excessive sleepiness?
Evaluation
1. Which of the currently available subjective sleepiness scales can most reliably predict a moderate- to high-risk of vehicular accidents related to excessive sleepiness?
2. What is the role of HLA analysis in the evaluation of patients with suspected narcolepsy?

3. When is cerebrospinal fluid hypocretin-1 determination useful for patients with suspected narcolepsy?
4. How useful is actigraphy in the evaluation of patients with complaints of excessive sleepiness?
5. What is the role of MSLT in the evaluation of excessive sleepiness? MWT? Psychomotor vigilance task testing? Driving simulators?
6. What is the best way to evaluate persons with excessive sleepiness who are employed in the transportation industry (e.g., pilots, bus drivers, interstate truck drivers)?

Therapy
1. How useful is sleep extension as therapy for the different causes of excessive sleepiness?
2. How effective is scheduled napping in reversing excessive sleepiness?
3. How effective and safe is caffeine as therapy of excessive sleepiness?
4. Can physical activity effectively reverse excessive sleepiness?
5. How effective and safe are the various stimulant agents in treating excessive sleepiness?
6. Are the newer wake-promoting agents more effective and safer than older psychostimulants as therapy of excessive sleepiness?
7. Which agents have proven efficacy in the treatment of cataplexy in patients with narcolepsy?

## Sleep Related Breathing Disorders
*Snoring*
Clinical Features
1. What are the consequences of untreated chronic snoring?

Evaluation
1. When is polysomnography indicated in the evaluation of patients presenting with snoring? Upper airway imaging, including cephalometrics? Acoustic imaging reflectometry?

Therapy
1. How effective and safe are nasal decongestants and steroids as therapy of snoring? Internal and external nasal dilators? Oral devices? Nasal surgery? Laser assisted uvulopalatoplasty or uvulopalatopharyngoplasty? Palatal implants? Radio frequency tissue ablation?

*Obstructive Sleep Apnea*
Clinical Features
1. What factors increase the risk of developing obstructive sleep apnea? Among women during menopause?
2. What factors can predict the development of complex sleep apnea?

Evaluation
1. What is the role of structured questionnaires in the evaluation of obstructive sleep apnea? Upper airway imaging including cephalometrics? Home continuous nocturnal pulse oximetry?
2. What is the role of attended vs. unattended in-laboratory polysomnography in the evaluation of obstructive sleep apnea? Portable sleep monitoring? Automated continuous positive airway pressure analysis?

Therapy
1. Are nasal decongestants and steroids effective as therapy for obstructive sleep apnea? Positional therapy? Weight management? Pharmacologic therapy?
2. Should mild OSA be treated?
3. What long-term beneficial effects are associated with positive airway pressure therapy for obstructive sleep apnea?

4. What are the advantages of expiratory pressure release devices compared to conventional continuous positive airway pressure in the therapy of obstructive sleep apnea?
5. What are the indications for bilevel positive airway pressure therapy in patients with obstructive sleep apnea?
6. When should automated continuous positive airway pressure devices be used in the evaluation or therapy of patients with obstructive sleep apnea?
7. What is the role of adaptive servo ventilation in the treatment of sleep-related breathing disorders?
8. What is the best way to determine the optimal positive airway pressure?
9. What factors influence compliance to positive airway pressure therapy?
10. Does the use of heated humidification improve positive airway pressure compliance? Systematic education? Pressure ramping?
11. Are hypnotic agents useful for helping patients acclimatize to positive airway pressure therapy?
12. What is the role of behavioral therapy in improving compliance to positive airway pressure therapy?
13. Does objective monitoring of compliance improve patient adherence to positive airway pressure therapy?
14. How effective and safe are mandibular advancement oral devices for mild to moderate obstructive sleep apnea?
15. How effective and safe are oral devices for severe obstructive sleep apnea?
16. What factors predict the success, failure or subsequent complications following oral device therapy for obstructive sleep apnea?
17. Is a repeat polysomnography indicated following oral device therapy for obstructive sleep apnea?
18. How effective and safe are tongue retaining oral devices for mild to moderate obstructive sleep apnea?
19. Is nasal surgery effective and safe as therapy of obstructive sleep apnea? Radiofrequency tissue ablation? Palatal implants? Uvulopalatopharyngoplasty? Base of tongue surgeries? Maxillary-mandibular advancement?
20. What combination of surgical procedures offers the highest likelihood of therapeutic success of obstructive sleep apnea?
21. When is follow-up evaluation appropriate after upper airway surgery for obstructive sleep apnea?

*Central Sleep Apnea*
Clinical Features
1. What factors increase the risk of developing Cheyne Stokes respiration?
Evaluation
1. What is the role of continuous home nocturnal pulse oximetry in the evaluation of patients with suspected Cheyne Stokes respiration?
2. How reliable is a single night polysomnography in the evaluation of patients with suspected Cheyne Stokes respiration?
3. Are portable sleep studies useful in the evaluation of patients with suspected Cheyne Stokes respiration?
Therapy
1. How effective is oxygen therapy for central sleep apnea? Adaptive servo ventilation?
2. What therapies are effective for Cheyne Stokes respiration?

<u>Circadian Rhythm Sleep Disorders</u>
Clinical Features
1. What risk factors predict susceptibility to jet lag? Shift work disorder?
Evaluation
1. What is the role of sleep logs in the evaluation of circadian rhythm sleep disorders? Horne-Ostberg scale? Actigraphy? Markers of circadian rhythms (e.g., dim light melatonin onset or minimum core temperature)? Polysomnography? Portable sleep monitoring?
Therapy
1. How effective is chronotherapy for delayed sleep phase syndrome? Phototherapy? Melatonin? Hypnotic agents? Vitamin B12?
2. How effective is chronotherapy for advanced sleep phase syndrome? Phototherapy, melatonin or hypnotic agents?
3. What therapies are effective for irregular sleep-wake pattern? Non-24 hour rhythms?
4. What measures can prevent or minimize symptoms of Jet lag? Facilitate recovery?
5. What therapies are effective in improving daytime sleep in patients with shift work disorder? Counteract excessive sleepiness during shift work?

<u>Restless Legs Syndrome/Periodic Limb Movement Disorder</u>
Clinical Features
1. What risk factors predict the development of restless legs syndrome?
Evaluation
1. What laboratory tests are useful in the evaluation of patients with restless legs syndrome/periodic limb movement disorder?
2. When is polysomnography indicated in the evaluation of patients with restless legs syndrome?
3. How reliable is a single polysomnographic study in detecting the presence of periodic limb movements during sleep?
4. What is the role of immobilization tests in the evaluation of patients with restless legs syndrome?
Therapy
1. Are exercise and physical therapy helpful for the therapy of restless legs syndrome?
2. How useful are dopamine precursors or agonists in the therapy of restless legs syndrome or periodic limb movement disorder? Benzodiazepine agents or anticonvulsants? Iron supplementation? Opioid agents?

- sadly, half a decade later, many (and more others) remain unanswered.

Once again, I am indebted to the many authors for the excellent commentaries they have generously provided. This book is dedicated to Dolores Grace Zamudio and Zoe Lee-Chiong.


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## Pediatric Sleep Medicine

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**183  Delaying school starting time by one hour: some effects on attention levels in adolescents.** Lufi D, Tzischinsky O, Hadar S. *J Clin Sleep Med. 2011 Apr 15;7(2):137-43.*

**186  Does an intervention that improves infant sleep also improve overweight at age 6? Follow-up of a randomised trial.** Wake M, Price A, Clifford S, Ukoumunne OC, Hiscock H. *Arch Dis Child. 2011 Jun;96(6):526-32.*

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## Aging

**200  Zolpidem and zopiclone impair similarly monotonous driving performance after a single nighttime intake in aged subjects.** Bocca ML, Marie S, Lelong-Boulouard V, Bertran F, Couque C, Desfemmes T, Berthelon C, Amato JN, Moessinger M, Paillet-Loilier M, Coquerel A, Denise P. *Psychopharmacology (Berl). 2011 Apr;214(3):699-706.*

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# Sleep Neurobiology

**Transcranial electrical currents to probe EEG brain rhythms and memory consolidation during sleep in humans.** Marshall L, Kirov R, Brade J, Mölle M, Born J. *PLoS One. 2011 Feb 14;6(2):e16905.*

*How does 5 Hz theta-transcranial direct current stimulation affect brain wave activity?*

| *Subjects* | *Methods* | *Outcomes* |
|---|---|---|
| Healthy persons<br>• Regular sleep-wake cycle<br>• Medication-free<br>• Non-smokers<br>• Comparable education level<br><br>Experiment 1 (SWS): n = 25<br>• Gender: 56% F<br>• Age: 18-35 yrs (mean 23.9)<br><br>Experiment 2 (REM sleep): n = 16<br>• Gender: 50% F<br>• Age: 21-30 yrs (mean 24.3) | Assessments:<br>• PSG (EEG [Fz, C3, Cz, C4, P3, Pz, P4], vertical and horizontal EOG, EMG)<br>• Anodal 5 Hz theta- TDCS<br>   o Amplitude fluctuated between 0-260 μA<br>   o Five times 5 min stimulation every 6 minutes<br>• Declarative (word paired-associates) and procedural (finger sequence tapping, mirror tracing) memory tasks | Effect of 5 Hz theta-TDCS<br>• During SWS<br>   o EEG power spectral analyses: Decrease in EEG slow oscillation and spindle band activity<br>   o Decrease in declarative memory performance<br>   o PSG: Lightens sleep<br>• During REM sleep<br>   o EEG power spectral analyses: Increase in EEG gamma band activity |

EEG: electroencephalogram; EMG: electromyogram; EOG: electrooculogram; NREM: non-rapid eye movement sleep; PSG: polysomnography; REM: rapid eye movement; SOA: slow oscillatory activity; SWS: slow wave sleep; TDCS: transcranial direct current stimulation

### Conclusion
Anodal 5 Hz theta-transcranial direct current stimulation during sleep specifically modulated cortical network activity and memory function dependent upon brain state and the characteristic electroencephalographic rhythms.

### Commentary
This study investigates the effects of tDCS on brain activity during sleep. The different sleep stages play an important role in consolidation of declarative as well as procedural memory.[1] Slow-wave sleep (SWS) mostly occurs in the first half of the night and is characterized by slow oscillatory activity below 1 Hz in the human electroencephalogram (EEG). By contrast, rapid eye movement (REM) sleep is predominant in the later part of the night. While retention of declarative memories has been associated with processes reflected mostly by sleep spindle- and slow oscillatory EEG activity,[1,2] REM sleep is deemed more important for consolidation of procedural memories, although data are inconsistent.[1,3]

In this study anodal tDCS oscillating at a frequency of 5 Hz theta activity was applied during sleep bilaterally at frontolateral locations (F3, F4) and at the mastoids. In humans, theta oscillations occur in REM sleep (and wakefulness), but not in SWS.[4,5] In a first experiment, subjects were stimulated during SWS. In a second experiment, with different subjects stimulation was applied during REM sleep within the second half of the night. Theta-tDCS at the transition into SWS reduced EEG power in the slow oscillation (< 1 Hz), delta frequency (1 – 4 Hz) as well as the frontal slow spindle frequency (8 – 12 Hz) band ($P < 0.01$ for all). Application of theta-tDCS during SWS sleep lightened sleep acutely during the 1-minute post-stimulation intervals: time spent in SWS was reduced ($P < 0.001$), while time spent in stage 2 sleep was increased ($P < 0.005$). Most importantly, at the behavioral level, theta-tDCS during SWS sleep strongly impaired the consolidation of declarative memory. Consolidation of the procedural memory task, however, was not affected by the stimulation.

In contrast to stimulation at the transition into SWS (first experiment), theta-tDCS during REM sleep did not affect EEG spectral power in frequencies below 15 Hz, but strongly increased faster gamma band activity (25 – 45 Hz). Theta-tDCS during REM sleep had no effect on sleep architecture during the later half of the night, and also failed to affect consolidation of both the declarative and procedural memories.

In a previous study[2] application at the transition into SWS of anodal slow oscillatory-tDCS (0.75 Hz, which is conform to the frequency of the endogenous slow oscillatory activity in humans) enhanced slow oscillatory and slow spindle activity. Moreover, slow oscillation stimulation had a positive effect on the consolidation of declarative memories. Thus, at the transition into SWS during which endogenous slow oscillatory activity emerges, slow oscillatory-tDCS and theta-tDCS revealed opposite effects on both post-stimulation endogenous EEG activity and behavior. During REM sleep in which EEG activity in the theta frequency is more likely to be enhanced, 5 Hz theta-tDCS facilitated gamma band activity, which probably reflects an inherent coupling between theta and gamma network activity, as can be observed in the human neocortex for memory formation processes during waking.[6]

The specific effect of frequency with oscillating transcranial electric stimulation is supported by other recent studies.[7-9] Taken together, data convincingly show the strong dependence of EEG-activity and behavioral effects on the tuning between frequency of oscillatory-tDCS and ongoing activity of the cortical network. This renders both the frequency of oscillatory-tDCS as well as the timing in a dynamically changing cortical network relevant for stimulation outcomes. These features make oscillatory-tDCS a powerful tool to investigate non-invasively the neurophysiologic and/or functional relevance of specific EEG rhythms.

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# Sleep Deprivation and Fragmentation

**Acute sleep deprivation reduces energy expenditure in healthy men.** Benedict C, Hallschmid M, Lassen A, Mahnke C, Schultes B, Schiöth HB, Born J, Lange T. *Am J Clin Nutr. 2011 Jun;93(6):1229-36.*

*Does acute total sleep deprivation modify subsequent daytime energy expenditure?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 14 healthy males<br>• Age: 22.6 ± 0.8 yrs<br>• BMI: 23.9 ± 0.5 kg/m$^2$ | Randomized 2-condition crossover study<br><br>Protocol for each 24-hr session (regular sleep-wake cycle or SD):<br>• Baseline period (1800 h – 2300 h)<br>• Nighttime intervention period (2300 h –0700 h) in which subjects slept or stayed awake<br>• Postintervention period (0700 h–1800 h)<br><br>Assessments:<br>• Resting and postprandial energy expenditure (by indirect calorimetry) on the morning after regular sleep or SD<br>• Repeated measures of ghrelin, leptin, norepinephrine, cortisol, thyreotropin, glucose and insulin over 24 h period<br>• Free-choice food intake from a buffet in the late afternoon<br>• Core body temperature | Compared to 8-hr sleep duration, total SD was associated with:<br>• Decreased resting and postprandial energy expenditure assessed on the subsequent morning by 5%* and 20%** respectively<br>• Increased morning plasma ghrelin concentrations***<br>• Increased nocturnal and daytime levels of thyreotropin, cortisol and norepinephrine[#]<br>• Increased morning postprandial plasma glucose concentrations[##]<br>• Higher CBT during the night, and this pattern reversed on the subsequent day<br><br>Variable changes in food intake were noted and did not differ between sleep and wake conditions |

SD: sleep deprivation; *$P < 0.05$; **$P < 0.0001$; ***$P < 0.02$; [#]$P < 0.05$; [##]$P < 0.05$

*Conclusion*
One night of total sleep deprivation reduced energy expenditure the next morning.

*Commentary*
Levels of morbid obesity are rising throughout the Western world. Although high calorie content of food and advertising play a large part, an additional factor, chronic sleep deprivation, may also contribute. Sleep deprivation has been found to stimulate appetite and actual food intake.[1,2] In addition, sleep deprivation appears to increase the rewarding property of food stimuli, as suggested by a recent functional magnetic resonance imaging study.[3] These effects of laboratory sleep deprivation are hypothesized to result from sleep deprivation-induced increases in morning plasma ghrelin concentrations.[4] This hormone is mainly produced by the stomach and causes hyperphagia while decreasing energy expenditure.[5]

Taken together, these data suggest that a chronic lack of sleep may produce obesity by increasing food intake. However, the reader should bear in mind that weight gain requires that, over a long period, the energy intake exceeds the energy expenditure (also known as positive energy balance). Against this background, we aimed to elucidate the role of sleep loss on energy expenditure in a homogenous sample of healthy young men. To this aim, according to a randomized and balanced crossover design, all subject participated in two 24-h conditions (sleep and TSD), each of which comprised a baseline period of wakefulness (1800 h–2300 h) followed by a nighttime intervention period (2300 h–0700 h) in which subjects slept or stayed awake, and a post-intervention period (0700 h–1800 h). In the morning after regular sleep or TSD. Energy expenditure was measured by indirect calorimetry (IC) before and after a standard breakfast. We also measured free-choice food intakes from a rich test meal buffet offered in the late afternoon, and took blood samples to measure hormones involved in the regulation of whole-body energy homeostasis.

The primary finding was that a single night of missed sleep reduced the resting metabolic rate (fasting energy expenditure expressed as kilojoules per minute) by ~5 % and the postprandial metabolic rate (i.e., the thermic effect of food) by ~20 % relative to the 8-hour sleep condition. Compared to sleep, TSD was also associated with increased morning plasma ghrelin concentrations. Changes in food intakes were variable, and no differences between wake and sleep conditions were detected.

Based on our results, it is tempting to speculate that a drop in energy expenditure because of sleep loss may constitute a mechanism that, in conjunction with decreased physical activity[6] and an increased food intake[7] after sleep deprivation, may foster the association between chronic sleep curtailment and obesity. However, using partial sleep deprivation paradigms, others did not observe significant reductions in the 24-h energy expenditure.[2,8] This suggests that the energy expenditure-lowering effect of TSD is a transient phenomenon that might be counterbalanced across the day. In line with this view, and considering the close relation between the metabolic rate and core body temperature,[9] 24-h measurements of core body temperature did not differ between the sleep and TSD conditions in our study. Nevertheless, considering that the reduced postprandial metabolic rate in the morning after TSD indicates that the metabolic efficiency to store nutrients is increased in a time during which sleep deprivation exerts its strongest enhancing effects on hunger and appetite, our data provide a potential mechanism by which a chronic lack of sleep increases the risk to develop obesity in humans. Supporting this assumption, previous research has shown that high-fat feeding provided at the incorrect circadian time (i.e., when animals usually rest) leads to greater weight gain in mice than isocaloric feeding at the normal circadian time.[10]

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**Intermittent-sprint performance and muscle glycogen after 30 h of sleep deprivation.** Skein M, Duffield R, Edge J, Short MJ, Mündel T. *Med Sci Sports Exerc. 2011 Jul;43(7):1301-11.*

*Does 30-h sleep deprivation and associated changes in mood and muscle glycogen content affect self-paced, intermittent-sprint performance, pacing strategies and neuromuscular function?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 10 male subjects<br>• Team-sport athletes<br>• Age: 21 ± 3 yrs<br>• Wt: 81.5 ± 9.5 kg<br>• Height: 178.6 ± 9.2 cm<br>• VO2max: 56.8 ± 5.3 ml·kg$^{-1}$·min$^{-1}$<br>• Minimal variation in sleep duration and quality | Protocol included:<br>• 1 (single day) baseline session<br>• 2 counter-balanced, consecutive-day exercise sessions (30-min graded exercise run on a treadmill and 50-min self-paced ISE protocol) separated by either normal night sleep or SD<br><br>Assessments:<br>• 15-m maximal sprint performance<br>• Distance covered (m) during sub-maximal exercise between sprints<br>• Sleep quality (questionnaire) and duration (actigraphy) measured from 2 days prior until the end of trials (~ 60 h)<br>• Muscle glycogen content from *vastus lateralis* biopsy samples<br>• Pre and post exercise maximal isometric knee extensor contractions (measurements of voluntary force and activation)<br>• HR, core temperature, capillary blood lactate and glucose, RPE and POMS questionnaire | Effects of SD included:<br>• Slower sprint times<br>• Less bounding distance covered<br>• No effect on total distance covered during sub-maximal efforts<br>• Less distance covered during initial and final 10 min of the ISE protocol<br>• Reduced maximal voluntary force and voluntary activation<br>• Reduced pre-exercise muscle glycogen<br>• Increased negative POMS<br>• No effect on RPE |

HR: heart rate; ISE: intermittent sprint exercise; POMS: Profile of Mood States; RPE: Rating of Perceived Exertion; SD: sleep deprivation

*Conclusion*
Sleep deprivation and the associated reduction in muscle glycogen concentration and mood state profile resulted in significantly reduced neuromuscular recruitment and intermittent-sprint performance in male, team-sport athletes.

*Commentary*
Team sport athletes are often exposed to circumstances that are not conducive for sufficient sleep quantity or quality.[1] As such, team sport athletes are susceptible to environments resulting in sleep deprivation (SD) before or after training and/or competition. The degree of SD has been shown to range from minor disruptions, such as late bedtimes or early rises, to extensive (overnight) SD.[1] As sleep is reported to be important for the restoration of metabolic processes such as fuel substrates,[2] regulation of hormone secretion such as cortisol and growth hormone and maintaining cognition such as memory and reaction times,[3] SD may have a deleterious effect on team sport performance. Although the effect of SD on team sport performance has not been examined, previous literature that incorporates physical components common to team sports such as self-paced exercise,[4] muscle strength,[5] and lower body power[6] have all been reported to be reduced following SD.

During the present study, subjects completed a single-day baseline session followed by two consecutive-day experimental trials that included an identical exercise protocol. During the evening between the consecutive-day experimental trials, subjects were randomly assigned a normal night sleep (CONT; 8.5 $\pm$ 1.7 h) or sleep deprivation (SD; 0 $\pm$ 0 h) that accumulated to 30-h sleep deprivation. The exercise protocol included 30 min graded treadmill running for 10 min at 60, 70 and 80% $VO_{2max}$ each, followed by a 10 min recovery and a 50 min self-paced, intermittent-sprint exercise (ISE) protocol. The ISE protocol included repeated 15 m maximal sprint every minute, interspersed by sub-maximal efforts of hard running, jogging, walking or bounding for the remainder of the minute. Profile of Mood States (POMS) and neuromuscular tests of 15 maximal voluntary contractions were recorded pre- and post-exercise for assessment of voluntary force and activation on all days. Heart rate, core temperature and rating of perceived exertion (RPE) were recorded throughout each exercise protocol.

Results indicate that 30-h SD has a negative effect on intermittent-sprint performance in male team-sport athletes. More specifically, maximal sprint times were significantly slower following SD compared to CONT. Total distance covered during the sub-maximal efforts (hard running, jogging and walking) were not different between conditions; however, analysis of pacing strategies indicate less distance was covered during the initial and final 10 min of the protocol due to reductions in hard running distance covered during SD. POMS questionnaires highlighted that SD had a negative effect on mood states, while muscle biopsy analysis revealed that pre-exercise muscle glycogen content was significantly reduced following SD compared to CONT. Finally, voluntary force during the maximal isometric contractions of the right knee extensors was reduced following SD due to a reduction in muscle recruitment (voluntary activation).

The present study indicates that during repeated sprint exercise, the deleterious effects of sleep loss on perceptual mood states may have resulted in a decline in neuromuscular recruitment pre- and post-exercise, which may relate to the reduction in pacing strategies observed during sub-maximal and maximal sprint performance. Previously, Oliver et al.[4] have reported reductions in 30 min self-paced exercise performance following 30-h SD; however, Martin and Haney[7] have reported no difference in blinded changes in treadmill grade to maintain a set RPE following either a controlled night sleep or 30-h

SD. These studies, in conjunction with the present study, indicate when the athlete knows the effects of SD on exercise intensity selection, a conscious down-regulation of exercise performance may be present.

A second theory that explains the reduced intermittent-sprint performance is the decreased muscle glycogen concentration following SD. While the differences in glycogen content were significant, the difference in pre-exercise values was unlikely to be physiologically significant to exclusively explain the difference in intermittent-sprint performance. Therefore, it is likely SD itself in conjunction with the reduced glycogen content and the negative mood state profile associated with the sleep loss were also responsible for the reduction in exercise performance, pacing strategies, maximal voluntary force and recruitment in team sport athletes. However, the level of contribution each of these factors had on performance is unclear.

Notwithstanding, team sport athletes should engage in environments that are conducive to sleep before and after competition to avoid potentially suffering acute SD and reducing subsequent exercise performance. If SD cannot be avoided, athletes should supplement their diet with additional carbohydrate to counter the minor but potentially negative effects sleep loss has on muscle glycogen content. Further, interventions that improve perceived mood states might also be of benefit to athletes when in a sleep-deprived state.

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**Partial sleep deprivation reduces phase advances to light in humans.** Burgess HJ. *J Biol Rhythms. 2010 Dec;25(6):460-8.*

*Does partial sleep deprivation affect circadian phase shifts in humans?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 13 young healthy individuals | Repeated-measures counterbalanced design study<br><br>Subjects underwent 2 study conditions (baseline sleep, dim-light circadian phase assessment, 3-day phase-advancing protocol with morning BL [4 30-min pulses of bright light (~5000 lux) separated by 30-min intervals of room light beginning at 8 hrs after DLMO] and another phase assessment):<br>• No SD: 8-hr sleep opportunity per night<br>• With partial SD: kept awake for 4 hr in near darkness (< 0.25 lux) followed by a 4-hr sleep opportunity per night | Average phase advance:<br>• Without SD: 1.8 ± 0.6 h<br>• With partial SD: 1.4 ± 0.6 h*<br><br>Partial SD reduced phase advances (ranging from 0.2 to 1.2 hrs) in 77% of subjects |

BL: bright light; DLMO: dim light melatonin onset; SD: sleep deprivation; *P < 0.05

*Conclusion*
Partial sleep deprivation reduced circadian phase shifts to bright light.

*Commentary*
In 2003, inspired by the growing scientific interest in the effects of short sleep on human physiology, Charmane Eastman and I designed a pilot study to simulate the effects of short nights on human circadian timing.[1] Specifically, we were interested in what happened when people delayed their bedtimes, because wake times were more likely to be fixed due to work and family responsibilities. So we asked people to go to bed at 10 pm for at least a week and in another condition to stay up until 1 am for at least a week. The two conditions were counterbalanced across subjects. Importantly, all subjects slept at home and so were exposed to realistic light intensities. We also asked the subjects to always wake at 7 am and get at least 5 minutes of outdoor light between 7-8 am each morning, to mimic the morning light exposure many of us receive each day. At the end of each condition the subjects came to our laboratory so we could measure their dim light melatonin onset (DLMO) – the most reliable marker of circadian timing in humans. We did not expect to see any effect of later bedtimes on circadian timing given the morning bright light exposure. After all, the morning bright light was potentially the brightest light these subjects received each day and it occurred at a time when the human circadian clock is relatively sensitive to light.[2] So we were quite

surprised to find that staying up 3 hours later for at least a week delayed the DLMO by 0.6 hours – despite the daily morning bright light. The most parsimonious explanation of this result was that humans are more sensitive to the dim evening ambient light in their homes than previously appreciated (~ 40 lux on average).

In a follow up repeated measures study, we asked subjects to follow a 6-hour sleep schedule for 2 weeks at home versus a 9-hour sleep schedule for 2 weeks at home. After each condition, we examined the phase advance in the DLMO in response to bright morning light in the laboratory.[3] We found phase advances and subsequently phase delays to late night light[4] were dramatically reduced by 40-50% in the short versus long sleep condition. These findings suggested that the societal trend towards shorter sleep episodes was inadvertently reducing circadian responsiveness to light. This reduced responsiveness to light could lead to circadian misalignment and the associated negative health consequences.[5-8] The question was how were short nights reducing circadian responsiveness to light? We considered three probable causes of the reduced circadian response to light: (1) the partial sleep deprivation during the short nights,[9,10] (2) the additional evening light exposure during the short nights, and (3) the photoperiodic history of short nights.[11] In investigating the first potential mechanism, we found that partial sleep deprivation did reduce the circadian response to morning light,[12] but the effect was modest and could not explain the 40-50% reduction in phase shift magnitude that we observed in our original study. In terms of the second potential mechanism, we are completing a study where we minimized sleep deprivation but increased the duration of evening light exposure. Preliminary results suggest that chronic exposure to relatively dim ambient light in the evening can significantly reduce the circadian system's response to morning light – potentially explaining the results of our very first pilot study. We are now just beginning to investigate the third potential mechanism of photoperiodic history by studying habitual short and long sleepers and their response to bright morning light. We remain very interested in the interactions between voluntary social human behavior and home lighting, and their effects on the functioning of the human circadian clock.

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**Short sleep duration increases energy intakes but does not change energy expenditure in normal-weight individuals.** St-Onge MP, Roberts AL, Chen J, Kelleman M, O'Keeffe M, RoyChoudhury A, Jones PJ. *Am J Clin Nutr. 2011 Aug;94(2):410-6.*

*Does short sleep duration affect energy balance?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 27 participants:<br>• Gender: 48% F<br>• Age: 35.3 ± 5.2 y<br>• BMI: 23.6 ± 1.3 kg/m$^2$<br>• Regular sleep duration: 7-9 hrs per night | Randomized crossover study<br><br>All subjects underwent, in random order, for nights each of either:<br>• Short sleep condition: 4 hrs per night (1-5 AM)<br>• Habitual sleep condition: 9 hrs per night (10 PM-7 AM)<br><br>Protocol for each 6-day period:<br>• Controlled feeding of weight maintaining diet for days 1-4<br>• Ad libitum food intake on days 5-6<br><br>Assessments:<br>• Food intake (on day 5)<br>• Energy expenditure (doubly labeled water method) over each 6-day period<br>• RMR: indirect calorimetry on day 5 | Compared to 9-h bedtimes, short sleep resulted in:<br>• Greater total energy intake on day 5:<br>  ○ 4-h: 2813.6 ± 593.0 kcal<br>  ○ 9-h: 2517.7 ± 593.0 kcal*<br>• Higher total fat and saturated fat intakes<br>  ○ 4-h: 112 ± 35 and 37 ± 48 g<br>  ○ 9-h: 92 ± 35 and 28 ± 18 g<br>• No difference in RMR<br>  ○ 4-h: 1455.4 ± 129.0 kcal/d<br>  ○ 9-h: 1486.5 ± 129.5 kcal/d<br>• No difference in total energy expenditure<br>  ○ 4-h: 2589.2 ± 526.5 kcal/d<br>  ○ 9-h: 2611.1 ± 529.0 kcal/d<br>• No difference in 5-day energy balance |

BMI: body mass index; RMR: resting metabolic rate; *P = 0.023

### Conclusion
Four nights of reduced sleep, i.e., four hours nightly, led to greater energy and fat intakes with no compensatory change in energy expenditure levels in normal weight adults.

### Commentary
There is much epidemiological support for an association between sleep duration and obesity.[1, 2] Cross-sectional and longitudinal studies in both adults and children show greater prevalence of obesity and larger weight gains over time in short sleepers, generally < 7 h sleep/night for adults and at least 2 h shorter sleep than recommended for children, compared to normal sleep duration (8-9 h for adults and

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age-appropriate recommended sleep for children). Although epidemiological studies show associations between sleep and weight status, they do not provide causal proof. Clinical studies, however, have lent support to the hypothesis that short sleep duration can lead to weight gain and obesity. Studies by Spiegel et al. have shown that restricting sleep to 4 h/night leads to lower leptin and higher ghrelin levels with corresponding greater feelings of appetite being reported in normal weight men. These data suggest that short sleep leads to a hormonal profile that would predispose to increased food intake relative to normal sleep.

In order to determine whether sleep restriction leads to a positive energy balance, we enrolled 30 normal weight men and women to participate in a randomized, crossover controlled study of 2 sleep periods.[3] Under one condition, participants spent 9 h/night in bed (10 PM – 7 AM [habitual sleep]) whereas in the other condition they were restricted to 4 h/night in bed (1 AM – 5 AM [restricted sleep]). Each sleep period lasted 5 nights/6 days. During the first 4 days, food intake was fixed; the last 2 days were *ad libitum* feeding. Food intake and resting metabolic rate (RMR) were measured on day 5. Total energy expenditure over each 6-day period was assessed by doubly labeled water. Participants ate 296 kcal more after 4 nights of restricted sleep compared to habitual sleep. Although not significant, RMR was lower by 31 kcal/d after a period of restricted sleep relative to habitual sleep. However, when we assessed energy balance over the 5-day study period, including the 4 days of controlled feeding, the difference in energy balance between restricted and habitual sleep was not significant (179 kcal/d). Our food intake results support previous reports by Nedeltcheva et al.[4] and Brondel et al.[5] who also observed greater food intake during periods of restricted sleep compared to habitual sleep. Data on energy expenditure are mixed with some studies showing reduced RMR[6] and others showing increased total energy expenditure[7] with total sleep deprivation compared to 8-h sleep in men.

This study is the largest study to date to examine the impact of sleep duration on energy balance and the first to enroll sufficient men and women to examine sex differences. Our data suggested that the effect of sleep duration on food intake may be stronger in women than in men, supporting findings that the relationship between self-reported sleep duration and body composition may be stronger in women than in men.[8] More research is necessary to further examine potential sex differences in the role of sleep duration on energy balance.

Although information from clinical studies has come forth to explain the association between sleep duration and weight status observed in the epidemiological literature, much remains to be learned. There seems to be a consensus among clinical studies that restricting sleep increases food intake but the neuroendocrine controls involved in the regulation of food intake during altered sleep states remain to be fully elucidated. Data on the impact of sleep restriction on energy expenditure are mixed and the full effects are difficult to ascertain based in part on the complexity and variability of total energy expenditure. Total energy expenditure is composed of RMR, thermic effect of food, physical activity energy expenditure and non-exercise activity thermogenesis. Each of these components could be influenced by sleep state. In addition, the energy expended in each sleep stage and how selective changes in various sleep stages with sleep restriction affects sleeping metabolic rate remains to be studied. Finally, studies should be done in both men and women to determine whether components of the energy balance equation are differentially affected by sleep duration in men and women.

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**Sleep deprivation facilitates extinction of implicit fear generalization and physiological response to fear.**
Kuriyama K, Soshi T, Kim Y. *Biol Psychiatry. 2010 Dec 1;68(11):991-8.*

*Does total sleep deprivation affect physiologic response to fear and implicit fear recognition?*

| Subjects | Methods | Outcomes |
|---|---|---|
| Two groups of 14 healthy young subjects<br>• Control<br>• Sleep deprived (total SD) | Assessments of event recognition performances with aversive (motor vehicle accident films) and nonaversive episodic memory stimuli on days 1,3 and 10:<br>• Explicit event<br>• Implicit emotion<br>• Physiological response | Event recognition performances were similar in both groups<br><br>Compared to controls, SD extinguished:<br>• Generalization of implicit fear recognition for nonaversive stimuli (day 3)<br>• All physiological and generalized fear responses (days 3 and 10) |

SD: sleep deprivation

***Conclusion***
Sleep deprivation reduced effects of generalization of recognized and conditioned fear during sleep.

***Commentary***
Although evidence of sleep-dependent learning has been condensed across a wide variety of mnemonic domains, including emotional and fear-conditioned memory,[1] it remains unknown whether sleep deprivation helps prevent posttraumatic stress disorder (PTSD). In order to fill this gap, we examined the effects of total sleep deprivation on subsequent enhancement of contextual aversive memory in healthy humans. Specifically, we assessed 3 different modalities of recognition such as explicit event recognition, implicit fear recognition, and conditioned fear responses. It has been suggested that these recognition processes are separately consolidated during the subsequent sleep period.[2]

All subjects in a sleep-deprived (SD) and a sleep-controlled (SC) group were exposed to two categories of movie sets: one on safe driving and one on a motor vehicle accident. These movies showed a typical city street from the viewpoint of the driver. Subjects in the SD group were totally deprived of initial nocturnal sleep after movie exposure. Those in the SC group were allowed a normal night's sleep. Recognition tasks were conducted 3 times—one, three, and ten days—after the movie exposure. The subjects were presented with still pictures of the movie both with and without contextual cues. Event recognition and emotion recognition procedure were used to estimate explicit episodic and implicit emotion recognition, respectively. Skin conductance response was measured to assess fear conditioning via electrodes attached to the maniphalanx.

The results showed that sleep deprivation extinguished effects of the generalization of recognized and conditioned fear during sleep. A chief pathophysiology of PTSD has now been considered as hyper-consolidation or hypo-extinction of fearful emotion associated with a traumatic memory.[3] Thus, sleep deprivation after a traumatic event might help prevent PTSD symptoms by depriving the traumatized

individual of the neuroplasticity needed to consolidate fearful emotion associated with the traumatic event. However, event recognition was not affected by sleep deprivation in this study. This finding is inconsistent with previous research.[4] Aversive event memory may be more flexible; thus, recovery sleep on the day following sleep deprivation might compensate for disrupted memory consolidation. Psychological stressors often deteriorate the quality and quantity of sleep.[5] Our results also suggest that insomnia as an acute stress response might provide prophylactic benefits in reducing the symptoms related to trauma.

Prolonged or intractable PTSD often involves chronic insomnia symptoms.[6] Research has shown that sleep promotes the generalization of extinction of conditioned fear.[7] Thus, sleep deterioration in chronic PTSD might cancel out the benefits from sleep and delay spontaneous trauma recovery or recovery provided by psychotherapies or medications. Therefore, sleep deprivation strategies are likely not applicable to chronic PTSD. Although, sleep deprivation might be beneficial for preventing PTSD symptoms in response to an acute, traumatic stressor, chronic insomnia symptoms should be treated.

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**Sleep restriction over several days does not affect long-term recall of declarative and procedural memories in adolescents.** Voderholzer U, Piosczyk H, Holz J, Landmann N, Feige B, Loessl B, Kopasz M, Doerr JP, Riemann D, Nissen C. *Sleep Med. 2011 Feb;12(2):170-8.*

*Is long-term memory consolidation affected by sleep restriction after learning?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 88 healthy adolescents | Subjects were randomized to 5 different sleep protocols (that excluded daytime sleep) for 4 consecutive nights: <br>• 9 h TIB <br>• 8 h TIB <br>• 7 h TIB <br>• 6 h TIB <br>• 5 h TIB <br><br>Assessments prior to the sleep restriction protocol: <br>• Declarative (word-pair task) <br>• Procedural memory (mirror tracing task) encoding <br><br>Assessment after 2 recovery nights following sleep protocol and 4 weeks later: <br>• Recall | Consequences of SR: <br>• No significant impact on declarative or procedural memory consolidation <br>• High preservation of SWS amount on PSG |

PSG: polysomnography; SR: sleep restriction; SWS: slow wave sleep; TIB: time in bed

***Conclusion***
Among healthy adolescents, sleep restriction did not negatively impact declarative and procedural memory consolidation.

***Commentary***
There is broad evidence that sleep, as opposed to waking, facilitates the consolidation of both declarative and procedural memory.[1] Basic science studies suggest that NREM sleep characteristics, such as sleep spindles or EEG slow wave activity, may contribute to the strengthening of newly acquired memory traces.[2] Epidemiological studies indicate that sleep restriction and increased daytime sleepiness are associated with poor cognitive performance[3] and various health risks, such as depression and obesity.[4,5] Within clinical populations, such as in patients with primary insomnia[6,7] or obstructive sleep apnea,[8] deficits of the memory consolidating effect of sleep have been observed.

Assessing the impact of sleep on cognition and memory in adolescents is of particular interest since this developmental period is characterized by profound changes in sleep and is especially critical for learning. Previous studies on the interplay between sleep, learning and memory in children and adolescents have

shown ambiguous results. Our study aimed at reflecting the often chronic nature of sleep loss and was designed to investigate the effects of different extents of sleep restriction (5 experimental groups with 9, 8, 7, 6, or 5 hours of time in bed) over a period of 4 nights on sleep and long-term memory consolidation in adolescents. Cognitive and memory performance were assessed at baseline and at two recall sessions after two recovery nights, following the sleep restriction protocol and 4 weeks later. In contrast to the initial prediction, we observed that sleep restriction over 4 nights did not diminish declarative or procedural memory consolidation.

Further results of this study[9] have additionally shown a lack of effect of the sleep restriction protocol on the evening and morning cortisol levels. The hormone cortisol is a major mediator of stress-related effects, and sleep has been shown to have a moderate but stable inhibitory effect on the secretion of cortisol. In some studies, sleep loss or reduced sleep quality had been demonstrated to result in increased cortisol levels.[10]

One salient explanation for the lack of effects of sleep restriction on cognition, memory and cortisol in our study seems to be the observed preservation of the amount of slow wave sleep in the sleep restricted conditions. Slow wave sleep has been shown to be involved in both memory consolidation and cortisol regulation, and the homeostatic preservation of slow wave sleep might have precluded adverse effects on memory and cortisol. Notably though, this compensatory mechanism was not sufficient to prevent a significant increase in objective daytime sleepiness (multiple sleep latency test), suggesting a differential susceptibility of the sleep/wake, endocrinological and cognitive systems to sleep restriction.

It is important to note that we only investigated four nights of partial sleep restriction. It is expected that periods of complete sleep deprivation or prolonged sleep restriction lead to an impairment in cognitive and memory performance and to an activation of the stress system. Furthermore, sleep restriction might preferentially affect children or adolescents exposed to a higher number of stressors. Thus, sleep loss had particularly detrimental effects on children with low socioeconomic status that is frequently associated with an elevated number of stressors.[11] In contrast, our sample was characterized by a high socioeconomic status and relatively low levels of stress. Following this notion, detrimental effects of sleep restriction could be unmasked only if a certain threshold of stress is exceeded.[12] Future studies are needed to investigate the critical threshold of sleep loss and the interaction with other stressors in adolescence.

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# Hypersomnia

**Effect of levothyroxine on prolonged nocturnal sleep time and excessive daytime somnolence in patients with idiopathic hypersomnia.** Shinno H, Ishikawa I, Yamanaka M, Usui A, Danjo S, Inami Y, Horiguchi J, Nakamura Y. *Sleep Med. 2011 Jun;12(6):578-83.*

*Is thyroid hormone therapy effective for idiopathic hypersomnia?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 9 persons with IH<br>• Mean age of diagnosis: 23.8 ± 13.7 yrs<br>• Mean duration of hypersomnia: 8.1 ± 13.3 yrs<br>• Age: < 60 yrs<br>• BMI: < 25 kg/m2<br>• No treatment for hypersomnia<br>• No psychotropic agents<br>• Normal serum T3, T4 and TSH | Prospective, open-label study<br><br>Assessments (at baseline and 2,4 and 8 weeks after daily oral administration of levothyroxine [25 µg]):<br>• Sleep architecture (PSG)<br>• Subjective daytime somnolence (ESS)<br>• MSLT | Mean TST (hrs):<br>• Baseline: 12.9 ± 0.3<br>• At 2 treatment weeks: 11.0 ± 1.4<br>• At 4 treatment weeks: 9.1 ± 0.7<br>• At 8 treatment weeks: 8.5 ± 1.0<br><br>ESS score:<br>• Baseline: 17.8 ± 1.4<br>• At 2 treatment weeks: 12.8 ± 3.7<br>• At 4 treatment weeks: 8.8 ± 2.3<br>• At 8 treatment weeks: 7.4 ± 2.8<br><br>No adverse effects were reported |

BMI: body mass index; ESS: Epworth Sleepiness Scale; IH: idiopathic hypersomnia with long sleep time; MSLT: multiple sleep latency test; PSG: polysomnography; SOREMP: sleep onset REM period; T3: triiodothyronine; T4: thyroxine; TSH: thyrotropin; TST: total sleep time

***Conclusion***
Treatment with levothyroxine for over 4 weeks reduced total sleep time and improved excessive daytime somnolence in persons with idiopathic hypersomnia, and was well tolerated.

***Commentary***
Idiopathic hypersomnia was formerly characterized as prolonged sleep episodes, excessive sleepiness, or excessively deep sleep, which lasted for over 6 months. Multiple sleep latency test (MSLT) reveals a reduced mean sleep latency and less than two sleep onset rapid eye movement (REM) sleep periods (SOREMPs). In contrast to narcolepsy, idiopathic hypersomnia lacks specific clinical features such as cataplexy and characteristic polysomnographic features indicating alterations in rapid eye movement

(REM) sleep. While narcolepsy is treated with modafinil for excessive daytime sleepiness and antidepressants for cataplexy and abnormal REM sleep, psychostimulants are not effective for excessive daytime sleepiness in most patients with idiopathic hypersomnia. Naps are of no use because they are lengthy and not refreshing. A strategy treating EDS in patients with idiopathic hypersomnia has not yet been established, and investigation to identify an appropriate strategy for pharmacological intervention is necessary.

This study aims to investigate the effect of a thyroid hormone on prolonged nocturnal sleep and excessive daytime somnolence in patients with idiopathic hypersomnia. In the present study, subjects with latent hypothyroidism and sleep apnea syndrome were excluded.

While mean sleep time and EDS began to reduce in the 2nd treatment week, nocturnal sleep times still exceeded 10 hours in most of the patients. After treated for over 4 weeks, mean nocturnal sleep time was less than 10 hours and EDS was also reduced in all subjects, which did not meet criteria for idiopathic hypersomnia. We demonstrated that treatment with 25 micrograms of levothyroxine for over 4 weeks improved prolonged nocturnal sleep and EDS, and levothyroxine was well tolerated.

There have been several studies that investigated the association between hypothalamo-pituitary-thyroid (HPT) axis and alertness. Thyrotropin releasing hormone (TRH) has shown to be distributed widely in the CNS, and its receptors are reported to exist in structures such as pituitary, cortex, brainstem, thalamus, hippocampus, amygdala and spinal cord. Besides its role in stimulating the release of thyroid stimulating hormone (TSH) and prolactin, TRH has been shown to exhibit various neuromodulating effects that are separate from its hormonal effects. These effects include CNS stimulant and antidepressant effects and neurotrophic effects. The clinical application of exogenous TRH, however, appears to be greatly limited, because of a short biological half-life and limited access to the CNS. Therefore, biologically stable TRH analogs have been developed for possible clinical application. Several reports have demonstrated the association between TRH and alertness in narcolepsy, while the association remains unclear in other diseases such as idiopathic hypersomnia and sleep apnea syndrome. There have been reports that investigated the effect of TRH analogs in narcolepsy dogs. Acute and chronic oral administration of CG-3703, a TRH analog, was demonstrated to significantly reduce daytime sleep as well as cataplexy. The effect of CG-3703 was also demonstrated to appear rapidly, while the effect of levothyroxine required about a month in our study. TRH and TRH analogs are also known to enhance dopaminergic transmission in the nucleus accumbens, which is important for locomotor activation and arousals. It is possible that the effect of TRH on sleep and wakefulness may be mediated by enhancement of dopamine turnover, which is a common mechanism for most CNS stimulants. TRH analogs could be beneficial for excessive daytime sleepiness, but evidence has not accumulated in other types of hypersomnia such as idiopathic hypersomnia. In addition, previous studies demonstrated that oral administration of TRH analog did not cause significant changes in serum T3, T4 and TSH, and concluded that the effect may be independent of its effect on the thyroid system.

We fixed inclusion and exclusion criteria with careful deliberations. Our study, however, has some limitations since it was an open-label trial. Further studies using a double-blind design or a crossover design with a larger sample size are recommended. Second, we have not investigated what proportion of the patients with idiopathic hypersomnia respond to levothyroxine administration, because only 9 subjects were enrolled in the present study. To realize the effect of levothyroxine in idiopathic hypersomnia, it may be helpful to elucidate the difference in somnological or hormonal properties between responders and non-responders.

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# Insomnia

**Daytime symptom patterns in insomnia sufferers: is there evidence for subtyping insomnia?** Sánchez-Ortuño MM, Edinger JD, Wyatt JK. *J Sleep Res. 2011 Sep;20(3):425-33.*

*Does different insomnia diagnoses have distinctive profiles of daytime symptom?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 332 persons with insomnia<br>• Gender: 66% F<br>• Age (median): 46 yrs | Profile analysis via multidimensional scaling on the validity of ICSD-2 insomnia diagnoses | Analysis identified distinct prototypical patterns of daytime profiles:<br>• Mood disturbance and low sleepiness:<br>   o Insomnia associated with mental disorder (the most severe daytime form of insomnia)<br>   o Idiopathic insomnia<br>• Poor sleep hygiene, daytime tension and low fatigue<br>   o Psychophysiological insomnia<br>   o Inadequate sleep hygiene |

ICSD-2: International Classification of Sleep Disorders, 2nd ed; OSA: obstructive sleep apnea; RLS: restless legs syndrome

### Conclusion
Different insomnia diagnoses were associated with distinct patterns of daytime features, namely mood disturbance and low sleepiness with insomnia associated with a mental disorder and idiopathic insomnia, and poor sleep hygiene, daytime tension and low fatigue with psychophysiological insomnia and inadequate sleep hygiene.

### Commentary
Currently, two of the most contentious issues in the development of new nosological systems for insomnia are 1) the differentiation between the DSM-IV-TR primary insomnia and insomnia associated with a mental disorder, and 2) the distinction among the primary ICSD-2 "insomnias", such as psychophysiological insomnia and inadequate sleep hygiene, for example. Within this framework, studies that seek to empirically determine which presenting clinical features (if any) may be useful in differentiating between insomnia subtypes, and in providing clues to both their pathophysiology and treatment response, represent an important area of research.[1,2]

Arguably, in contemporary insomnia nosologies (e.g. DSM-IV-TR and ICSD-2), the wake-time features accompanying the nighttime symptoms (e.g., excessive arousal, depression symptoms and poor sleep hygiene) tend to be the core and discriminating factors distinguishing among insomnia diagnostic categories. However, in practice, those daytime symptoms overlap, and it often is difficult for the

clinician to discriminate among insomnia diagnostic subtypes based on their presenting daytime symptoms. Indeed, this is reflected by the fact that many insomnia diagnostic categories are associated with poor reliability.[3]

In this study, we used an innovative statistical method, called profile analysis via multidimensional scaling (PAMS), to identify the core profiles of daytime symptoms (i.e., fatigue, tension, depression, anger, poor sleep hygiene, sleepiness) exhibited by individuals complaining of insomnia. This procedure estimates the major profile patterns, called prototypical profiles, present in a given data set, and it also provides, for each individual included in the data set, a number of parameters, such as (a) *weights*, indicating the degree to which his/her observed scores "matches" each one of the identified prototypical profiles, and (b) a *level* parameter, denoting the severity of the symptoms (i.e., whether the individual has scored below or above average overall when compared to the rest of the sample).[4,5] As can be seen, PAMS yields a continuous representation of individual differences, which is more likely to approximate the true structure of the insomnia syndromes.

Our results suggested 4 core phenotypic manifestations of wake-time features. At the center of each core profile of daytime features is a prototypical "person" who manifests those symptoms represented by the profile. Therefore, the profile defines a kind of theoretical ideal or a latent standard against which the "real cases" can be assessed. No one individual matches the theoretical standard perfectly, but different insomnia sufferers approximate each of those profiles to different degrees.

In this study, we used the individuals' weights on the identified prototypical profiles to investigate the concurrent validity of clinically assigned ICSD-2 diagnoses. Our results indicated that the diagnoses of insomnia associated with a mental disorder and idiopathic insomnia included individuals sharing a specific pattern of daytime symptoms characterized primarily by mood disturbance, whereas the diagnoses of psychophysiological insomnia and inadequate sleep hygiene included individuals exhibiting mainly poor sleep hygiene practices and some elevation of tension/arousal. Although preliminary, these findings tentatively suggest two spectra of insomnia with a presumably distinct underlying etiology, i.e., learned and non-learned insomnia, but with a practical distinction between them of degree rather than kind. Admittedly, future studies should consider the addition of nighttime symptoms to the equation, in order to more precisely delineate descriptions of prototypical insomnia patients.

Perhaps, it is more realistic to assume that insomnia syndromes, regardless of their etiology, have more shared than specific variance. Therefore, dichotomous diagnostic rules will very likely result in loss of information. Prototype matching could then represent a more fruitful approach when trying to classify individuals and predict, for instance, treatment response or morbidity outcomes. Nonetheless, clinical dimensions to be measured in order to derive the prototypical insomnia profiles, as well as tools to measure those, are important issues to be addressed upfront.

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**Dissection of the factors driving the placebo effect in hypnotic treatment of depressed insomniacs.**
McCall WV, D'Agostino R Jr, Rosenquist PB, Kimball J, Boggs N, Lasater B, Blocker J. *Sleep Med. 2011 Jun;12(6):557-64.*

*What are the factors responsible for improvement in sleep in persons receiving placebo in clinical trials of hypnotics?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 60 adults with depression and insomnia | Randomized, double-blind clinical trial<br><br>Protocol:<br>• Open-label fluoxetine for 9 weeks<br>• Randomization to either eszopiclone (3mg) or placebo at bedtime after the 1st week of fluoxetine | Evidence of the following with placebo:<br>• Regression to the mean for ISI and HDRS<br>• Expectancy in self-reported WASO, ISI, and dichotomous remission/non-remitter measurement of ISI<br>• Social desirability affecting self-reported TST |

HDRS: Hamilton Depression Rating Scale; ISI: Insomnia Severity Index; TST: total sleep time; WASO: wake after sleep onset

*Conclusion*
Several factors, including regression to the mean, expectancy and social desirability for subjective sleep parameters, were evident in the placebo arm of this clinical hypnotic trial.

*Commentary*
Patients with insomnia tend to improve when assigned to receive placebo medication in randomized, double-blind clinical trials (RCT).The importance of the placebo effect may seem obvious today, but its existence was doubted just 10 years ago.[1] While improvement during placebo may seem as a boon in the context of clinical care as usual, placebo-related improvement is a major problem in the identification of new drug treatments, as it makes real drug-placebo differences harder to detect. Indeed failure to prove efficacy prevents > 80% of new CNS drugs from passing from Phase II testing through FDA approval.[2] RCTs for insomnia are well-suited for a critical examination of what factors promote the placebo response.

Multiple factors have been proposed as drivers of the observed improvement seen during placebo treatment. These include regression to the mean (RTM), expectancy, and social desirability.[3] RTM describes the tendency of the observed values that are furthest from the mean to move toward the mean at the time of a subsequent observation. Indeed RTM says that the further the first observation is away from the mean, the more the subsequent observation of the same individual will move toward the mean. Expectancy is the belief on the part of a human participant in a RCT that they will improve with treatment. Higher degrees of expectancy have previously been shown to predict a greater response to sham forms of cognitive behavior therapy for insomnia. Social desirability is the tendency on the part of some persons to exaggerate their good virtues in an effort to be favorably viewed by others. In a RCT, the assumption is

that high degrees of social desirability will lead to higher rates of improvement with placebo, as participants play out the role of the 'good patient' who responds to treatment.

We examined these factors in 60 depressed, outpatient insomniacs who were free of primary sleep disorders.[4] The participants were assigned to open-label fluoxetine (FLX) 20 mg for 9 weeks, and also randomized them to eszopiclone (ESZ) 3mg or placebo at bedtime in a 1:1 ratio after the first of the 9 weeks. Efficacy measures included daily reports of sleep latency (SL), wake after sleep onset (WASO), and total sleep time (TST), as well as the Insomnia Severity index (ISI), and the Hamilton Rating Scale for Depression (HRSD). The ISI was examined both as a continuous measure and as a dichotomous measure of remission versus non-remission.

The impact of the RTM, expectancy and social desirability on the efficacy measures was tested with general linear models for repeated measures, while the dichotomous outcomes were examined with logistic regression.[5] We found that there was evidence for regression to the mean for the continuous measurement of the ISI and the HRSD. There was evidence for expectancy in WASO, continuous measurement of ISI, and dichotomous remission/non-remitter measurement of ISI. Specifically, high levels of expectancy inflated the ISI response rate in the placebo group, but not the ESZ group. In other words, high degrees of expectancy would be expected to narrow the difference in efficacy of the ISI in a clinical trial. Finally, we found evidence of social desirability affecting self-reported TST.

The principal meaning of this study is that improvement in insomniacs assigned to placebo treatment can be expected in those patients who have extreme values of sleep measures at baseline, as this promotes RTM. Also, a favorable placebo response might also be seen in insomniacs who have a high degree of expectancy at baseline. The implication is that the efficiency of insomnia RCT, and the power to detect differences between real drug and placebo, might be enhanced by paying attention to the baseline characteristics of the prospective test subject.

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**Effectiveness of ramelteon for insomnia symptoms in older adults with obstructive sleep apnea: a randomized placebo-controlled pilot study.** Gooneratne NS, Gehrman P, Gurubhagavatula I, Al-Shehabi E, Marie E, Schwab R. *J Clin Sleep Med. 2010 Dec 15;6(6):572-80.*

*Can ramelteon benefit persons with insomnia who are starting positive airway pressure therapy for sleep apnea?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 21 adults with the following:<br><br>• Insomnia complaint >1 month<br>• AHI ≥ 5 with symptoms<br>• Age > 60 yrs<br>• Cognitively intact | Parallel group, randomized, double-blind, placebo-controlled pilot effectiveness clinical trial<br><br>Subjects were randomized to either (for 4 weeks):<br>• APAP with ramelteon (8 mg)<br>• APAP with placebo<br><br>Assessments :<br>• Polysomnography at 4 weeks (SOL)<br>• APAP adherence<br>• PSQI<br>• ISI<br>• ESS<br>• FOSQ<br>• SF-36 | Compared to placebo, ramelteon was associated with:<br>• Shorter PSG SOL (by 28.5 +/- 16.2 min)*<br>• No differences in AHI, subjective SOL, SE, PSQI global score, ESS or APAP adherence |

AHI: apnea hypopnea index; APAP: auto-titrating positive airway pressure; ESS: Epworth Sleepiness Scale; FOSQ: Functional Outcomes of Sleep Questionnaire; ISI: Insomnia Severity Index; OSA: obstructive sleep apnea; PSG: polysomnography; PSQI: Pittsburgh Sleep Quality Index; SE: sleep efficiency; SF-36: Short Form 36; SOL: sleep onset latency; *95% C.I. 8.5 min to 48.6 min, effect size 1.35, P = 0.008

*Conclusion*
In person with insomnia who are starting positive airway pressure therapy for sleep apnea, ramelteon reduced objective, but not subjective, sleep onset latency.

*Commentary*
In sleep medicine, as with many other fields, we tend to view diagnoses as distinct entities. A patient may present, for example, with sleep apnea, restless legs syndrome or bruxism. We are comfortable addressing each of these diagnoses as separate disorders in our patient assessment/plan based on the extensive evidence-based guidelines that exist for each of these separate conditions. However, the potential interplay between these different disorders within one patient is an area in which we have much less insight and must rely instead on our anecdotal experience because there is a marked paucity of evidence-based guidelines for cases where multiple diagnoses co-exist. Does improving one condition lead to improvements in the other? Where should we start with our treatment? This limited body of

research in comorbid conditions is understandable because randomized controlled trials tend to focus on well-defined clinical conditions in order to minimize confounding effects. In certain cases, though, there is a high prevalence of comorbid illness and dedicated research examining those conditions may be warranted. This is the case for insomnia and sleep apnea, especially in older adults.[1]

Consider insomnia symptoms: their prevalence in older adults ranges from 10-30% depending upon the definition.[2] Sleep apnea is also highly prevalent, with up to 20% of older adults having an AHI > 15 events/hr.[3] While we often think of daytime sleepiness and snoring as hallmarks of sleep apnea syndrome, it is important to note that the International Classification of Sleep Disorders defines insomnia as a potential symptom of sleep apnea as well.[4] Nocturnal apneas or hypopneas may lead to arousals that then result in an awakening and subsequent perceptions of insomnia.[1] Increased activity of the hypothalamic-pituitary-adrenal axis in sleep apnea patients may also contribute to sleep fragmentation,[5] although this has been questioned.[6] Whatever the etiology, in general, 22-55% of patients with sleep apnea will have insomnia symptoms.[1]

In this pilot study, we identified older adult patients with both insomnia complaints and an apnea-hypopnea index ≥ 5 events/hr who had not yet started positive airway pressure therapy for their sleep apnea. All subjects were started on auto-titrating positive airway pressure (APAP) therapy, and half were also placed on ramelteon 8 mg at bedtime and the other half received an identical-appearing placebo. We obtained polysomnography and questionnaire measures after four weeks of treatment.

We observed that subjects had a reduction in their objective polysomnography-derived sleep onset latency in the ramelteon arm relative to the placebo arm during the first four weeks of APAP therapy. It is interesting that this benefit was due to a combination of a 10.7 min reduction in sleep onset latency in the ramelteon group and a 17.8 min worsening of the sleep onset latency in the placebo group. This suggests that APAP may create discomfort that can increase sleep onset latency in older adults with insomnia. When considering insomnia symptoms in general, both groups had a small improvement in their Insomnia Severity Index score with APAP, implying some benefit for insomnia symptoms when patients are treated for their sleep apnea. However, neither group had a clinically meaningful change in their Insomnia Severity Index score and other broader measures, such as the Pittsburgh Sleep Quality Index, did not show a consistent pattern. Furthermore, subjective measures of sleep onset latency did not improve. Thus, while some patients with insomnia symptoms in the setting of sleep apnea will benefit from positive airway pressure therapy for their sleep apnea, a large number will continue to have residual symptoms. Future research is clearly necessary to provide evidence-based guidance on how to manage these patients.

Other interesting findings include the fact that ramelteon was generally well tolerated without significant worsening of the AHI while on APAP and that APAP adherence was about 40-50% at 4 weeks. This adherence rate is similar to that noted in other studies using positive airway pressure and suggests that older adult patients with insomnia can be adherent to sleep apnea treatment.[7]

Lastly, we did not observe significant changes in other study outcome measures, but it is important to note that this is a pilot study; thus, the absence of a statistically significant change (either improvement or worsening) cannot be construed to indicate lack of an intervention effect.

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**Heart rate and heart rate variability in subjectively reported insomnia.** Spiegelhalder K, Fuchs L, Ladwig J, Kyle SD, Nissen C, Voderholzer U, Feige B, Riemann D. *J Sleep Res. 2011 Mar;20(1 Pt 2):137-45.*

*Is insomnia associated with changes in nocturnal heart rate and heart rate variability?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 58 persons with primary insomnia<br><br>46 healthy controls | 4,581 nocturnal short-term (5-min) PSG ECG recordings were analyzed for HR and HRV (time and frequency domain measures) | Compared to healthy controls, those with primary insomnia had:<br>• Lower wake-to-sleep HR reduction<br>• Lower SDNN<br>• No difference in resting HR<br><br>In subjects with insomnia and objectively determined short sleep duration, parasympathetic activity was reduced with decreased:<br>• High frequency power of HRV<br>• RMSSD<br>• pNN50 |

ECG: electrocardiography; HR: heart rate; HRV: heart rate variability; pNN50: successive RRIs that differ by more than 50 ms; PSG: polysomnography; RMSSD: root mean square of successive RRI differences; SDNN: standard deviation of RR intervals

*Conclusion*
Persons with insomnia displayed lower wake-to-sleep reduction in heart rate.

*Commentary*
According to epidemiological studies, insomnia is associated with increased cardiovascular mortality.[1] However, it is yet to be determined whether this link is mediated by known cardiovascular risk factors, for example hypertension,[2] resting heart rate (HR),[3] or heart rate variability (HRV).[4] The current study aimed at investigating the association between primary insomnia, defined as subjectively reported sleep disturbance in the absence of any other pathology or substance intake, and alterations in polysomnographically determined nocturnal HR and HRV. A total of 4,581 nocturnal short-term electrocardiographic recordings (5 min each) from 104 participants (58 with primary insomnia and 46 healthy controls) were evaluated for HR as well as for time and frequency domain measures of HRV. The study sample was obtained by reviewing the data of an archival database. Any psychiatric disorders or occult sleep disorder pathology were ruled out. All participants were free of any psychoactive, cardiac or antihypertensive medication at least 1 week prior to the sleep laboratory examination.

In the primary insomnia group, we found a lower wake-to-sleep HR reduction, which was shown previously to be an independent risk factor for cardiovascular diseases,[5-6] and a lower standard deviation

of RR intervals (SDNN) compared to healthy controls. However, between-group differences in resting HR were not found. Although resting HR was higher in insomnia patients than in controls during NREM and REM sleep, interindividual variance overwhelmed the between-group difference. Furthermore, previous results of an increase in sympathovagal balance and a decrease in parasympathetic nocturnal activity in objectively determined insomnia[7] could not be confirmed in our sample of self-report insomnia patients. Accordingly, alterations in sympathovagal balance and parasympathetic nocturnal activity might represent a specific feature of patients with objectively reduced sleep duration. In line with this, exploratory analyses of a subset of our insomnia patients – those with more severe objective sleep disturbance – revealed reduced parasympathetic activity, as indicated by decreased high frequency power of HRV. Of note, with respect to HRV parameters, we were surprised by the huge inter-individual variance in the data. In summary, our study provided additional data for the existence of alterations of autonomic functions during sleep in insomnia. This might be clinically relevant, given that changes in resting HR and HRV are associated with cardiovascular mortality. A lower wake-to-sleep HR reduction as well as a lower SDNN were found in subjectively reported insomnia, while resting HR and frequency domain measures of HRV were normal. Our conclusion is that a lower wake-to-sleep HR reduction and alterations in HRV variables might, at least partially, mediate the increased rates of cardiovascular morbidity and mortality observed in insomnia patients.

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**Meta-analytic review of the impact of cognitive-behavior therapy for insomnia on concomitant anxiety.**
Belleville G, Cousineau H, Levrier K, St-Pierre-Delorme MÈ. *Clin Psychol Rev. 2011 Jun;31(4):638-52.*

*Does cognitive behavioral therapy for insomnia improve comorbid anxiety?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 216 clinical trials of CBT-I<br>• 72 reported data on anxiety | Systematic search using PsycInfo, Medline, and Proquest Dissertations and Theses | CBT-I had a small-moderate effect on anxiety<br>• Combined effect size of CBT-I on anxiety was 0.406* |

CBT-I: cognitive behavioral therapy for insomnia; *95% CI 0.318-0.493

### Conclusion
The impact on anxiety of cognitive behavioral therapy for insomnia was small to moderate in persons with insomnia with or without anxiety.

### Commentary
Anxiety and insomnia are two disorders frequently encountered together. In clinical settings, it is more probable for patients to report both problems together than either disorder in isolation: 70% to 90% of patients with an anxiety disorder report insomnia,[1-3] and individuals with insomnia commonly report elevated levels of anxiety,[4, 5] presleep arousal,[6] worries and intrusive thoughts,[7,8] and stress.[9-11] However, empirically-supported treatments for anxiety disorders do not usually include sleep management strategies, and cognitive-behavior therapy for insomnia (CBT-I) does not specifically address anxiety symptoms. Moreover, the literature on treatment efficacy often focuses on a single disorder, excluding participants with comorbid anxiety and insomnia. Psychologists encountering patients with concomitant anxiety and sleep problems are left with a clinical dilemma, namely to decide whether to implement one treatment only or to implement a combined treatment for anxiety and insomnia, and in what order to implement the respective treatments.

The little available data suggests that the presence of simultaneous anxiety and insomnia creates a clinical portrait that is considerably more complex than that of either disorder in isolation. Still, the impact of treatment for one disorder on the evolution of the other disorder remains unclear; to our knowledge, it has never been the primary focus of a study. In 2010, we conducted a systematic review of the impact of cognitive-behavioral therapy (CBT) for anxiety disorders on sleep disturbances.[12] Although we reviewed 1205 trials of CBT for anxiety disorders, we found only 19 studies that reported its effect on sleep. These very limited findings revealed that, overall, CBT treatment for anxiety disorders had a positive, but moderate, impact on sleep (combined effect size of 0.527). We tentatively concluded that successful treatment for any anxiety disorder would have a positive impact on associated sleep disturbances, but that residual sleep problems are to be expected. Clearly, another conclusion was that many more studies were needed to inform this issue.

The aim of our second review – the paper discussed here – was to do the exact opposite, namely to evaluate the impact of CBT-I on concomitant anxiety. Of the 216 CBT-I trials reviewed, 72 (33.3%) reported data on anxiety. The combined effect size of CBT-I on anxiety was 0.406, indicating a small to moderate effect of CBT-I on concomitant anxiety. For clinicians, our findings suggested that CBT-I would

not necessary eliminate anxiety for individuals with insomnia; for some of these patients, CBT-I will simply not be a sufficient intervention. There are many possible explanations for this. The number of CBT-I sessions targeting anxiety-provoking beliefs about sleep may be insufficient to influence anxiety. Also, individuals with insomnia may develop sleep-unrelated behaviors (e.g., avoidance of interpersonal contact due to fear of conflict or poor time management) and cognitions (e.g., rumination or catastrophizing); over time, these attitudes and behaviors may result in a full-blown anxiety problem that is either unrelated or not entirely related to sleep. Since residual anxiety enhances the risk of relapse after an insomnia treatment, it is essential that clinicians conduct a careful assessment of residual anxiety during or following CBT-I, even after its successful completion.

The main research implication of our review was that the assessment of anxiety in studies of insomnia treatment is neither common nor rigorous enough. We were very surprised to find that only 72 (33.3%) of the 216 reviewed CBT-I trials reported data on anxiety and, moreover, that anxiety (and anxiety-related constructs, such as arousal, stress and worry) was measured with 31 different questionnaires or questionnaire subscales. Twenty measures were used only once. There is an obvious lack of consensus among insomnia researchers regarding the assessment of anxiety. The solution resides in the use of empirically based assessment instruments for anxiety.[13] Improved standards for the assessment of anxiety in CBT-I trials are necessary.

In conclusion, although empirically supported treatments exist for both anxiety and insomnia disorders, most available studies to date have focused on treating a single disorder at a time, selecting particular participants who do not necessarily represent well those that are seen in clinical settings. What would be more helpful from now on is to include participants with both anxiety and insomnia symptoms, to assess the impact of one specific treatment on both types of symptoms, and to study which combination of treatments would be more successful to overcome both anxiety and insomnia problems and restore quality of life to patients.

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**Mindfulness-based stress reduction versus pharmacotherapy for chronic primary insomnia: a randomized controlled clinical trial.** Gross CR, Kreitzer MJ, Reilly-Spong M, Wall M, Winbush NY, Patterson R, Mahowald M, Cramer-Bornemann M. *Explore (NY). 2011 Mar-Apr;7(2):76-87.*

*How effective is mindfulness-based stress reduction as a therapy for persons with primary chronic insomnia?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 30 adults with primary chronic insomnia<br><br>27 subjects completed treatment | Randomized controlled trial<br><br>Subhects were randomly assigned (2:1) to either:<br>• MBSR: mindfulness meditation training (8 weekly 2.5 hour classes plus a day long retreat) along with ongoing home meditation for 3 months<br>• PCT: 3 mg of eszopiclone nightly for 8 weeks, followed by 3 months of prn use<br><br>Assessments (at pretreatment, posttreatment [8 weeks] and at 5 months):<br>• ISI<br>• PSQI<br>• Sleep diaries<br>• Wrist actigraphy | MBSR resulted in:<br>• Decreased SOL (actigraphy) by 8.9 min* between baseline and 8-week follow-up<br>• Significantly improved ISI, PSQI, and diary-measured TST, SOL, and SE** between baseline and 5-month follow-up<br><br>Changes from PCT were of comparable magnitude |

ISI: Insomnia Severity Index; MBSR: mindfulness-based stress reduction; PCT: pharmacotherapy; PSQI: Pittsburgh Sleep Quality Index; SE: sleep efficiency; SOL: sleep onset latency; TST: total sleep time; *$P < .05$; **$P < .01$

***Conclusion***
A program of mindfulness-based stress reduction and sleep hygiene shortened subjective and objective sleep onset latency, improved measures of insomnia severity and sleep quality, and subjective total sleep time and sleep efficiency in persons with primary chronic insomnia.

***Commentary***
Chronic insomnia is associated with poor health outcomes and diminished quality of life, and although existing therapies can improve sleep outcomes, most people do not obtain effective insomnia treatment.[1] Instead, many patients take sedative hypnotics for years without addressing the underlying causes of their sleep disorder and despite troublesome side effects. Mindfulness training has been identified as a promising approach to treating chronic insomnia.[2] Mindfulness is maintaining present-centered, non-

judgmental awareness and an attitude of acceptance and openness. It is both an innate trait and an ability that can be enhanced with training.

Complementary therapies that enhance mindfulness are rising in popularity, accompanied by evidence that increased mindfulness is linked to stress reduction, adherence, early self-diagnosis and healthy lifestyle choices. Mindfulness training reduces symptoms of depression and anxiety and impacts specific brain regions, providing mechanistic insight into clinical studies showing that increased mindfulness enhances symptom awareness, reduces emotional arousal, and facilitates health-promoting behaviors.[3,4]

The practice of mindfulness throughout the day is posited to enable one to make intentional, skillful choices such as responding to stressors with appropriate actions, as opposed to acting on "automatic pilot" with conditioned responses that can be emotionally arousing or harmful. At bedtime, mindfulness is hypothesized to disrupt rumination and worry, reduce verbal over-regulation and facilitate the disengagement necessary to fall asleep.[2] At present, there is limited experimental or imaging evidence to support hypothesized cognitive processes or physiologic pathways responsible for the health benefits of mindfulness, but this is a dynamically evolving area of research.[4] Mindfulness training had been shown to provide durable improvements to sleep quality among patients with chronic medical or psychological problems, but it had not been evaluated as a therapy for primary chronic insomnia in a controlled trial until we conducted this study.[5,6]

The study objective was to determine if patients with primary chronic insomnia who received mindfulness training would achieve clinically meaningful reductions in insomnia severity, comparable to the impact of nightly use of an FDA-approved sedative hypnotic. Thirty patients with primary chronic insomnia were randomized 2:1 to either Mindfulness-Based Stress Reduction (MBSR, n = 20) or pharmacotherapy (PCT, n = 10) consisting of 3 mg of eszopiclone nightly for 8 weeks followed by 3 months of use as needed. All patients received 10 minutes of sleep hygiene instruction at the start of treatment. Adherence and adverse events were monitored in both treatment arms.

MBSR is an 8-week standardized program of mindfulness training. The program consists of 8-weekly 2.5 hours classes and a 6-hour silent retreat with a trained instructor.[7] In class, MBSR participants learn to focus their attention through a variety of meditative techniques including breath awareness, sitting and walking meditations, a guided body scan and gentle hatha yoga. Participants are trained to perceive their immediate emotional and physical state, including pain or discomfort, and to let thoughts come and go in awareness with no attempt to change, suppress or elaborate on thoughts. In this way, participants become exposed to the positive and negative content of their thoughts, and do not get absorbed in thought, caught up in planning for the future or worrying about the past. During the study follow-up period, MBSR participants were encouraged to practice mindfulness for 20 minutes a day.

Patients were assessed before treatment, at the end of the 8-week active treatment period and 3 months after treatment (5 months from baseline). No statistically significant differences in sleep outcomes were found between MBSR and PCT over time. MBSR participants reported large improvements (effect sizes > .80) on the Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Sleep Self-Efficacy Scale (SSES) and Dysfunctional Beliefs about Sleep Scale (DBAS) at the end of 8-weeks, and 5-month scores showed even greater improvements. MBSR participants reported sleep diary changes that were large and clinically meaningful – total sleep time increased by over 30 minutes, sleep onset latency was reduced by > 20 minutes and average sleep efficiency was 85% by 5 month follow-up. By the end of the 8-week program, MBSR participants were falling asleep 9 minutes sooner based on actigraphy.

All study patients scored above the ISI cutoff for insomnia. Half of the MBSR patients met rigorous criteria for recovery from insomnia at the end of the study.  MBSR participants also reported high treatment satisfaction and no adverse events. The time commitment associated with MBSR was not a deterrent to most participants.  Whereas patients in the PCT arm obtained similar benefits to sleep outcomes, their treatment satisfaction scores were not high, and several patients reported adverse events.

This study is significant because it provides initial evidence for the efficacy of a widely available complementary and alternative therapy, MBSR, as a viable treatment for chronic insomnia. Our findings suggest that a standard MBSR program, when combined with a brief sleep hygiene presentation, is able to achieve reductions in insomnia symptoms, improvements in sleep quality and rates of remission and recovery comparable to regular use of an FDA-approved sedative hypnotic. Study limitations are a sample size not large enough to establish equivalence between MBSR and PCT and the absence of placebo controls.  Strengths are a screening protocol that included a psychologist's interview with the SCID-IV, evaluation by a sleep physician, a prospective sleep diary to confirm diagnosis, and adherence monitoring using MEMS® Caps.  The impact of this study is relevant for patients and health professionals. Given the minimal risks, modest cost, widespread availability and benefits of MBSR that go beyond insomnia, chronic insomnia patients may be encouraged to try MBSR.

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**Propofol-induced sleep: efficacy and safety in patients with refractory chronic primary insomnia.** Xu Z, Jiang X, Li W, Gao D, Li X, Liu J. *Cell Biochem Biophys. 2011 Jul;60(3):161-6.*

*Is propofol useful and safe to use in persons with refractory primary insomnia?*

| *Subjects* | *Methods* | *Outcomes* |
|---|---|---|
| 103 persons with refractory chronic primary insomnia<br>• Gender: 57% F<br>• Age: 28-60 yrs<br><br>Study groups:<br>• Propofol: n = 64<br>• Placebo: n = 39 | Randomized, double-blind, placebo-controlled study<br><br>Subjects were randomly assigned to either:<br>• Propofol : 3.0 g/l in a 2-h continuous IV for 5 consecutive nights<br>• Placebo: physiologic saline infusion<br><br>Assessments (before, at the end of the 5-day treatment, and 6 months after treatment):<br>• LSEQ<br>• PSG<br>• Adverse effects | Propofol infusion was associated with:<br>• Improved subjective and objective assessments of sleep in 62% of subjects (change was immediate and persisted for 6 months)<br>• No serious adverse events |

IV: intravenous; LSEQ: Leeds Sleep Evaluation Questionnaire; PSG: polysomnography

*Conclusion*
Propofol infusion resulted in immediate and sustained improvements in objective and subjective measures of sleep in some persons with refractory primary insomnia.

*Commentary*
The findings of Xu and colleagues are impressive in that, to our knowledge, they are the first trial to demonstrate maintenance of treatment gains in insomnia following discontinuation of pharmacotherapy. Additionally, the magnitude of Improvements in polysomnographically recorded and subjectively reported sleep are equal to or greater that those reported for traditional hypnotics.  However, some caution and critical consideration must be given to their findings.

Propofol is a widely used pharmacologic agent that is primarily used to induce general sedation in the surgical or critical care environment. Its advantages include its rapid onset of action, its rapid clearance, and that its effect can be titrated easily. Common and potentially dangerous adverse effects include respiratory failure and hypotension.  Hence, its administration in the United States is limited to closely monitored hospital or surgical environments.  The drug came to notoriety in 2009 when it was discovered that the popular musical artist Michael Jackson used it as a treatment for his persistent chronic insomnia (in conjunction with the use of other anxiolytic medications) and died as a result.

The authors concluded that propofol infusion over two hours for five consecutive nights in patients with refractory chronic primary insomnia and no other significant medical or psychiatric comorbidities may be safe and effective. Although the study results may be exciting, its practicality seems limited. Propofol is not a safe medication outside of a medically monitored environment. It can cause loss of the upper airway, particularly at sub-anesthetic doses, as well as respiratory depression. In fact, it is a commonly used agent for rapid sequence intubation preceding mechanical ventilation for patients with respiratory failure. It is also known to potentially cause hypotension, requiring the administration of saline and, at times, vasoactive medications. Some of these common adverse effects can have life threatening consequences. Therefore, the cost for its use in the treatment of insomnia may be prohibitive, reflecting the need for a monitored facility, overnight anesthesia staff, and treatment for possibly significant adverse effect.

However, insomnia, like depression, is known to have a complicated relationship to many physical conditions, such as coronary artery disease. Aggressive treatment of insomnia, like that of depression, may be shown to be cost effective. Much attention has been given to the treatment of refractory depression. There are exciting studies using other general anesthetics, such as ketamine, for the treatment of depression.[1] Additionally, electro-convulsive therapy (ECT) is a validated treatment for refractory depression, and must also be conducted in a monitored setting. Therefore, cost benefit analysis may yet show utility for the very aggressive treatment of insomnia.

Finally, the study authors state there is a need to help patients with chronic refractory insomnia to "restore their sleep homeostasis." Given the findings of this study, it is tempting attribute therapeutic effects to a change in the sleep homeostat. However, we must be cautious in the use of this term for several reasons. First, the homeostatic process of sleep is only one of several interactive systems that control sleep and wakefulness.[2] Second, emerging models of insomnia strongly support the presence of an insomnia phenotype characterized by normal sleep promoting systems in the context of wake promoting system abnormalities.[2] As Xu and colleagues have stated, propofol acts on multiple sleep-relevant systems through modulation of inhibitory (GABA) and excitatory (glutamate) neurotransmitters. Accordingly, achievement of sleep homeostasis in the general sense, as represented by sustained improvements on polysomnographic and subjective measures of sleep, is likely the result of changes across sleep and wake promoting systems rather than just the sleep homeostat. Additionally, the authors report that subjects in the study indicated a restored confidence in their ability to sleep following propofol treatment. Given this statement and the well-established psychophysiological component of chronic insomnia, it is likely that treatment effects in this study partially represent the result of psychophysiological changes. It is amazing what a good night's sleep (or five nights of propofol induced sleep) can do for attitudes and expectations regarding the nocturnal and daytime symptoms of insomnia.

Overall, Xu and colleagues show that propofol may be useful for the treatment of refractory chronic insomnia, but further safety studies and cost benefit studies must be done.

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**The relationship between media use in the bedroom, sleep habits and symptoms of insomnia.** Brunborg GS, Mentzoni RA, Molde H, Myrseth H, Skouverøe KJ, Bjorvatn B, Pallesen S. *J Sleep Res. 2011 Dec;20(4):569-75.*

*Does use of media and electronic devices affect sleep and influence symptoms of insomnia?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 2500 persons drawn randomly from the Norwegian national registry<br>• Age: 16-40 yrs<br><br>816 respondents completed the questionnaire | Postal questionnaire study<br><br>Assessments:<br>• Frequency of use of computers, television sets, DVD players, game consoles and mobile telephones and listening to music/radio in their bedrooms<br>• Sleep habits on weekdays and at weekends/days off<br>• Symptoms of insomnia | Using a computer in the bedroom was associated with 'often' compared to 'rarely':<br>• Later rise on weekdays and at weekends/days off<br>• Later turning off of lights to go to sleep on weekends/days off<br>• More sleep hours at weekends/days off<br>• Greater discrepancy between turning off the lights to go to sleep on weekdays and at weekends/days off<br><br>Using a mobile telephone in the bedroom at night was associated with 'often' compared to 'rarely':<br>• Later turning off of lights to go to sleep on weekdays and at weekends/days off<br>• Later rise at weekends/days off<br><br>The use of the other media was associated with no such differences<br><br>No significant differences in symptoms of insomnia with use of media and electronic devices |

**Conclusion**
Use of certain electronics in the bedroom, mobile phones and computer, were associated with later sleep onset on weeknights and longer total sleep time on weekends/off nights; use of television, game consoles and music didn't have a similar association. No association was found between frequent use of any of the studied electronics and increased symptoms of insomnia.

*Commentary*

Electronic media use is on the rise and, until now, its impact on sleep habits and insomnia has rarely been studied. The few studies in adults that have been done have shown inconsistent findings. Studies focused primarily on use in pediatric populations have shown some important trends. These studies presented evidence that having televisions, game consoles, and mobile telephones in their bedrooms was associated with later bedtimes and shorter total sleep times in children.

Depression, anxiety, age and gender have been variously associated with insomnia rates as well as types and amounts of electronic media use. For instance, talking on the telephone is more common among females, while video gaming is more common in males. Additionally, electronic media use, in general, and later bedtimes appear more common in younger people.

This study investigated the relationships between frequency of use of various electronic media and sleep habits as well as symptoms of insomnia. Control methods were utilized for possible confounding factors such as depression, anxiety, age and gender. Women tended to have earlier bedtimes on weekdays and weekends, but earlier wake times only on weekends, than men. Women also reported more insomnia symptoms. Younger adults were found to have later bedtimes and wake times both on weekdays and weekends. Anxiety and depression were both associated with decreased total sleep time and symptoms of insomnia.

In terms of sleep habits, this study showed close to a 20 minute shift in mid-point of sleep in those who used computers and mobile phones before bedtime, and greater variability in sleep and wake times. Interestingly, total sleep times were not significantly decreased. No association was found regarding use of other electronic media including TV, DVD player, game consoles, and listening to music/radio in bed in terms of sleep habits. There was no significant association found between any of the electronic media use and symptoms of insomnia.

This study was an important effort, given the increasing use of all forms of electronic media, to help the sleep community understand the impact this sort of media may have on sleep habits as well as any correlation that might exist with symptoms of insomnia. This article is of particular interest to those of us who work with young adults and must advise them on good sleep hygiene practices.

This study was limited by the age range evaluated, as insomnia has been found to be more prevalent in much older adults. Additionally, it focused on frequency, rather than duration, of use of electronic media. There may be more negative associations with degree of use. This points to the need to study further this group longitudinally and in more detail with regard to frequency, timing and duration of media use, so that we may examine which, if any, of these dimension affect sleep habits and symptoms of insomnia. Cultural limitations are also present. As an example, the cohort for the study slept an average of 1 hr 17 minutes longer on weekends than has been reported as a cultural norm in the US. The authors were validated in their decision to control for gender by the observation that men used game consoles more than women, and women used mobile phones more than men. Further, age was an important variable with younger adults using significantly more media.

The study supports current recommendations to limit computer and cell phone use before bedtime. It may be that these forms of media, by employing multiple senses, are more cognitively alerting than other forms of electronic media. The association between some forms of electronic media use and anxiety and depression begs the question of possible therapeutic effects of these media. Future studies might

examine whether sleep quality and duration in those with anxiety and/or depression symptoms are improved by use of certain types of electronic media, such as listening to music. Use of electronic media has become ubiquitous. In the face of that reality, it is important to identify its potential impact, both positive and negative, on our sleep. This study contributes to our knowledge of this subject.

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# Sleep Related Breathing Disorders

**A convenient expiratory positive airway pressure nasal device for the treatment of sleep apnea in patients non-adherent with continuous positive airway pressure.** Walsh JK, Griffin KS, Forst EH, Ahmed HH, Eisenstein RD, Curry DT, Hall-Porter JM, Schweitzer PK. *Sleep Med. 2011 Feb;12(2):147-52.*

*Does an expiratory positive airway pressure nasal device effectively treat obstructive sleep apnea in persons who will not use continuous positive airway pressure therapy?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 59 persons with OSA who refused CPAP or used CPAP < 3 h per night<br>• ≥ 18 years old<br>• Patent nasal airway<br>• No severe respiratory or cardiac disorder<br>• No other sleep disorder<br><br>47 subjects tolerated EPAP device for ~ 1 week<br><br>43 patients met AHI entry criteria (>15, or >10 with daytime complaint)<br>• Gender: 37% F<br>• Age: 53.7 ± 10.9 yrs | Case series study<br><br>Subjects were asked to use an expiratory positive airway pressure nasal device<br><br>Assessments using PSG:<br>• At baseline (PSG1): n = 47<br>• After 2 weeks of EPAP treatment (PSG2): n = 43<br>• After 5-7 weeks of EPAP treatment in subjects who demonstrated efficacy at PSG2 (PSG3): n = 24<br><br>Other assessments:<br>• ESS<br>• FOSQ<br>• Daily adherence diary<br><br>Definitions:<br>• Efficacy – AHI < 10 at PSG2; > 50% reduction in AHI from PSG1 to PSG2; or >30% reduction in AHI from PSG1 to PSG2 with a decrease in EDS | Change in mean AHI of subjects who met AHI entry criteria:<br>• PSG1: 43.3 ± 29.0<br>• PSG2: 27.0 ± 26.7*<br><br>Change in mean AHI in subjects who met efficacy criteria:<br>• PSG1: 31.9 ± 19.8<br>• PSG2: 11.0 ± 7.9<br>• PSG3: 16.4 ± 12.2*<br><br>Change in mean ESS scores:<br>• PSG1: 12.3 ± 4.8<br>• PSG2: 11.1 ± 5.1<br>• PSG3: 8.7 ± 4.4**<br><br>Change in FOSQ:<br>• PSG1: 15.3 ± 3.1<br>• PSG3: 17.3 ± 1.7***<br><br>Average device use: 92% of sleep hours |

AHI = apnea hypopnea index; CPAP: continuous positive airway pressure; EDS: excessive daytime sleepiness; EPAP: expiratory positive airway pressure; ESS: Epworth Sleepiness Scale; FOSQ: Functional Outcomes of Sleep Questionnaire; OSA: obstructive sleep apnea; PSG: polysomnography; *P < 0.001; **P = 0.001; ***P = 0.001

*Conclusion*

An expiratory positive airway pressure nasal device improved both apnea hypopnjea indices and subjective sleepiness in some persons with obstructive sleep apnea.

*Commentary*

While continuous positive airway pressure (CPAP) is the gold standard in the treatment of OSA in adults, many individuals are unable to tolerate CPAP or refuse to use it. This study adds to the literature evaluating the efficacy of expiratory positive airway pressure (EPAP) in the treatment of OSA across a wide range of disease severity. Importantly the study demonstrates that many patients who have had difficulty using CPAP report good tolerance and adherence with the EPAP device, at least over a short-term period. However, while average AHI decreased significantly for the group, clinically important reduction in AHI was demonstrated in about 50% of patients. Characteristics that predict treatment response could not be identified. Nonetheless, those patients who showed meaningful reductions in AHI also demonstrated meaningful improvements in ESS and FOSQ, similar to the improvements seen in individuals who use CPAP for a month. Limitations to this study include the absence of a sham or other comparative treatment, and lack of counterbalancing of baseline and treatment nights. The adherence data in our sample may be artificially high because the data were obtained by diary rather than by an objective method. Frequent interaction by study staff may also have contributed. Thus, high adherence may not generalize to routine clinical use.

Additional data on this EPAP device have been published. In a multicenter, sham-controlled clinical trial in patients with mild to severe OSA, Berry et al[1] found that this nasal EPAP device significantly reduced the AHI at one-week and three-month time points, and by three months, subjective daytime sleepiness was improved compared to the sham treatment. In a subsequent paper, Kryger et al[2] reported that subjects in the Berry et al study who had a positive clinical response to the device after three months continued to demonstrate improvement in AHI and daytime sleepiness after 12 months of open-label treatment. Long-term adherence to EPAP was excellent with median reported usage of 89% of nights and 83% of patients who entered the extension study still using the device at 12 months.

Patel et al[3] reported that therapeutic efficacy with the device was observed over a wide range of disease severity. Similar to our findings, approximately 50% of subjects demonstrated a clinically significant response, and no consistent predictors of response were identified. They state that efficacy was associated with the ability to generate and maintain elevated end expiratory pressures, and suggest that the primary mechanism of action is tracheal traction caused by increased lung volume. However, increased $CO_2$ or maintaining end expiratory pressure into inspiration onset could also contribute. The excellent commentary by Owens et al[4] on the Patel et al article reminds us that obstructive sleep apnea is likely a multifactorial disease with specific factors (airway anatomy, arousal threshold, lung volume, ventilator control and pharyngeal muscle recruitment) contributing differentially in individual patients. Thus, a better understanding of OSA pathophysiology may be key to understanding the mechanism of action through which EPAP successfully treats sleep apnea and predicting which patients may benefit from its use.

Consideration of the published EPAP results reminds us of the limitations of PSG-determined reduction in AHI as an OSA treatment endpoint. While normalization of AHI is logical and well accepted as an efficacy standard, a high level of adherence with treatment is needed for a similarly high degree of treatment effectiveness. In some cases, a less efficacious treatment with high adherence may be a comparable or better alternative than a highly efficacious treatment with poor adherence.

In summary, available data suggest that this EPAP device may be a useful therapeutic option for some patients, particularly those unable or unwilling to use CPAP, assuming there is careful clinical follow-up. Long-term studies with expanded outcome measures, including cardiovascular and metabolic metrics, are needed.  Future research should also include both patients who are naïve to CPAP as well as patients who show good adherence with CPAP treatment.

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**A novel approach to prediction of mild obstructive sleep disordered breathing in a population-based sample: the Sleep Heart Health Study.** Caffo B, Diener-West M, Punjabi NM, Samet J. *Sleep. 2010 Dec;33(12):1641-8.*

*Is there a reliable method for predicting mild obstructive sleep apnea?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 5,530 participants of SHHS, a community-based study | Modern ensemble learning algorithms for a data-mining approach for prediction of mild obstructive SDB<br><br>Data were divided into training (n = 4,147) and validation (n = 1,383) sets for varying thresholds for predicting the probability of a high RDI to assess performance of the algorithm | Post-test odds of an RDI > 7 were 2.20 times that of the pre-test odds in the light of a positive classification by the algorithm, and 0.48 times lower in the presence of a negative classification<br>• Sensitivity: 0.66<br>• Specificity: 0.70<br><br>Variables having the largest impact on prediction performance (in rank order):<br>• Neck circumference<br>• BMI<br>• Age<br>• Snoring frequency<br>• Waist circumference<br>• Snoring loudness<br>• Gender<br>• Minutes to fall asleep<br>• Dozing off while reading<br>• Heart attack |

BMI: body mass index; RDI: respiratory disturbance index; SDB: sleep disordered breathing; SHHS: Sleep Heart Health Study

***Conclusion***
Advanced data mining methodology based on input from routine clinical data produced a sensitivity of 66% and a specificity of 77% for predicting mild sleep apnea (respiratory disturbance index > 7) in a community cohort study.

***Commentary***
Novel prediction methodology can potentially provide clinical prediction of obstructive sleep apnea without the application of a full or partial sleep study.[1] Prior to the work of Caffo et al., prediction methodology focused on obese, high risk, populations or those already referred for clinical evaluation, and did not use modern prediction methodology.[2-11] Related work focused on population-based predictors of sleep disordered breathing.[12-14]

Caffo et al. used data from the Sleep Heart Health Study,[15] a large longitudinal study of sleep in community dwelling adults. Sleep metrics were obtained via in-home polysomnograms. Ensemble learning methods were used to predict mild sleep apnea, defined as an RDI > 7. A participant's neck circumference, BMI, age, snoring frequency, and waist circumference had the most influence on prediction (listed from greatest to least influence). These variables were followed by how loudly the participant snored, gender, sleep latency, whether or not he or she fell asleep while sitting and reading, and heart attack history.

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**A retrospective case series of adaptive servoventilation for complex sleep apnea.** Brown SE, Mosko SS, Davis JA, Pierce RA, Godfrey-Pixton TV. *J Clin Sleep Med. 2011 Apr 15;7(2):187-95.*

*How effective is adaptive servo ventilation in treating complex sleep apnea in a community hospital-based sleep disorders center?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 25 consecutive subjects with OSA<br>• Age: 59.8 ± 16.5 y<br>• BMI: 30.4 ± 6.1 kg/m$^2$<br>• AHI: 48.5 ± 30.2/h<br><br>18 subjects met criteria for CompSA<br>• CAI: 10.8 ± 16.0/h | Retrospective study<br><br>Subjects with CompSA underwent ASV titration<br><br>Assessments (at baseline, on CPAP/BPAP and on ASV):<br>• AHI<br>• CAI<br>• RAI<br><br>Definitions:<br>• CompSA – SDB that is predominantly OSA at baseline and predominantly CSA on CPAP/BPAP (CAI ≥ 5/hr) | AHI did not improve on CPAP/BiPAP: 44.4 ± 25.9/hr*<br><br>CAI tripled on CPAP/BiPAP: 34.8 ± 24.2/hr vs. 10.8 ± 16/hr at baseline**<br><br>On ASV, AHI decreased to 3.6 ± 4.2/hr and CAI dropped to 0.7 ± 2.2/hr***<br><br>RAI also improved on ASV but not on CPAP/BiPAP |

AHI: apnea hypopnea index; ASV: adaptive servo ventilation; BMI: body mass index; BPAP: bilevel positive airway pressure; CAI: central apnea index; CompSA: complex sleep apnea; CPAP: continuous positive airway pressure; CSA: central sleep apnea; OSA: obstructive sleep apnea; PAP: positive airway pressure; PSG: polysomnography; SDB: sleep disordered breathing; *P = 0.54; **P < 0.001; ***P < 0.001

***Conclusion***
Adaptive servo ventilation was superior to continuous/bilevel positive airway pressure therapy in reducing apnea hypopnea index, central apnea index and respiratory arousals related to complex sleep apnea.

***Commentary***
The emergence or persistence of central apneas during continuous positive airway pressure/bilevel positive airway pressure (CPAP/BPAP) titration for obstructive sleep apnea is a challenging phenomenon identified as a new syndrome termed complex sleep apnea (CompSA). Estimates of the prevalence among patients with obstructive apnea are as high as 20%,[1,2] a non-trivial proportion. Although recent studies have suggested that the central apneas which define CompSA will resolve in many cases after a period of CPAP/BPAP therapy, estimates of the fraction that do not improve sufficiently range from 11% to 50%.[1,3,4,5] From that standpoint alone, the availability of an acutely effective form of therapy is important. Furthermore, untreated central apnea can be associated with significant morbidity, as suggested by a multicenter study of CPAP therapy for congestive heart failure wherein heart transplant-free survival failed to improve when central sleep apnea (CSA) remained unresolved.[6] Also, patients can

grow discouraged/resistant to alternative forms of positive airway pressure therapy when sent home on a device that does not provide clinical improvement in a timely fashion, and there is added financial burden from additional sleep studies and device trials.

Adaptive servo-ventilation (ASV) is a novel bilevel positive airway pressure modality relying on variable inspiratory pressure, a back-up rate, and either a target minute ventilation or peak flow designed to limit post-hypocapnic compensatory CSA. ASV treatment for CSA was first reported in 2001 in patients with congestive heart failure,[7] and a recent review details subsequent success in treating CompSA.[8] Although a handful of existing studies have found ASV superior to traditional positive airway pressure devices (CPAP or BPAP) in treating CompSA, other investigators have reported less favorable results.[9]

These previous reports on efficacy of ASV in CompSA have come from large research-oriented medical centers where ASV has sometimes been evaluated with additional experimental techniques - like $CO_2$ infusion or added dead space - currently not available in non-academic institution-based sleep clinics.[10,11] Our study of ASV was conducted as part of the routine evaluation of patients presenting to a community hospital sleep disorders center. We retrospectively evaluated our first 25 consecutive patients undergoing ASV titrations who met the following inclusion criteria: diagnostic apnea hypopnea index (AHI) ≥ 5/hr in either full-night or split-night polysomnography *and* central apnea index (CAI) > 5/hr both across the entire CPAP/BPAP titration and at the final (best) CPAP/BPAP pressure. Although most patients underwent CPAP titrations only, BPAP in the spontaneous mode was also titrated in a subset when time permitted or if CPAP was not tolerated.

Neither the overall AHI nor RAI improved significantly on CPAP/BPAP, whether these indices were derived from the entire titration or just the final pressure settings. Though obstructive apneas and hypopneas were improved significantly on CPAP/BPAP, as expected, central apneas significantly worsened. ASV, in contrast, effectively treated both the obstructive and central components to the respiratory disturbance so that an AHI of ≤ 10/hr was achieved in 92% of cases (AHI ≤ 5/hr in 80%). Central apneas were virtually eliminated on ASV.

Although our study had certain limitations stemming largely from its retrospective design (like a somewhat heterogeneous patient sample reflective of a community clinic), the dramatic improvements we witnessed across subjects on ASV add weight to our conclusion that ASV is superior to CPAP/BPAP, at least acutely, in stabilizing disordered breathing in assorted patients meeting criteria for CompSA. Our findings also add to a growing literature indicating that CompSA is a real physiological entity not attributable to artifacts of CPAP/BPAP titration such as air leakage, as has been suggested.

Research on CompSA remains sparse, and the American Academy of Sleep Medicine has yet to establish any guidelines for treatment.[12] We hope that our study encourages others to report on their experience with various modalities to treat CompSA to help empower clinicians in choosing the best course of treatment.

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**A simplified model of screening questionnaire and home monitoring for obstructive sleep apnoea in primary care.** Chai-Coetzer CL, Antic NA, Rowland LS, Catcheside PG, Esterman A, Reed RL, Williams H, Dunn S, McEvoy RD. *Thorax. 2011 Mar;66(3):213-9.*

*Can a screening questionnaire followed by home sleep oximetry reliably detect persons with obstructive sleep apnea?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 157 persons (first 79 in the development group and the next 78 in the validation group) | Evaluation of diagnostic accuracy to predict OSA of a two-stage model consisting of: <br>• Screening questionnaire developed from sleep surveys, demographic and anthropometric data <br>• ROC curve analysis used to validate ApneaLink against full PSG | Factors predictive of OSA that were incorporated into the screening questionnaire included: <br>• Snoring <br>• Waist circumference <br>• Witnessed apneas <br>• Age <br><br>Two-stage diagnostic model was associated with: <br>• Development group <br>  o Sensitivity: 0.97 <br>  o Specificity: 0.87 <br>• Validation group <br>  o Sensitivity: 0.88 <br>  o Specificity: 0.82 |

AUC: area under curve; HSM: home sleep monitoring; OSA: obstructive sleep apnea; PSG: polysomnography; ROC: receiver operating characteristic

***Conclusion***
A two-stage diagnostic model utilizing a screening questionnaire and home sleep oximetry accurately identified the presence of obstructive sleep apnea.

***Commentary***
Obstructive sleep apnea (OSA) is highly prevalent in the community, with recent data showing that 17% of the general adult population have an AHI ≥ 15/hr.[1] With increasing availability of effective therapies for OSA, such as continuous positive airway pressure (CPAP), and concern regarding the potential health-related consequences of OSA, there has been a steady rise in demand and growing waiting lists for laboratory-based sleep services. Alternative, validated strategies for the diagnosis and management of OSA, which are simple, cost-effective and easily accessible, are urgently needed to address the increasing burden of disease.

Primary care physicians and their practice nurses are ideally positioned to take on greater responsibility for the identification and management of OSA. Surveys conducted in primary care have revealed that one-third of patients who visit their primary care physician have a high pre-test probability of OSA,[2] yet the

disease frequently remains undiagnosed and under-treated.[3] Enhanced awareness and management of OSA in primary care would require improved educational opportunities and training of primary care providers, accompanied by simple diagnostic tools which are suitable for routine clinical use in a busy primary care setting.

In this study, we developed and validated a two-stage diagnostic strategy for moderate to severe OSA (AHI ≥ 30/hr) in primary care consisting of (1) a simple 4-item screening questionnaire, followed by (2) home oximetry monitoring using an ApneaLink device (ResMed, Australia). 157 patients at both high and low risks for OSA were divided into a development group (n = 79) and a validation group (n=78). Patients who were recruited from primary care practices completed sleep surveys, including the Epworth Sleepiness Scale and Berlin Questionnaire, and underwent simultaneous home monitoring with full polysomnography and an ApneaLink device.

The results revealed four items to be predictive of a diagnosis of OSA: (1) obesity, in terms of waist circumference; (2) snoring (3) witnessed apneas and (4) age > 50 years, which were incorporated into a screening tool called the "OSA50" questionnaire with a simple 10-point scoring algorithm (ROC area under the curve [AUC] 0.84, 95% CI 0.75-0.94, $P < 0.001$). ApneaLink oximetry with a 3% dip rate ≥ 16/hr was highly predictive of OSA with ROC AUC of 0.95 (95% CI 0.91-1.0, $P < 0.001$). In the validation sample, the combined 2-stage diagnostic model had a sensitivity of 88%, specificity of 82% and overall diagnostic accuracy of 83%.

The simple, 4-item OSA50 questionnaire is likely to be of greater appeal to primary care physicians than the longer and more complex Berlin questionnaire.[4] The Berlin questionnaire is the only other screening tool previously designed for use in primary care but has had little uptake by primary care physicians in the decade since its introduction. Other clinical prediction tools for OSA, such as the MAP index,[5] SACS[6] or STOP-BANG[7] questionnaires have been created and validated in sleep clinic or tertiary care settings, but not in primary care populations.

In recent years, there has been growing interest in ambulatory management strategies for OSA involving the use of screening tools, portable home monitoring and auto-titrating CPAP, as well as investigation into the role of alternative health care providers, such as sleep-trained nurses, in the management of OSA. Results from a number of randomised controlled trials (RCTs) conducted in sleep clinic settings have demonstrated comparable outcomes for patients managed using ambulatory approaches compared to standard laboratory-based care.[8-11] As a follow-up to our study, we have recently completed an RCT to investigate an ambulatory management strategy for OSA in primary care utilizing the skills of primary care physicians and community-based nurses. The results, which appear promising, are currently awaiting publication.

A study by Pietzsch et al[12] has sparked recent debate about the cost-effectiveness of portable home monitoring for OSA. Their health economic analysis revealed that full-night PSG with CPAP therapy was more cost-effective than unattended home monitoring for the management of OSA, due largely to its superior diagnostic accuracy. However, as pointed out in an accompanying editorial,[13] several assumptions used in their modelling (e.g., that there would be dramatic reductions in cardiovascular events with CPAP use, and that patients who had a false-positive home sleep study would have the same long term compliance with CPAP as those correctly diagnosed) could have magnified the effects of false-negative and false-positive results and elevated the costs of portable monitoring.

Nevertheless, this simplified, 2-stage diagnostic strategy of screening questionnaire and home monitoring may help pave the way for increasing identification and management of OSA in the primary care setting, and ultimately improve patient access to sleep services.

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**Cardiac resynchronization therapy and obstructive sleep-related breathing disorder in patients with congestive heart failure.** Shalaby A, Atwood CW, Selzer F, Suffoletto M, Gorcsan Iii J, Strollo P. *Pacing Clin Electrophysiol. 2011 May;34(5):593-603.*

*Does cardiac resynchronization therapy improve sleep-related breathing disorder in persons with heart failure?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 19 men with CHF eligible for CRT<br>• NYHA class III<br>• Age: 67.2 ± 7.5 yrs<br>• Race: 79% Caucasian<br>• Cause: 74% Ischemic<br>• ESS: 7.3 ± 4.0<br>• PSQI: 7.4 ± 3.1<br>• MLHFQ: 36.9 ± 21.9<br>• AHI: ≥15, <50 | Subjects were randomized to either AOP/DDD or VDD<br><br>Assessments: 2 PSG (12 weeks apart) | At follow-up, no improvements were noted in:<br>• SE<br>  ○ Baseline: 65.3 ± 16.6%<br>  ○ Follow-up: 68.3 ± 17.9%<br>• SaO2 nadir<br>  ○ Baseline: 83.5 ± 5.3%<br>  ○ Follow-up: 82.8 ± 4.6%<br>• AHI<br>  ○ Baseline: 21.5 ± 15.3<br>  ○ Follow-up: 24.9 ± 21.9 |

AHI: apnea hypopnea index; AOP/DDD: atrial overdrive pacing; CAI: central apnea index; CHF: congestive heart failure; CRT: cardiac resynchronization therapy; ESS: Epworth Sleepiness Score; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NYHA: New York Heart Association; PSG: polysomnography; PSQI: Pittsburgh Sleep Quality Index; SaO$_2$: oxygen saturation; SE: sleep efficiency; SRBD: sleep related breathing disorder; VDD: atrial synchronous pacing

***Conclusion***
Cardiac resynchronization therapy failed to improve obstructive sleep apnea among elderly persons with heart failure.

***Commentary***
Our study confirms previous findings, brings forth new ones, while stimulating further research and innovation.[1] In a group of patients eligible for cardiac resynchronization therapy on the basis of congestive heart failure (CHF), low ejection fraction, and prolonged QRS duration, sleep related breathing disorder (SRBD) of at least moderate degree was found to be highly prevalent. SRBD has been previously demonstrated to be a prevalent co-morbidity in CHF patients and shown to be consequential to patient outcome. The implication for modern practice is to recognize the importance of screening for and treating SRBD in CHF patients. CPAP remains the mainstay of therapy for SRBD and has been demonstrated to have beneficial effects in patients with CHF and obstructive or central types of SRBD. However, in CPAP therapy, non-adherence remains a significant problem, driving the search for other therapeutic

modalities, including pacing. While the initial promise of overdrive atrial pacing in patients with standard indication for pacing has been refuted in multiple trials, the possible benefit from cardiac resynchronization therapy (CRT) for CHF patients has not been fully assessed. Cardiac resynchronization, by pacing the left ventricle, has demonstrated effectiveness in improving CHF outcomes, left ventricular remodeling and a favorable impact on neuro-hormonal balance. It would be plausible to expect a positive impact for CRT on SRBD associated with CHF.

In most reports, SRBD in patients with CHF has been predominantly central. In our cohort however, we mainly encountered obstructive SRBD. This may have been related to the high level of beta-blocker utilization, the relatively high BMI, or both. Obstructive SRBD may exacerbate CHF while CHF in turn may contribute to obstructive SRBD by increasing interstitial edema of upper airway tissue particularly during recumbency.

In our study, resynchronization pacing with or without atrial overdrive pacing did not alleviate SRBD. This is clearly at odds with the aggregate findings of multiple small-scale studies that describe CRT-induced improvement in central SRBD. The available evidence for CRT effect on obstructive SRBD has been conflicting as we outline in the discussion. In a meta analysis of multiple small series, Lambda et al. found CRT to reduce AHI significantly in patients with central, but not in those with obstructive, SRBD.[2]

Our study highlights the difficulty of recruitment and retention in clinical trials involving multiple in-house sleep studies. We believe we built a level of rigor into the study by sufficiently removing the screening study from the implant time to avoid a placebo effect from the implant itself while avoiding the possible confounding effect of operative anesthesia. The screening study was conducted in a pacing naive state. We only included those with a moderate degree of SRBD and we conducted follow-up studies at meaningful time intervals that would correlate to improvement in CHF induced by CRT. However, it is possible that a positive effect for CRT may have been missed due to the relatively small number in the study. A multicenter trial utilizing portable sleep studies or capitalizing on sleep monitoring capabilities of implanted devices might avoid the limitations inherent to smaller single center studies.

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**Comparative effects of two oral appliances on upper airway structure in obstructive sleep apnea.**
Sutherland K, Deane SA, Chan AS, Schwab RJ, Ng AT, Darendeliler MA, Cistulli PA. *Sleep. 2011 Apr 1;34(4):469-77.*

*What are the differential effects on upper airway structures of two forms of oral appliance for treatment of obstructive sleep apnea?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 39 persons undergoing oral appliance treatment for OSA<br>• Gender: 36% F<br>• Age: 50 ± 10.7 yrs<br>• BMI: 29.2 ± 5.5 kg/m$^2$<br>• AHI: 26.9 ± 17.1 hr$^{-1}$ | Cohort study<br><br>Assessment:<br>• UA MRI during wakefulness at baseline [no appliance], with MAS and with TSD in randomized order<br>    o Airway size<br>    o Position of UA soft tissues<br>    o Cephalometric measurements<br>• PSG | UA size<br>• Airway size was increased more by TSD than MAS<br>• Both MAS and TSD altered airway dimensions in the velopharynx and oropharynx, but not hypopharynx<br>• Velopharyngeal airway space showed an equivalent alteration in shape to a more stabilizing laterally orientated ellipse with both appliances; however absolute lateral and AP diameters were greater with TSD<br>• Oropharnygeal dimensions were increased to a similar extent with MAS and TSD<br><br>Soft tissue movements<br>• Lateral displacement of the parapharyngeal fat pads and pharyngeal walls away from the airway was greater with TSD<br>• Tongue and soft palate moved forward and upwards with TSD compared to a downward movement of the tongue observed with MAS<br>• Base of tongue muscles moved forward with MAS but backward with TSD<br><br>Cephalometric assessment |

| | | |
|---|---|---|
| | | • Forward movement of the mandible with MAS and backward with TSD (SNB angle)<br>• Lower face height increased to a greater extent with TSD<br>• Superior displacement of the hyoid bone was equivalent with both appliances |

AHI: apnea hypopnea index; AP: antero-posterior; BMI: body mass index; MAS: mandibular advancement splint; MRI: magnetic resonance imaging; OA: oral appliance; OSA: obstructive sleep apnea; PSG: polysomnography; SNB: sella-nasion-point B angle; TSD: tongue stabilizing device; UA: upper airway

*Conclusion*
Both mandibular advancement splints and tongue stabilizing devices altered upper airway structure, but patterns and degree of change differed between devices.

*Commentary*
Due to inherent issues with tolerance and low compliance to CPAP, there is a considerable need for other treatment options for OSA. Oral appliances are currently the primary alternative and improve OSA by mechanically altering upper airway configuration and modifying upper airway function. Mandibular advancement splints (MAS), which attach to the dentition and hold the jaw in a protruded position, are the predominant type of oral appliance used. Numerous studies exist supporting their efficacy to the extent that they are now recommended as a first-line treatment for OSA.[1] However other oral appliance designs are in existence, although used less commonly. Tongue stabilising devices (TSD) feature a preformed bulb that holds and protrudes the tongue outside the oral cavity using suction. Investigations into the efficacy of TSD are more limited; however, tongue protrusion using such devices has been shown to improve OSA and symptoms with demonstrated reductions in AHI, arousal frequency, oxygen saturation and daytime sleepiness.[2,3]

A recent randomized crossover trial compared the efficacy of MAS and TSD in treating OSA and found similar improvements in terms of AHI reduction.[3]

The different mechanisms by which these two appliance types improve upper airway geometry (tongue vs. jaw protrusion) are likely to have different effects on airway space and movement of the surrounding soft tissues. However, the upper airway effects of tongue compared to jaw protrusion with these appliances had not been previously investigated. We used airway and soft tissue MRI analyses to assess the effects of MAS and TSD on upper airway structure during wakefulness. In terms of upper airway size, both appliances seem to have similar effects on the oropharyngeal airway space, whereas TSD increases velopharyngeal size to a greater extent than MAS. We additionally segmented individual upper airway soft tissue structures to understand the movement patterns that occur with wearing of each appliance. Soft tissue movements were assessed by measuring displacement of the centroid of each structure (a point analogous to the centre of mass of an object) between images without and with appliance. This method

was able to detect differences in movement patterns generally indicating greater displacement of tissue centroids with TSD compared to MAS. However, some appliance-specific movements were also noted, including anterior movement of the base of tongue muscles with MAS but posterior displacement with TSD. Although this method of analyses gives some insight into the upper airway effects of these appliances, reducing complex tissue structures to a single point is likely to be an oversimplification. This method would be unable to account for more global changes in morphology of tissue structures that may be important for treatment response. Additionally, image capture was obtained over many minutes and therefore the analysed images are an average over multiple respiratory cycles. The upper airway and genioglossus tissue show particular movement patterns throughout inspiration and expiration.[4,5] The effects on respiratory cycle dependent movements may be more complex and relate specifically to treatment response.

Differential soft tissue movements and changes in upper airway dimensions may help explain treatment response to oral appliances. In the current study, efficacy data in terms of effects on AHI for both appliances were only available in a subset of 18 out of 39 patients with comparative imaging. However, there was some indication that velopharyngeal size increased to a greater extent in TSD responders defined as ≥ 50% reduction in AHI. We have previously shown favorable changes in airway size in MAS responders compared to non-responders.[6] Global airway volume changes were not linearly related to AHI reduction. However, this is not surprising as treatment response to oral appliances is likely due to a multitude of factors including both structural and functional effects on the upper airway.

Understanding the effects of different oral appliance types on specific bony and soft tissue movements gives greater insight into their treatment effects. Although TSD appears to be effective in a smaller amount of people compared to MAS and be less well tolerated,[3] there appear to be specific upper airway structural benefits. Such studies give understanding to the structural effects of oral appliances and insights into the mechanisms behind treatment response that is likely to improve patient selection for oral appliance treatment. However, expensive imaging costs and intensive analysis precludes using such techniques clinically to understand structural responses and relationship to efficacy. Therefore, simple, prediction methods are still needed to translate such research findings into clinical practice.

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**Effect of palatal implants on continuous positive airway pressure and compliance.** Gillespie MB, Wylie PE, Lee-Chiong T, Rapoport DM. *Otolaryngol Head Neck Surg. 2011 Feb;144(2):230-6.*

*Can palatal implants reduce therapeutic continuous positive airway pressures and improve compliance to therapy in persons complaining of excessively high pressures?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 51 persons with OSA and with CPAP pressure settings ≥ 7 cm $H_2O$ who were dissatisfied with CPAP due to pressure-related complaints <br> • Gender: 16% F <br> • Age: 51.7 ± 9.6 yrs <br> • BMI: 35.3 ± 6.1 <br> • AHI: 44 ± 22 <br> • $SaO_2$ nadir: 83 ± 8 <br> • Mean daily CPAP use: 5.6 ± 2.2 hrs | Randomized, placebo-controlled, double-blind study <br><br> Subjects were randomized to palatal implants (n = 26) or sham procedure (n = 25) <br><br> Assessments: <br> • PSG at 90 days to determine therapeutic CPAP settings <br> • CPAP compliance with 90-day compliance card report <br> • ESS <br> • FOSQ <br> • VAS | 90-day CPAP titration <br> • No significant pressure reduction <br> • No difference between groups <br><br> Average daily CPAP use <br> • No significant increase <br> • No difference between groups <br><br> Improved CPAP satisfaction at 90 days in active vs. sham group <br><br> Improved CPAP comfort, ESS and FOSQ in both groups with no difference between groups |

CPAP: continuous positive airway pressure; ESS: Epworth Sleepiness Scale; FOSQ: Functional Outcome of Sleep Questionnaire; OSA: obstructive sleep apnea; VAS= Visual Analog Scale

**Conclusion**
Palatal implants failed to reduce continuous positive airway pressures or improve treatment compliance in persons with obstructive sleep apnea.

*Commentary*
Continuous positive airway pressure (CPAP) is the first-line therapy for moderate to severe obstructive sleep apnea (OSA) syndrome.  It is estimated, however, that only 50% to 70% of CPAP users are adherent to the recommended minimal usage of 4 hours per night for 5 nights a week.[1] Therefore, adherence to CPAP is a critical problem that needs to be addressed in order to improve sleep-related health outcomes.

Reasons for poor CPAP adherence are varied, but include adverse side effects, poor health-related insight, social concerns, and financial factors. With regard to adverse-side effects of CPAP, patients commonly report pressure intolerance, difficulty exhaling and mask leak.[2] Pressure related complaints are infrequent at pressures below 10 cm $H_2O$ but become increasingly common at higher CPAP pressures.[3] A trend toward better CPAP adherence and greater CPAP satisfaction was found in patients treated with flexible pressure delivery (e.g., C-Flex) compared to CPAP suggesting the possibility of improved CPAP adherence with lower mean pressure levels;[4] however, other studies have failed to show improved CPAP use with auto-CPAP or BPAP intervention.[5]

The Pillar palatal implant system (Medtronic, Jacksonville, FL) is a minimally invasive treatment for snoring and mild apnea thought secondary to palatal flutter and closure during sleep. The procedure involves the insertion of three 18-millimeter Dacron threads in the muscular layer of the soft palate to induce a fibrotic reaction over a 90-day period that results in increased palatal stiffness. In a case series of 21 OSA patients on CPAP therapy, insertion of Pillar implants significantly reduced the mean CPAP pressure from 11.2 to 9.3 cm of H2O.[6]

A multi-center, double blind, randomized controlled trial was design to test whether insertion of the Pillar implant system would result in a reduction in the therapeutic CPAP pressure and improve CPAP compliance over a 90-day trial period. Patients ≥ 18 years of age diagnosed with moderate to severe OSA (AHI > 15) with poor CPAP satisfaction due to high pressure, difficulty with exhalation, mask leak, and nasal discomfort were offered participation at several sites throughout the U.S. Patients who enrolled in the study completed a baseline physical examination, Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ), 10 cm visual analog scales (VAS) of CPAP comfort and satisfaction, and a baseline CPAP titration using a standardized protocol to determine the optimal pressure setting. The subjects then wore CPAP for a 2-week period at the newly prescribed pressure to allow for baseline CPAP usage collection with a smart card. At this point, 26 patients were randomized to receive the active implant and 26 to receive the sham procedure. Both active and sham procedures were performed with pre-loaded Pillar devices that prevented the surgeon and subject from knowing whether actual implants were placed. After a 90-day period to allow for full fibrosis from the implants, 90-day smart card compliance data was collected as well as a repeat ESS, FOSQ, VAS, followed by a second overnight CPAP titration using the same rigorous protocol to re-establish optimal CPAP pressure. Following the study, patients in the sham group were offered the Pillar implant if interested.

The results found no significant difference between active and sham groups with regard to gender distribution, age, BMI, neck circumference, AHI, and mean daily CPAP use. The optimal CPAP titration pressure was lower for both the sham (1.1 cm $H_2O$) and active (0.6 cm $H_2O$) groups with no significant difference between groups. Similarly, there was no significant increase in average daily CPAP use between the sham and active subjects. Both sham and active groups demonstrated improved CPAP satisfaction as measured by VAS, with the active group demonstrating significantly greater improvement in satisfaction compared to the sham group. Likewise, both groups demonstrated improvements in CPAP comfort as measured by VAS without significant difference between the groups. The study failed to reach its enrollment goal of 100 subjects due to loss of the study sponsor; however, the current trend suggest that it is unlikely that a significant difference would have been observed for the primary outcomes had the study reached enrollment.

In summary, the study failed to demonstrate reduced CPAP pressure or improved CPAP compliance with placement of Pillar palatal implants. Pillar implants did improve CPAP satisfaction but the reasons for this are unclear and may be deserving of further study.

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**Effects of continuous positive airway pressure on fatigue and sleepiness in patients with obstructive sleep apnea: data from a randomized controlled trial.** Tomfohr LM, Ancoli-Israel S, Loredo JS, Dimsdale JE. *Sleep. 2011 Jan 1;34(1):121-6.*

*Does continuous positive airway pressure decrease fatigue in persons with symptomatic obstructive sleep apnea?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 59 persons with OSA | Double-blind trial<br><br>Subjects were randomized to (3-week intervention period):<br>• Therapeutic CPAP<br>• Placebo CPAP<br><br>Assessments:<br>• MHSI (fatigue/vigor)<br>• POMS (fatigue/vigor)<br>• ESS | Compated to placebo, therapeutic CPAP was associated with:<br>• Significantly reduced AHI<br>• Decreased fatigue and increased vigor*<br>• Reduced ESS scores in subjects with excessive sleepiness at onset of treatment** |

AHI: apnea hypopnea index; CPAP: continuous positive airway pressure; ESS: Epworth Sleepiness Scale; MFSI: Multidimensional Fatigue Symptom Inventory-Short Form; OSA: obstructive sleep apnea; POMS: Profile of Mood States - Short Form; *$P < 0.05$; **$P < 0.05$

***Conclusion***
Continuous positive airway pressure at therapeutic settings significantly reduced fatigue and increased energy in persons with obstructive sleep apnea.

***Commentary***
Obstructive sleep apnea (OSA) is a common disease with significant and, at times, devastating consequences. Continuous positive airway pressure (CPAP) can correct many of the comorbidities associated with OSA. Unfortunately, CPAP is an unpopular treatment and, at times, it can be difficult to motivate patients to comply with recommended use. Some of the most distressing symptoms of OSA are increased fatigue and lack of energy, symptoms that patients are more likely to endorse than the more commonly assessed construct of sleepiness.[1] There is good evidence that CPAP reduces sleepiness, but few studies have examined the effect on fatigue.[2,3]

We set out to investigate whether CPAP could reduce fatigue and increase energy in a relatively short treatment period of three weeks in OSA patients with a minimum AHI of 10. The positive expectancy set works both on prescribers and recipients of CPAP and for this reason we used a double blind, placebo-control comparing therapeutic CPAP to placebo CPAP. The use of stringent controls was important as we observed improvements in both the active and placebo groups; however, the improvements were significantly stronger in the CPAP group. Additionally, we were able to show convergent validity, with reductions in fatigue and increases in energy observed on three independent measures. Convergent validity is sparse in the clinical literature, and that coupled with the stringency of blinding in the trial increases our confidence in the validity of the findings.

We know that obesity, metabolic syndrome, depression, and cardiovascular comorbidities are common in OSA clinical samples. By definition, participants in clinical trials are precisely demarcated. The abundant exclusionary criteria necessary to secure a homogeneous study sample population often limit the representativeness and generalizability of the findings. One limitation of our study was that it enrolled relatively "healthy" patients with OSA, and it is unclear if the signal that we observed will be brighter or dimmer in the general population of OSA patients who suffer from multiple comorbid conditions.

Our findings bolster the academic literature demonstrating the benefits of CPAP therapy. Since motivation to perform healthy behaviors is influenced in part by the belief of benefit from the behavior, we hope that our findings will encourage OSA patients to pursue CPAP treatment with more alacrity.

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**Efficacy of rapid maxillary expansion in children with obstructive sleep apnea syndrome: 36 months of follow-up.** Villa MP, Rizzoli A, Miano S, Malagola C. *Sleep Breath. 2011 May;15(2):179-84.*

*What is the long-term outcome in children with dental malocclusion and sleep disordered breathing following rapid maxillary expansion?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 10 children with sleep disordered breathing<br>• Whose parents refused an adenotonsillectomy<br>• With deep, retrusive or crossbite at orthodontic evaluation<br>    ○ High narrow palate, n = 10<br>    ○ Crossbite, n = 6<br>    ○ Deep or retrusive bite or both, n = 4<br>• Who completed a 12-month therapeutic trial using RME<br>• Age: 6.6 ± 2.1 yrs<br>• Gender: 50% F<br>• Race: Caucasian<br>• BMI: 16.7 ± 3.6 Kg/m$^2$<br>• Tonsillar hypertrophy<br>    ○ Mild, n = 3<br>    ○ Moderate, n = 4<br>    ○ Severe, n = 2 | Prospective longitudinal study<br><br>Assessments:<br>• PSG (at baseline [T0], after 1 year [T1] and after 2 years at end of orthodontic treatment [T2])<br>• Personal and family history at T0, T1, T2<br>• Otorhinolaryngologic examination<br>• Orthodontic assessments at T0, T1, T2 | Number of children with moderate/severe tonsillar hypertrophy<br>• At T1: decreased significantly from 6 to 0<br>• At T2: increased from 0 to 1<br><br>AHI and SaO$_2$<br>• T0 to T1: AHI decreased and SaO$_2$ improved significantly.<br>• T1 to T2: no change in AHI and SaO2<br><br>Treatment failure at T2: 20%<br><br>No child experienced adverse effects with RME |

AHI: apnea hypopnea index; BMI: body mass index; OSA: obstructive sleep apnea; PSG: polysomnography; RME: rapid maxillary expansion; SaO2: oxygen saturation; SDB: sleep disordered breathing

### Conclusion
Rapid maxillary expansion resulted in improvements in clinical and polysomonographic signs and symptoms of pediatric sleep disordered breathing in the majority of children treated with this modality.

### Commentary
Orthodontic and craniofacial abnormalities in children with obstructive sleep apnea syndrome (OSAS) have been widely described though often ignored. Children with OSAS may have a narrow and long face, with large tonsils, a narrow upper airway, maxillary constriction and/or some degree of mandibular retrusion.[1,2] Rapid maxillary expansion (RME) is a dentofacial orthopedic treatment procedure routinely used in young patients to treat constricted maxillary arches; it is also considered a potential additional treatment in children presenting with OSAS, correcting posterior cross bite and widening the maxilla and maxillary dental arch, which reduce maxillary constriction and mouth breathing.[3-6] Pirelli et al[3]

demonstrated that RME is a valid treatment for OSAS in children without enlarged tonsils and adenoids, and another study demonstrated a partial response to adenotonsillectomy in children with OSAS and several facial abnormalities, involving the maxilla and mandible, suggesting that RME may be helpful to resolve OSA in these cases.[7]

We have previously evaluated the effectiveness of RME at 12 months as early orthodontic treatment for mild-to-moderate OSAS in young children with dental malocclusion. Fourteen treated subjects completed the study and follow-up; polysomnographic recordings showed that maxillary expansion resulted in a significant decrease in the AHI, hypopnea obstructive index and arousal index, even in patients with mild or severe tonsillar hypertrophy.[4] In view of those findings, the aim of this prospective longitudinal study was to evaluate the long-term outcome in the same group of young children (aged 4–10 years) with dental malocclusion successfully treated with RME. After treatment, the AHI decreased and the clinical symptoms had resolved.

These promising findings confirm that RME devices may be useful in the treatment of pediatric OSAS and provide further information on their long-term efficacy, and our long-term findings suggest that orthodontic treatment in children with dental malocclusion and OSA should be started as early as possible in the childhood period.

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**Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold.** Eckert DJ, Owens RL, Kehlmann GB, Wellman A, Rahangdale S, Yim-Yeh S, White DP, Malhotra A. *Clin Sci (Lond). 2011 Jun;120(12):505-14.*

*Can a non-benzodiazepine benzodiazepine receptor agonist alter the respiratory arousal thresholds and apnea hypopnea indices in persons with obstructive sleep apnea?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 17 persons with untreated OSA<br>• Without major hypoxemia (nadir $SaO_2$ >70%) | Double-blind, randomized, crossover trial<br><br>Following a baseline PSG, subjects were randomized to receive (on two additional nights 1 week apart) either placebo or eszopiclone (3 mg) immediately before an 8-h PSG (with an epiglottic pressure catheter to quantify the respiratory arousal threshold)<br><br>Definition:<br>• Low arousal threshold: 0 to -15 cm $H_2O$ | Compared to placebo, eszopiclone use resulted in:<br>• Increased respiratory AT by 18% (i.e., more pronounced negative epiglottic pressure immediately prior to arousal)*<br>• Decreased AHI by:<br>  o 23% (for the group)<br>  o 42% in subjects with low AT*<br>• Increased TST<br>• Improved SE<br>• Did not alter respiratory event duration or markers of hypoxemia |

AHI: apnea hypopnea index; AT: arousal threshold; OSA: obstructive sleep apnea; PSG: polysomnography; $SaO_2$: arterial blood oxygen saturation; SE: sleep efficiency; TST: total sleep time; *P < 0.01

*Conclusion*
In persons with untreated obstructive sleep apnea but without marked oxygen desaturation, eszopiclone given immediately prior to sleep increased the respiratory arousal threshold and lowered the apnea hypopnea index (AHI), with the greatest reductions in AHI occurring in those with a low respiratory arousal threshold.

*Commentary*
The underlying causes of obstructive sleep apnea (OSA) vary between patients.[1,2] Arousal from sleep to respiratory stimuli (e.g. upper airway narrowing/closure) is a fundamentally important physiological response. This form of arousal has been shown to be closely related to the magnitude of negative intrathoracic pressure generation immediately prior to arousal.[3] Experimentally, the ease with which an individual wakes up to a respiratory stimulus (the respiratory arousal threshold), can be quantified with the use of an esophageal or an epiglottic pressure catheter as the nadir pressure just prior to respiratory load-induced cortical arousal. In line with the variable causes of OSA, the respiratory arousal threshold varies considerably between patients. For example, some patients only require a minor perturbation to breathing (e.g. a small degree of upper airway narrowing) to elicit an arousal (a low arousal threshold) and others require more marked stimuli (e.g. prolonged airway closure) (a high arousal threshold).

The use of sedative medications in OSA patients has historically been discouraged due to concerns of impairment of protective arousal mechanisms believed to be essential for respiratory event termination and upper airway myorelaxant effects. However, on the basis of improved understanding of OSA pathogenesis, several observations have been brought to light including:

1) Most OSA patients have some periods of stable breathing in which respiratory events become temporarily absent at some stage of the night.[4]

2) While in some instances arousal from sleep can be an essential protective mechanism for airway opening during a respiratory event (i.e. in those with a high arousal threshold), not all respiratory events terminate with a cortical arousal, and awakening prematurely to respiratory stimuli (i.e. in those with a low arousal threshold) may perpetuate the OSA breathing cycle.[5]

The precise mechanisms as to why a low arousal threshold may be pathophysiologically disadvantages in OSA remain unresolved. However, we know that the upper airway dilator muscles are less responsive to respiratory stimuli (e.g. $CO_2$ and negative upper airway pressure) during sleep, and that periods of spontaneous breathing stability in OSA are associated with marked increases in the largest upper airway dilator muscle, genioglossus.[6] Therefore, more marked respiratory stimuli for a greater duration is required for adequate upper airway dilator muscle activation during sleep compared to wakefulness. Thus, premature awakening (a low arousal threshold) may limit adequate exposure to the levels of respiratory stimuli that are required to promote upper airway muscle dilatation and breathing stability in some OSA patients. Accordingly, it has been proposed that attempting to increase the respiratory arousal threshold to prevent frequent premature arousals in the appropriately selected patients (i.e. those with a low arousal threshold) may promote stable breathing and be therapeutically advantageous.

On the basis of this rationale, we completed a randomized, double-blind, placebo controlled trial using the non-benzodiazepine sedative, eszopiclone.[7] This medication was selected as this class of sedative is believed to have less upper airway myorelaxant properties than benzodiazepines, although this remains to be systematically tested. Patients with marked hypoxemia (nadir $SaO_2 < 70\%$) were excluded from the trial as it was felt that impairing arousal in these individuals would worsen, not improve, breathing stability and blood gas disturbances. Interestingly, of 6 OSA patients that were excluded from participation in the main trial due to this criterion, all had high arousal threshold values. The remaining 17 OSA patients that completed the trial had predominately low to moderate arousal threshold values. For the group as a whole, 3 mg of eszopiclone significantly increased the respiratory arousal threshold, lowered the AHI, increased total sleep time, improved sleep efficiency, and lowered the arousal index. When residual respiratory events did occur, they were not of increased duration or associated with worsening hypoxemia. In the 8 OSA patients identified as having a low arousal threshold (defined as > -15cmH$_2$O of epiglottic pressure immediately prior to arousal), reductions in the AHI occurred invariably and were most pronounced. The study findings also suggest that approximately one third of untreated OSA patients may have a low arousal threshold and may be amenable to this novel approach.

These data provide new insight as to the importance of a low arousal threshold in OSA pathogenesis. Furthermore, these findings raise the possibility that certain sedative medications may be of therapeutic benefit in carefully selected OSA patients (i.e. those with a low arousal threshold). While these exciting data pave the way for future investigation, many unanswered questions need to be addressed before this approach can be considered clinically. For example: 1) what are the cardiovascular effects of an AHI reduction with a sedative medication versus no treatment?; 2) are arousal threshold and AHI reductions with a sedative maintained over time?; 3) what are the effects of this approach on OSA symptoms?, and 4) are there simplified strategies to ensure that only the appropriate patients (i.e. those with a low

arousal threshold) are targeted for this approach and avoided in those in whom OSA would be predicted to worsen with a sedative (i.e. those with a high arousal threshold)? To summarize, these findings not only provide new pathophysiological insight, they also offer hope than non-CPAP therapeutic alternatives may be a realistic possibility in the future for carefully selected OSA patients. Ultimately, to achieve this goal, improved understanding of the various underlying pathophysiological causes of OSA in individual patients is required.

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**Flexible pressure delivery modification of continuous positive airway pressure for obstructive sleep apnea does not improve compliance with therapy: systematic review and meta-analysis.** Bakker JP, Marshall NS. *Chest. 2011 Jun;139(6):1322-30.*

*Does flexible pressure delivery of continuous positive airway pressure affect treatment compliance and outcomes?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 10 randomized trials (599 subjects) comparing flexible and standard CPAP in adult persons with OSA and ≥ 1 week follow-up<br><br>Compliance data could be extracted from 7 trials (514 subjects) | Meta-analysis<br><br>Systematic literature search of PubMed (1-1-2000 to 7-11-2010)<br><br>Assessments:<br>• Means, SE and sample sizes for all relevant outcome measures<br>• Objective compliance<br>• ESS<br>• MWT<br>• PVT | Compared with CPAP, flexible pressure resulted in:<br>• No improvement in compliance<br>• No improvement in ESS, MWT, PVT and residual OSA |

CPAP: continuous positive airway pressure; ESS: Epworth Sleepiness Scale; MWT: Maintenance of Wakefulness Test; OSA: obstructive sleep apnea; PVT: Psychomotor Vigilance Task

***Conclusion***
Flexible pressure settings in continuous positive airway pressure devices did not improve device compliance or treatment outcomes.

***Commentary***
Continuous positive airway pressure (CPAP) is the standard evidence-based treatment for moderate-to-severe obstructive sleep apnoea (OSA);[1,2] however, its effectiveness is often limited by high rejection rates and poor compliance.[3] Flexible pressure is a modification of standard CPAP delivery which aims to improve comfort and, therefore, compliance by reducing incoming pressure during early exhalation, returning to prescribed therapeutic pressure for the latter part of exhalation and subsequent inhalation.[4]

The first study of flexible pressure found a clinically and statistically significant improvement in compliance over standard CPAP.[5] Unfortunately as a non-randomized and incompletely blinded clinical trial, that study was open to a number of biases that turned out to be crucial as over the next few years a series of randomized controlled trials failed to replicate this effect.

Whilst none of the randomized controlled trials we were aware of reported a beneficial effect of flexible pressure, that did not rule out the possibility that when aggregated an important but subtle clinical effect was actually occurring. Each of the clinical trials on its own could have been underpowered to detect something we could see with all of them combined. As such, we felt that a systematic review and meta-analysis pooling all the available evidence in one place would be useful for practicing clinicians.

We independently searched a ten-year period of the PubMed database (2000-2010) in order to identify all randomised controlled trials of at least one week duration comparing flexible and standard pressure delivery in adult patients with OSA. Ten trials met our inclusion criteria, with a pooled sample size of 599 patients. We both extracted the data independently and then compared our results, collating descriptive characteristics of the samples as well as the mean, standard deviation and sample size for compliance, Epworth Sleepiness Scale (ESS) score, Maintenance of Wakefulness Test (MWT) sleep latency, Psychomotor Vigilance Task (PVT) reaction time, and residual apnea-hypopnea index (AHI).

Analyzable compliance data were reported in seven trials with a pooled sample size of 514 patients. The weighted mean difference in compliance between flexible and standard pressure was 0.16 hours/night (95% CI -0.09 to 0.42) in parallel studies and 0.20 hours/night (95% CI -0.26 to 0.66) in crossover studies. In addition to not meeting statistical significance, these differences of less than 15 minutes are unlikely to be clinically relevant.[6] Flexible pressure was also not associated with any significant improvement in subjective sleepiness (ESS score difference of < 1/24 points), objective sleepiness (MWT sleep latency difference of < 1 minute) or objective vigilance (PVT reaction time difference < 31 milliseconds). On a positive note, we did not detect a difference in disease control between the two treatment modes (AHI difference < 1 event/hour).

We concluded that despite the widespread clinical use of flexible pressure technology, it confers no additional benefit over standard CPAP. We discussed the possibility that flexible pressure may be useful as a rescue therapy in those patients struggling to become established on standard CPAP, but a subsequent in-press publication addressing the use of automatically-adjusting BPAP for this purpose found no significant effect.[7] There may still exist some patient sub-groups in which a significant difference in compliance is evident, such as those suffering from CPAP-induced aerophagia. Given the current absence of controlled clinical trials addressing this issue, clinicians must continue to rely on patient-by-patient judgment.

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**Identification by primary care clinicians of patients with obstructive sleep apnea: a practice-based research network (PBRN) study.** Mold JW, Quattlebaum C, Schinnerer E, Boeckman L, Orr W, Hollabaugh K. *J Am Board Fam Med. 2011 Mar-Apr;24(2):138-45.*

*What proportion of primary care patients is at risk for obstructive sleep apnea and how well do primary care clinicians currently identify them?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 1,357 subjects 30-64 yrs old (consecutive, prospective)<br>• Gender: 61% F<br>• Race: white 65%; black 16%; hispanic: 25%<br>• Age (mean): 47.5 ± 9.9 yrs<br>• BMI (mean): 30.2 ± 7.6<br><br>734 subjects ≥ 65 years old (consecutive, prospective)<br>• Gender: 60% F<br>• Race: white 82%; black 10.3%; hispanic 9.5%<br>• Age (mean): 73.9 ± 6.7<br>• BMI (mean): 27.8 ± 6.5<br><br>725 subjects with OSA diagnosis (retrospective, all):<br>• Gender: 43% F<br>• Age (mean): 52.7 ± 13.8 yrs<br><br>1,019 subjects ≥ 65 years old (retrospective, random sample):<br>• Gender: 61% F<br>• Age (mean): 74.7 ± 7.3<br><br>44 PCs randomly selected from 5 states (Florida, Alabama, Oklahoma, Connecticut and California)<br>• FM: 93%<br>• GIM: 7%<br>• Location: urban 30%; suburban 52%; rural 18%<br><br>18 sleep consultants used by participating PCs | Retrospective chart review<br><br>Assessments:<br>• BQ<br>• Interviews with PCs and sleep consultants<br>• Medical records abstraction<br>• Patient surveys | Among consecutive younger adult subjects being seen in primary care settings:<br>• 90% reported recent sleep-related symptoms (only 16.9% had reported them to their PC)<br>• 48.8% had high risk Berlin scores (estimated true prevalence of OSA was 15-22%)<br>• 10% had been diagnosed with OSA (50% by current PC)<br><br>Among consecutive older adult subjects being seen in primary care settings:<br>• 83% reported recent sleep-related symptoms (only 18%% had reported them to their PC)<br>• 38.6% had high risk Berlin scores (estimated true prevalence was 12-25%)<br>• 7% had been diagnosed with OSA (46% by current PC)<br><br>Among those with OSA:<br>• Sleep-related symptoms noted in 82% of records<br>  o Snoring: 58%<br>  o Daytime sleepiness: 45%<br>  o Apneic episodes: 27% |

| | | Among older adults without diagnosed OSA: <br> • Sleep-related symptoms recorded in 27% of records <br>     o Snoring: 3% <br>     o Daytime sleepiness: 4% <br>     o Apneic episodes: 1% <br><br> Among PCs: <br> • 23% reported routinely screening for OSA using Review of Systems <br> • < 1% used Berlin or Epworth questionnaires <br> • Estimated 84% of PSGs positive for OSA <br><br> According to sleep consultants: <br> • 67% of referrals for evaluation of OSA were from PCs <br> • Estimated 85% of PSGs positive for OSA |
|---|---|---|

FM: Family Medicine; GIM: General Internal Medicine; BQ: Berlin Questionnaire score; OSA: obstructive sleep apnea; PC: primary care clinician

### Conclusion

Many persons who saw their primary care clinicians were at high risk for obstructive sleep apnea, but were not being diagnosed or treated.

### Commentary

Population-based screening of United States adults estimate the prevalence of at least moderate OSA (defined, using PSG, as an AHI $\geq$ 15) to be between 2% and 7%.[1-4] AHI is almost twice as common in males as in females and two to ten times more common in 60 to 70 year-olds than in 30 to 40 year-olds.[1, 5-7] The 5-year incidence has been estimated to be as high as 10%, reflecting the effects of both age and a secular trend toward more risk factors, especially obesity, within the population.[5]

OSA is associated with obesity, insulin resistance, diabetes mellitus, systemic hypertension, pulmonary hypertension, heart attacks, congestive heart failure, strokes, sleep-related arrhythmias, nocturnal angina and mortality.[8-10] Individuals with an AHI of > 10 are 6.3 times more likely, and those with an AHI $\geq$ 34 are 15 times more likely to be involved in a motor vehicle accident. Several studies have found that identification and treatment of OSA with continuous positive pressure (CPP) devices reduces health care costs in the subsequent year, primarily because treatment decreases the cost of subsequent evaluation

and treatment of hypertension and cardiovascular disease, and treatment of OSA reduces hospital days by 50%.[11-14] However, treatment is not always well-accepted by patients.

The two evidence-based guidelines registered with the National Guidelines Clearinghouse appear to make the assumption that identification of patients with OSA is desirable. However, they stop short of recommending universal screening, suggesting that primary care clinicians identify patients at risk for OSA by taking into account risk factors such as obesity and increased neck circumference, using "a thorough Review of Systems" including questions related to OSA, and looking for medical conditions, such as hypertension and cardiovascular diseases.[15]

Given lingering uncertainties regarding the benefits and burdens associated with identification and treatment of OSA, the overall shortage of primary care clinicians, and primary care processes that are often inadequate to assure that risk factors, reviews of systems, and medical conditions are effectively combined into risk profiles, it should not be surprising that a majority of patients with OSA have not been identified. One study estimated that more than 80% of men and more than 90% of women with OSA remain undiagnosed.[3]

Our data suggest a large majority of patients who visit PCCs have sleep-related symptoms, but most do not spontaneously report them to their PCC, and they are rarely recorded in the medical record. Based upon their responses to the Berlin Sleep Questionnaire, 35 - 50% of patients seen on any given day are at high risk for OSA.[16-19] Few PCCs routinely screen patients for OSA. Clinicians who do screen use the Review of Systems administered during annual physical examinations. However, if this method is to be recommended, it should be noted that annual exams would have to be performed on all adult patients, and the Reviews of Systems would need include specific OSA symptoms. Many don't.[20] When PCCs do identify patients with concerning symptoms or signs, they appear to only refer those they are sure have OSA for diagnostic testing based upon positive polysomnograms rates of around 85%.

The high rate of sleep-related symptoms in patients attending primary care practices supports an earlier study conducted in 10 practices in Oklahoma, in which 99% of patients reported at least one sleep-related symptom.[21] In a larger study involving 1935 patients being seen in primary care practices in North Carolina, the proportion experiencing any sleep-related symptom was not reported, but more than 50% reported excessive daytime sleepiness, more than one-third had dozed off during daytime activities, and 13% reported that someone had witnessed apneic spells during sleep.[22]

The proportion of patients at high risk for OSA is not surprising. When the Berlin Sleep Questionnaire was administered to 1506 adults who participated in the 2005 National Sleep Foundation's *Sleep in America* poll, 31% of men and 21% of women were found to be at high risk.[23] Patients being seen on any given day in primary care practices are more likely to have symptoms and co-morbidities than members of community population samples.

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**Impact of nasal obstruction on obstructive sleep apnea.** Friedman M, Maley A, Kelley K, Leesman C, Patel A, Pulver T, Joseph N, Catli T. *Otolaryngol Head Neck Surg. 2011 Jun;144(6):1000-4.*

*Does nasal obstruction from packing following nasal surgery affect the severity of obstructive sleep apnea?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 49 subjects with snoring who were to undergo nasal surgery<br>• 23 with RDI ≥ 15<br>• 26 with RDI < 15 | Prospective, nonrandomized controlled study<br><br>Assessments: PSG within 30 days prior to surgery and on first night following nasal surgery with nasal packing in place (RDI, minimum $SaO_2$, ODI and snoring) | In subjects with mild, but not, moderate/severe OSA, nasal packing was associated with :<br>• Increase RDI: 5.2 ± 4.0 vs. 10.4 ± 10.0*<br>• Increased duration of snoring: 86.5% ± 13.1% vs. 79.3% ± 15.3%**<br>• Increased ODI: 7.6 ± 7.1 vs. 9.9 ± 7.4***<br><br>No change in mean minimum $SaO_2$ in either group |

ODI: oxygen desaturation index; OSA: obstructive sleep apnea; PSG: polysomnography; RDI: respiratory disturbance index; $SaO_2$: oxygen saturation; SDB: sleep disordered breathing; *P = .0001; **P = .008; ***P = .001

***Conclusion***
Postoperative nasal packing following nasal surgery worsened respiratory disturbance indices and oxygen desaturation indices in persons with mild, but not moderate-severe, obstructive sleep apnea.

***Commentary***
Patients with obstructive sleep apnea (OSA) often have concurrent nasal obstruction; as well, nasal obstruction has been implicated as an independent, etiological factor in the pathogenesis of OSA.[1,2] The role of nasal obstruction in OSA, however, remains a conjecture, as a review of the literature shows that there have been no conclusive studies or reviews that definitively mark nasal airway obstruction as a major causative factor in OSA.[3,4] Currently, no correlation has been found between the severity of OSA and nasal patency.[5] Similarly, studies assessing the impact of surgical procedures to eliminate nasal obstruction have shown variable outcomes.[6,7] The purpose of this study was to investigate the relationship between nasal obstruction and sleep-disordered breathing with a prospective controlled study.

In this study, the effect of postoperative nasal packing on sleep parameters was compared between patients with mild obstructive sleep apnea (OSA) and those with moderate/severe OSA. Forty-nine consecutive patients with a history of significant snoring and suspected OSA and nasal obstruction scheduled to undergo nasal septoplasty were recruited. A baseline preoperative overnight sleep study was performed 30 days prior to the nasal septoplasty. Patients were classified according to RDI as having mild OSA (RDI < 15) or moderate to severe OSA (RDI ≥ 15). Other metrics recorded included hours spent

asleep, oxygen desaturation index (ODI), mean minimum oxygen saturation, snoring statistics as well as BMI, age and gender. Participants underwent septoplasty at a tertiary care center, followed by bilateral postoperative nasal packing placement with Telfa dressings. A postoperative sleep study was performed in the hospital with postoperative nasal packing in place. Statistical analyses were then performed on and between each group to compare preoperative versus postoperative measures of snoring, apnea/hypopnea and oxygenation during sleep studies.

The 26 patients classified as having mild OSA did not differ from the 23 patients classified as having moderate to severe OSA in mean age (P = .436) or in gender distribution (P = .086). However, there were significant differences in BMI, snoring duration, mean RDI/ODI and minimum oxygen saturations. Following surgery, the 2 groups had similar percentage durations of snoring (P = .224), however, the moderate/severe OSA patients had a higher postoperative mean RDI, higher mean ODI and lower mean minimum oxygen saturation. In the mild OSA patients, significant increases in snoring duration (P = .008), RDI (P = .008) and ODI (P = .019) were identified. There was no change in mean minimum arterial oxygen saturation (P = .425). In patients with moderate to severe OSA, postoperative values for snoring duration, RDI, ODI and minimum arterial oxygen saturation were not different from preoperative values.

Our study indicates that patients with mild OSA experienced a worsening in objective measures of OSA following postoperative nasal packing that was not appreciated among the moderate/severe group. Intuitively, one would assume that nasal obstruction aggravates OSA by preventing airflow. The adaptive response is a switch to oral breathing, which results in a decreased hypopharyngeal airspace and increased airway resistance, exacerbating OSA. It is possible that, preoperatively, patients with mild OSA primarily experienced partial nasal airway obstruction, which was converted to complete obstruction following postoperative packing. Among this patient population, total obstruction aggravated OSA. Conversely, patients with moderate/severe OSA and multi level obstruction are likely chronic mouth breathers,[8,9] and obstructing the nasal airway has little impact on their respiratory function. Given that these populations of patients are likely dependent mouth breathers, nasal obstruction may create an increased expiratory positive pressure, analogous in principle to continuous positive airway pressure or expiratory positive airway pressure. Measures of snoring were not aggravated in patients with severe OSA, which was consistent with previous reports of nasal surgery being ineffective for reducing measures of snoring in patients with sleep-disordered breathing.

While correcting an obstructed nasal airway and restoring nasal patency have been established as important components of the management of OSA, studies have shown that surgical intervention to correct nasal occlusion has shown limited efficacy for the treatment of OSA.[6,7] Friedman et al[10] found that approximately 50% of patients who undergo nasal airway reconstruction will experience worse objective outcomes on a postoperative sleep study, even though they may show subjective symptomatic improvement. Recent studies have also reported that nasal procedures have been ineffective for treating OSA. In addition, nasal dilators for a collapsed nasal valve, and steroids to reduce swelling of the nasal turbinates in OSA patients with allergic rhinitis have proven to be ineffective in treating OSA. Further studies are needed investigating the effects of chronic obstruction before one can make a definitive conclusion about the role of nasal airway patency in sleep-disordered breathing.

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**Influence of continuous positive airway pressure on outcomes of rehabilitation in stroke patients with obstructive sleep apnea.** Ryan CM, Bayley M, Green R, Murray BJ, Bradley TD. *Stroke. 2011 Apr;42(4):1062-7.*

*Does treatment of OSA in persons following stroke improve motor and neuropsychological function?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 48 subjects with stroke and OSA in a stroke rehabilitation unit<br>• AHI ≥ 15<br>• Within 3 weeks of stroke onset<br>• CPAP naive<br><br>44 subjects completed the study | Randomized, open-label, parallel group trial<br><br>Subjects were randomized to:<br>• Fixed CPAP and standard care (4 weeks): n = 22<br>• Standard care (4 weeks): n = 22<br><br>Assessments (at baseline and 1 month):<br>• Canadian Neurological scale<br>• 6MWD<br>• Sustained attention response test<br>• Digit or spatial span-backward<br>• ESS<br>• SSS<br>• FI measure<br>• CMS assessment<br>• Neurocognitive function<br>• BDI | CPAP compliance: 5.0 ± 2.2 hrs per night<br><br>Compared to standard care, CPAP was associated with greater improvements in:<br>• Canadian neurological scale*<br>• Motor score of FI**<br>• Leg motor function on CMS***<br>• ESS*<br>• Affective component of BDI[#]<br><br>CPAP group had significant improvements in:<br>• 6MWD<br>• Digit and visual spatial span-backwards<br>• Berg balance scale<br><br>CPAP group had no significant improvement in:<br>• Vigilance<br>• Visuo-motor speed<br>• Hand dexterity |

6MWD: six minute walk distance; BDI: Beck Depression Inventory; CMS: Chedoke McMaster Stroke; CNS: Canadian Neurological Scale; CPAP: continuous positive airway pressure; ESS: Epworth Sleepiness Scale; FI: Functional Independence; OSA: obstructive sleep apnea; SSS: Stanford Sleepiness Scale; *P < 0.001; **P = 0.05; ***P = 0.001; [#]P=0.006

***Conclusion***
Continuous positive airway pressure therapy for obstructive sleep apnea in persons with subacute stroke improved acute neurological scores and motor function, and reduced subjective sleepiness, but did not improve vigilance or most indices of cognitive functioning.

***Commentary***

Recent studies have demonstrated a high prevalence of OSA in stroke patients.[1] Furthermore, observational prospective and cross-sectional studies have shown an increase in both morbidity and mortality in stroke patients with OSA.[2-5]

Although treatment of OSA in stroke patients in the acute, subacute and chronic phases of stroke is feasible, it is limited due to poor patient compliance and acceptance, which has varied between 18 and 80% in different studies.[6-9] Physical disabilities, cognitive problems and post-stroke depression are some of the factors contributing to this poor compliance and tolerance. Poor compliance (1.4 hours per night) was demonstrated in a previous randomized controlled trial of 6 months duration and probably was responsible for the lack of improvements in functional outcomes and depression scores.[7] The other randomized trial published at the time, despite adequate compliance, had failed to demonstrate a significant improvement in outcomes other than a reduction in depression scores. Patients in this study had predominantly central sleep apnea and were of older age (mean age of 78 years).[10]

Therefore, this study was developed to evaluate 4 weeks of CPAP treatment in patients in a stroke rehabilitation unit approximately 3 weeks following an acute stroke. Due to the inpatient nature of the study, CPAP related issues were resolved promptly and compliance was very good with an average daily use of 4.96 hours, equating to an approximate mean CPAP use of 88% of sleep time.

The primary and secondary outcomes chosen were composite measures to evaluate motor and neuropsychological function and subjective sleepiness. Participation and time spent in physiotherapy was evaluated to determine if treatment with CPAP altered either due to increased alertness or decreased fatigue or sleepiness.

Baseline characteristics of the stroke subjects were similar at baseline. Both the control and CPAP groups had a severe degree of obstructive sleep apnea (AHI, 33.3 vs. 38.5 events/hour, respectively). There were no differences in participation or amount of time spent in physiotherapy between the groups. The most pertinent findings were that, when compared to the control group, those in the CPAP group demonstrated significant improvements in the Canadian Neurological scale and reductions in the Epworth sleepiness scale. The improvements occurred predominantly in the motor function domains of the functional scales (e.g., FIM and Chedoke Mcmaster scale, CNS). There was a significant improvement in the 6MWD in the CPAP group but this was not statistically significant for between-group differences. Most notably there were no significant changes in vigilance, hand dexterity, viso-motor speed or most cognitive measures in the CPAP group.

The pathophysiological mechanisms underlying the motor and functional improvements but not cognitive improvements attained in this study are unclear, but may be as a result of enhanced neuroplasticity. More recently two other randomized controlled trials also demonstrated early neurological improvements in those treated with CPAP.[9,11] However, Parra and colleagues failed to demonstrate an improvement in survival or quality of life following 2 years follow-up.[9]

Overall, in this study, the observed differences in outcomes between the CPAP group and control groups were modest. Small numbers, the heterogenous nature of stroke and the short follow-up time may have contributed to the lack of any further discernible differences between the groups. Further research is needed in this area to delineate those stroke patients who would most benefit from treatment of obstructive sleep apnea.

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**Longer term effects of very low energy diet on obstructive sleep apnoea in cohort derived from randomised controlled trial: prospective observational follow-up study.** Johansson K, Hemmingsson E, Harlid R, Trolle Lagerros Y, Granath F, Rössner S, Neovius M. *BMJ. 2011 Jun 1;342:d3017.*

*Are improvements in obstructive sleep apnea following weight reduction from a very low energy diet maintained on long-term follow-up?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 63 men with moderate to severe OSA treated with CPAP <br> • Age: 30-65 yrs <br> • BMI 30-40 <br> • AHI ≥ 15 <br><br> 58 subjects completed the VLED period and started weight maintenance program <br><br> 44 completed the full program <br><br> 49 had complete measurements at 1 yr | Prospective observational follow-up study <br><br> Protocol: one-year weight loss program consisting of an initial VLED (9 weeks) followed by a weight loss maintenance program <br><br> Assessment: <br> • AHI (Watch PAT) at baseline, 9 weeks and 52 weeks <br> • ESS <br> • Body weight <br> • Waist and neck circumference <br> • % body fat <br> • Health related quality of life (SF-12 health survey) <br> • Metabolic syndrome <br> • Metabolic variables | Mean AHI: <br> • Baseline: 36 <br> • After VLED: reduced by 21* (weight was reduced by 18 kg**), <br> • After 1 yr: reduced by 17 (weight was reduced by 12 kg)*** <br><br> Improvements in AHI were greater in subjects with severe (-25) compated to moderate (-7) OSA at baseline[#] <br><br> At one year: <br> • 48%[##] of subjects no longer required CPAP <br> • 10%[###] had resolution of OSA (AHI < 5) <br><br> Weight loss was correlated with AHI at follow-up^ <br><br> Improvements noted at 1-yr follow-up: <br> • Metabolic variables (dyslipidemia, insulin resistance and metabolic syndrome) <br> • HTN (22% subjects with hypertension at baseline had complete resolution) <br><br> Adverse effects during VLED included: <br> • Constipation <br> • Dry lips |

| | | |
|---|---|---|
| | | • Gout<br>• Dizziness<br>• Increased ALT levels<br><br>Adverse effects during weight loss maintenance period:<br>• Gallstones<br>• Gout<br>• Kidney stones |

AHI: apnea hypopnea index; BMI: body mass index; CPAP: continuous positive airway pressure; HRQOL: health related quality of life; OSA: obstructive sleep apnea; VLED: very low energy diet; *95% CI -17 to -25; **P < 0.001; ***both P < 0.001; #P < 0.001; ##95% CI 35-60%; ###2-17%; ^β = 0.50 events/kg, 0.11-0.88; P = 0.013

### Conclusion
There was significant improvement in disease severity following a weight loss program in persons with obstructive sleep apnea.

### Commentary
About two-thirds of patient with obstructive sleep apnea (OSA) are either overweight or obese and weight loss seems to be a logical intervention in overall management. Randomized controlled trials have previously shown a positive effect of weight loss on obstructive sleep apnea. Tuomilehto et al enrolled 81 patients with mild OSA in a two-year post intervention follow-up study that included one year of lifestyle intervention followed by a year of observation. Seventy-one patients completed the study and results showed 47% reduction in the apnea hypopnea index in patients with mild obstructive sleep apnea after a very low energy diet (at 12 weeks), a 40% reduction with 11 kg weight loss after one year, and a 46% reduction with a 7 kg weight loss after two years.

In older patients (mean age 61) with type 2 diabetes, Foster et al were able to show a 24% reduction in the apnea hypopnea index after one year with 11 kg weight loss with intensive lifestyle intervention, while the apnea hypopnea index increased in control patients, representing 42% change between groups.

Several studies have shown dose-response association between weight loss and the apnea hypopnea index including Foster et al, Tuomilehto et al and in previous study done by current group. Lojander et al found that obstructive sleep apnea was improved with nurse-managed program that included very low calorie diet (500 kcal/day) and behavioral management. Kajaste et al showed satisfactory weight loss with a cognitive-behavioral weight loss program.

In addition to dietary interventions, weight loss surgery has also been shown to result in long-term improvements in obstructive sleep apnea. In a large Swedish study that enrolled 3477 patients, Grunstein et al found that 30% of the surgery group reported persistent sleep apnea at the two-year follow-up compared with 70% of the control group.

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**Nasal pillows as an alternative interface in patients with obstructive sleep apnoea syndrome initiating continuous positive airway pressure therapy.** Ryan S, Garvey JF, Swan V, Behan R, McNicholas WT. *J Sleep Res. 2011 Jun;20(2):367-73.*

*Which is a better patient interface for continuous positive airway pressure therapy – a nasal pillow or a standard nasal mask?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 21 persons with OSA and a successful CPAP titration <br> • Gender: 10% F <br> • Age: 49 ± 10 yrs <br> • AHI: 52 ± 22 | Crossover design <br><br> Subjects were randomized to 4 weeks of CPAP therapy (10 ± 2 cmH2O) via either NP or NM <br><br> Assessments: <br> • Objective compliance <br> • AHI <br> • QOL <br> • ESS <br> • CPAP side-effects | No difference between interfaces in: <br> • Compliance: 5.1 ± 1.9 h (NM) vs. 5.0 ± 1.7 h (NP)* <br> • AHI: 2.6 ± 2.7 (NM) vs. 3.0 ± 2.9 (NP)** <br> • Extend of improvement in QOL and ESS <br> • Overall preference: 57% (NM) vs. 43% (NP)*** <br><br> Use of nasal pillows was associated with: <br> • Less reported pressure on the face <br> • More reports of greater comfort <br><br> No correlation between applied CPAP pressure and compliance, AHI and ESS |

AHI: apnea hypopnea index; CPAP: continuous positive airway pressure; ESS: Epworth Sleepiness Score; NM: standard nasal mask; NP: nasal pillow; OSA: obstructive sleep apnea; QOL: quality of life; * P=0.701; **P = 0.509; ***P = 0.513

***Conclusion***
No differences in compliance, patient preference and effectiveness were found between nasal pillows and nasal masks used for continous positive airway pressure therapy.

***Commentary***
Continuous positive airway pressure (CPAP) is the treatment of choice in patients with obstructive sleep apnea syndrome (OSAS), particularly in moderate to severe cases. It acts to splint the airways open during sleep and the treatment has been shown to improve daytime sleepiness, alertness, quality of life; to reduce the risk of road traffic and occupational accidents; and to decrease cardiovascular morbidity and mortality. However, the device is cumbersome and compliance rates are only moderately satisfactory. Side effects with CPAP therapy are common and represent a key factor in impaired treatment adherence. Adverse consequences of CPAP treatment are often side effects directly related to the nasal mask and

include skin breakdown, air leaks, claustrophobia and mask dislodgement.[1] Different interfaces have been developed to overcome these problems but only limited data are available to demonstrate their effectiveness and, following the conclusion from a recent Cochrane review, the optimal interface for CPAP delivery remains unclear.[2] Nasal pillows are an alternative device and as there is less contact with the face, they may potentially lead to an improved side effect profile and hence, to greater patient satisfaction and compliance. The aim of the present study, therefore, was to test the hypothesis that a recently developed nasal pillow (Mirage Swift II, Resmed, UK) improves compliance, side effects, sleepiness and quality of life in OSAS patients initiating CPAP therapy in comparison to a standard nasal mask (Ultramirage, Resmed).[3] 21 Subjects were assigned to a 4-week period each of nasal pillows and a nasal mask in a randomized, crossover design. Outcome measures were objective compliance, quality of life (short form 36), subjective sleepiness (Epworth Sleepiness Score), CPAP side effects and preference; all variables were assessed using a validated questionnaire and by direct interview. Usage of nasal pillows resulted in less reported pressure on the face and more subjects found the nasal pillow a more comfortable device. However, compliance rates, objective and subjective effectiveness as well as side effect profile were similar, and there was no difference in overall preference for device at the end of the study.

These results support previous findings indicating that different interfaces may lead to improved comfort in individual cases but do not generally result in greater adherence to CPAP therapy.[4,5] Rather, compliance with CPAP is improved by a multidisciplinary approach taking into account patient characteristics, parameters of disease severity, aspects of the interface, factors relating to the initial exposure, in addition to psychological and social factors.

Importantly, the nasal pillow was equally effective to the standard nasal mask in reducing apneas/hypopneas as well as improving daytime sleepiness, and thus, could be considered as the initial choice, particularly if proper mask fitting cannot be achieved with a standard nasal mask.

Our study emphasizes the importance of assessing patients on an individual basis for the optimal interface with CPAP therapy.

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**Obstructive sleep apnea in patients with abdominal aortic aneurysms: highly prevalent and associated with aneurysm expansion.** Mason RH, Ruegg G, Perkins J, Hardinge M, Amann-Vesti B, Senn O, Stradling JR, Kohler M. *Am J Respir Crit Care Med. 2011 Mar 1;183(5):668-74.*

*Is there an association between the presence of obstructive sleep apnea and the rate of expansion of abdominal aortic aneurysms?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 127 persons in an AAA surveillance program<br>• Gender: 8% F<br>• Age: 67.9 ± 6 yrs<br>• Median interval between the first and last AAA measurements: 18 months* | Assessments:<br>• Retrospective analysis of annual AAA expansion using ultrasound<br>• ODI<br>• AHI | ODI > 10 was present in 40.5% of subjects<br><br>AHI > 10 was present in 41.5% of subjects<br><br>ODI > 30 was associated with faster median yearly AAA expansion rate** than an ODI 0-5 (n = 47*** or 6-15 (n = 43[#]) |

AAA: abdominal aortic aneurysm; AHI: apnea hypopnea index; CVS: cardiovascular; ODI: oxygen desaturation index; OSA: obstructive sleep apnea; *range 2-113 months; **2.9; quartiles 2/5.7 mm/y; ***1.2; quartiles 0/3.1 mm/y; [#]1.3; quartiles 0/2.7 mm/y; P < 0.05

*Conclusion*
Obstructive sleep apnea was prevalent in persons with abdominal aortic aneurysm, and was an independent risk factor for expansion of the latter.

*Commentary*
OSA is thought to cause vascular damage both as a result of direct shear stress via the substantial rises in blood pressure with each arousal from apneas,[1] and the intermittent hypoxia/reoxygenation which has been proposed as a cause of oxidative stress, endothelial dysfunction and vascular inflammation leading to atherosclerosis.[2]

An aortic aneurysm is a permanent focal dilatation of the aorta with respect to its original size and most commonly occurs between the renal and inferior mesenteric arteries. An abdominal aortic diameter greater than 3 cm is considered aneurismal[3] and is found in 4-9% of those aged over 60 yrs.[3-6] Smoking, atherosclerosis, hypertension and a family history are all associated with an increased risk of developing an aneurysm.[4,7]

There are some theoretical reasons why the abdominal aorta may be affected in OSA. Importantly, there are marked transient increases in blood pressure, as great as 80 mmHg, at the end of an obstructive apnea, as a result of the sympathetic burst accompanying the arousal that terminates the apnea.[8] These blood pressure swings would not only repeatedly expand the aneurysm, but they may also impose excessive shear stresses on blood vessel walls, which are thought to be important factors in the

development of atherosclerosis.[1] In addition, OSA has been shown to be associated with a diurnal increase in blood pressure.[9,10]

As treatment of OSA with CPAP therapy abolishes the blood pressure swings associated with apneas[11] and lowers diurnal blood pressure,[9] identification of a relationship between OSA and rate of aneurysm expansion would justify a subsequent randomized controlled trial to identify OSA as a modifiable risk factor. Therefore, we performed a study to assess the prevalence of OSA in those individuals with AAA.

In this study, 40% of the patients were found to have an ODI of > 10/h. Despite a considerable number of patients with OSA in this population, the ESS was within the normal range (< 10) in 82% of the patients. There was no overall correlation between ESS and either the AHI or ODI measures of OSA, although the ESS in the most severe group (ODI > 30) was significantly higher (mean of 9) compared to 5 in the mild group (ODI 6-15). This suggests that a subjective report of daytime sleepiness is not a suitable method for identifying potential cases of OSA in a cohort of patients with AAA.

AAA can be associated with life-threatening conditions including thrombosis, embolization and especially rupture.[6] It is still a matter of debate which factors contribute to rapid expansion of aneurysms seen in some patients.[12,13] This is the first study in which the potential relationship between OSA and aneurysm expansion in patients with AAA has been investigated. Our data show that patients with severe OSA had a significantly higher yearly aneurysm expansion rate than patients without, or only mild OSA, even when controlled for cardiovascular risk factors and medication use. Inspection of the data also suggests that there is not a simple linear dose-response relationship between OSA severity and AAA expansion rate, but perhaps a threshold effect; it may be that only the more pronounced and frequent intrathoracic pressure swings and sympathetic bursts (with resultant rises in blood pressure) seen in patients with severe OSA[8] lead to irreversible changes in aortic diameter.

We have shown that there is a high prevalence of OSA in a population of patients with abdominal aortic aneurysms. It is not possible to predict the presence of OSA in these patients by assessment of subjective sleepiness. Severe OSA may be a risk factor for more rapid abdominal aortic aneurysm expansion, and controlled trials investigating the effects of OSA therapy on aneurysm expansion rate are warranted to prove this relationship.

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**Racial/ethnic and socioeconomic disparities in the diagnosis and treatment of sleep-disordered breathing in children.** Boss EF, Smith DF, Ishman SL. *Int J Pediatr Otorhinolaryngol. 2011 Mar;75(3):299-307.*

*Do racial, ethnic, or socioeconomic health disparities exist for children with sleep disordered breathing?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 33 publications on racial/ethnic or socioeconomic differences in prevalence, diagnosis or surgical treatment of SDB in children<br>• 14 prospective cohort<br>• 4 retrospective cohort<br>• 12 cross-sectional<br>• 3 case-control | Qualitative systematic review of MEDLINE database through a 25-year period (ending 9/30/2010) by 2 analysts<br><br>Assessments:<br>• SDB prevalence<br>• Sleep quality and patterns<br>• Long-term sequelae of SDB<br>• Healthcare utilization (including T&A) | Findings in minority populations:<br><br>Black children (12 studies)<br>• At greater risk for persistence of SDB after T&A<br>• SDB was more prevalent compared to white children<br>• More nasal obstruction<br>• Lower oxygen desaturations<br>• More likely to develop SDB at a younger age<br>• Greater impairment in cognitive function and behavior associated with snoring<br>• Less likely than white children to have undergone T&A in predominantly black community (rural Mississipi)<br><br>Hispanic children (3 studies)<br>• More snoring, daytime sleepiness and witnessed apneas<br>• Less stage 3 and 4 sleep<br><br>Children from low SES (17 studies)<br>• At greater risk for SDB<br>• Displayed more parasomnias, insomnia, enuresis, gagging, noisy sleep and fatigue<br>• Increased likelihood of learning problems and lower GPA<br>• In U.S. (California), many |

| | | |
|---|---|---|
| | | specialists were unwilling to see children with public insurance |
| | | • In Scotland and Canada, low SES was associated with increased rates of tonsillectomy |

AT: adenotonsillectomy; GPA: grade point average; SDB: sleep disordered breathing; SES: socioeconomic status; T&A: tonsillectomy and adenoidectomy

*Conclusion*
Racial/ethnic and socioeconomic disparities were common among children with sleep disordered breathing.

*Commentary*
This report is a qualitative systematic review that summarizes existing evidence related to racial/ethnic and socioeconomic disparities in pediatric SDB. A "health disparity" is described as an "inequitable difference between groups in health, healthcare and developmental outcomes that are potentially systematic and avoidable."[1, 2] Because vulnerable populations are known to have worse health status, research into health disparities has been widely prioritized in recent years. Indeed, "eliminating health disparities" was one of two primary objectives for the Healthy People 2010 initiative.[3] Likewise, *equity* is one of 6 fundamental domains of quality healthcare delivery as defined by the Institute of Medicine.[4] This review represents the first effort to broadly quantify what is known about these sensitive health disparities, highlighting many areas for further research in pediatric sleep medicine. Specifically, barriers to evaluation and treatment of SDB for minority and socially vulnerable children should be elucidated in order to improve overall health outcomes.

SDB in children presents a significant public health burden. SDB comprises a range of sleep respiratory behaviors from primary snoring to obstructive sleep apnea. SDB is prevalent in 5-20% of the pediatric population, but occur more commonly in children with comorbidities such as obesity or Down's syndrome.[5,6] SDB in children has been associated with physical sequelae such as systemic and pulmonary hypertension, nocturnal enuresis and failure to thrive.[7-9] SDB is also known to have negative psychological and neurobehavioral sequelae in children including poor quality-of-life, hypersomnolence, hyperactivity, decreased attention and poor school performance.[10-13] Both quality-of-life and behavior in children with SDB improves following surgical therapy with T&A.[14-16] Moreover, T&A has been shown to reduce healthcare costs and utilization in children with OSA by up to 60%.[17]

In our systematic review, black race and low SES, among other racial/ethnic minorities, were found to be significant risk factors for SDB in children. Some proposed explanations for these differences have been attributed to factors such as household crowding, increased prevalence of obesity or higher exposure to secondhand smoke.[18-22] Treatment with T&A for minority children, however, was noted to vary. Two U.S. studies included in this review detailed poor access to otolaryngology subspecialty care and lower than expected T&A utilization for children with low SES, although these studies were based on small numbers of children from single geographical regions.[23,24] A more recent analysis, developed in response to findings from this systematic review, utilized nationally-representative data from the National Survey for

Ambulatory Surgery and demonstrated that increased need for T&A for children from minority race/ethnicities and from lower SES may not be met with current utilization trends, however reasons for poor utilization are not well-established.[25-27]

This report provides a foundation for research in health disparities related to SDB in children. Certainly, knowing the physical and neurocognitive consequences as well as decreased quality-of-life associated with SDB in children, minority and at-risk children could potentially experience greater benefit with prompt diagnosis and therapy for SDB. Future research should identify barriers to evaluation, diagnostic testing and treatment for SDB in at-risk or minority children. Furthermore, insight into cultural perspectives on significance of snoring and sleep problems, implications of surgical therapy, and quality of care related to SDB would be highly valuable.

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**Randomised controlled trial of auto-adjusting positive airway pressure in morbidly obese patients requiring high therapeutic pressure delivery.** Bakker J, Campbell A, Neill A. *J Sleep Res. 2011 Mar;20(1 Pt 2):233-40.*

*Which is more effective in treating obstructive sleep apnea - continuous positive airway pressure or auto-adjusting positive airway pressure?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 12 morbidly obese persons with severe OSA<br>• AHI: 75.8 ± 32.7<br>• BMI: 49.9 ± 5.2 kg m(-2)<br>• Pressure (mean): 16.4 cmH$_2$O | Randomized, single-blinded crossover trial<br><br>Subjects were randomized to CPAP or APAP for 6 nights separated by a 4-night washout<br><br>Assessment: PSG | Reduction in AHI:<br>• APAP: 9.8 ± 9.5<br>• CPAP: 7.3 ± 6.6*<br><br>Average 95th percentile pressure<br>• APAP: 14.2 ± 2.7 cmH$_2$O<br>• CPAP: 16.1 ± 1.8 cmH$_2$O **<br><br>Machine-scored AHI significantly higher than laboratory-scored AHI (using Chicago criteria) |

AHI: apnea hypopnea index; APAP: auto-adjusting positive airway pressure; BMI: body mass index; CPAP: continuous positive airway pressure; OSA: obstructive sleep apnea; PSG: polysomnography; *P = 0.35; **P = 0.02

### Conclusion
Compared to continuous positive airway pressure, auto-adjusting positive airway pressure for obstructive sleep apnea resulted in similar improvements in apnea hypopnes indices and lower average 95th percentile pressures.

### Commentary
Fixed continuous positive airway pressure (CPAP) is the first-line treatment for obstructive sleep apnea (OSA). However, the pressure required to splint the upper airway open varies not only between-patients, but also within-patients depending on factors such as sleep stage and position.[1] Hence, applying a fixed pressure means that some patients invariably receive a higher pressure than is strictly necessary during some portion/s of the night.

Sophisticated automatically-adjusting positive airway pressure (APAP) technology is available in some devices, which works by adjusting pressure on a breath-by-breath basis in response to flow limitation and airway obstruction. APAP has been used both as a long-term treatment option, and as a means of titration to determine an appropriate pressure for long-term treatment with fixed CPAP.[2] There are considerable advantages to both uses. If used long-term, the lower overall mean pressure delivered by APAP may reduce pressure-related side-effects and ultimately improve compliance, although the overall compliance benefit of APAP over CPAP is small.[3] If used as a titration device the need for an expensive laboratory-based manual titration is eliminated, reducing costs and expanding access to treatment. The major drawback to APAP is that the manufacturers make only limited information regarding the

technology public. There are substantial differences between devices in terms of the way flow limitation and obstruction are detected as well as the subsequent pressure response,[4] meaning that APAP remains as something of a 'black box'.

Prior to our *Journal of Sleep Research* study, we had observed that when APAP was applied to some morbidly obese patients during attended titration, it rarely reached very high pressures for extended periods, despite ongoing respiratory events. No published clinical trial had systematically assessed the use of APAP in OSA patients requiring high therapeutic pressures; we therefore sought to perform a pilot randomized controlled trial comparing residual disease with APAP and CPAP in patients with severe OSA requiring pressure ≥ 14cmH$_2$O, without major co-morbidity. A secondary aim was to compare the residual apnea hypopnea index (AHI) scored by the APAP device with the laboratory-scored AHI.

We recruited a consecutive sample of morbidly obese OSA subjects with confirmed manually-titrated pressure ≥ 14 cmH$_2$O (mean ± SD BMI 49.9 ± 5.2 kg/m$^2$, mean ± SD AHI 75.8 ± 32.7 events/hour, mean fixed pressure 16.4 cmH$_2$O, range 14-20). All underwent laboratory-based diagnostic polysomnography (PSG) and a separate manual CPAP titration following clinical guidelines,[5] before being randomized to receive CPAP or APAP (ResMed S8) for six nights at home separated by a four-night washout. A laboratory-based PSG with treatment took place at the end of each arm.

APAP and CPAP resulted in significant AHI reductions from baseline of > 85%. There was no significant difference in the laboratory-scored residual AHI, despite the mean 95th percentile pressure with APAP being almost 2 cmH$_2$O lower than with CPAP. However, we did not perform a third arm whereby patients were treated with fixed CPAP using their APAP-determined pressure; therefore, we cannot directly comment on the use of APAP as a titration device in this sample. Forty-five percent of the sample had a residual AHI above 5 events/hour with both APAP and CPAP, although the patients who were poorly treated with one mode were also poorly treated with the other. In both treatment modes, the device-scored residual AHI was significantly higher than the laboratory-scored AHI, by approximately 5 events/hour. We found no significant differences in compliance, Epworth Sleepiness Scale scores, or treatment comfort between modes.

At the time of publication, our study sample had a higher mean AHI, BMI and manually titrated pressure than any other randomized controlled trial comparing APAP and CPAP. We found no evidence of a clinically or statistically significant difference in residual AHI between the two treatments, suggesting that at this stage, the final long-term treatment choice can be determined by weighing up factors such as access to sleep facilities, cost concerns and patient/clinician preference. The fact that the ResMed S8 device overestimated rather than underestimated residual disease is of some comfort, however further studies need to be performed in larger samples with this device and others before metrics of this kind can be completely relied upon. Further research should also be directed towards assessing the suitability of APAP as a titration device in a variety of OSA sub-groups, including samples such as ours requiring high-pressure delivery. The rapid advances in positive airway pressure technology are highly beneficial to our field; however, we urge researchers to continue to investigate new treatment options, working in balanced partnership with device manufacturers, in order to guide clinical decisions as to how best to treat patients with OSA.

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**Sex differences in obstructive sleep apnoea in an elderly French population.** Sforza E, Chouchou F, Collet P, Pichot V, Barthélémy JC, Roche F. *Eur Respir J. 2011 May;37(5):1137-43.*

*What are the clinical, anthropometric and polygraphic gender differences among elderly persons with obstructive sleep apnea?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 641 persons<br>• Age (mean): 68 yrs | Assessments:<br>• Fat mass (DEXA)<br>• PSG<br><br>Definition: OSA – AHI of > 15 | OSA was present in 57%<br>• Mild: 34%<br>• Severe (AHI > 30): 23%<br><br>Compared to men, women had:<br>• Lower AHI<br>• Less severe hypoxemia<br>• Greater peripheral fat mass<br><br>No differences in clinical, anthropometric and DEXA data between women with and without OSA<br><br>HTN was significantly associated with OSA risk in women* |

AHI: apnea hypopnea index; BMI: body mass index; DEXA: dual-energy X-ray absorptiometry; DM: diabetes mellitus; HTN: hypertension; OSA: obstructive sleep apnea; *OR 1.52, P = 0.04

*Conclusion*
Among elderly persons with obstructive sleep apnea, women had lower apnea hypopnea indices and less severe hypoxemia than men.

*Commentary*
In obstructive sleep apnea (OSA), gender seems to affect the incidence of the disease, being more prevalent in men than in women with a male:female ratio of 8-10:1 or greater in clinical studies.[1] Multiple factors explain the reduced susceptibility to OSA in women, such as body fat distribution, upper airway shape and property, and hormonal influences.[2] Moreover, women with OSA are less likely to have the classic symptoms of OSA[2] and they had lower apnea hypopnea index (AHI), frequently confined to rapid-eye movement (REM) sleep. [3]

Since OSA in older adults may not have the same functional consequences seen in middle-aged adults, we examined the gender differences in sleep related symptoms, sleepiness, mood disorders, fat distribution and cardiovascular risk in 641 subjects aged 68 yr or older.

Compared to males, females had lower body mass index (BMI) and neck circumference (NC) and reported more frequent hyperlipidemia and history of anxiety and depression. Females did not complain of snoring and apnea at the Berlin questionnaire (P = 0.005), they self-perceived to be less sleepy at the Epworth

sleepiness scale, and were more anxious (P < 0.05) and depressed (P < 0.001). When we considered polygraphic data, females had less severe AHI and hypoxemia. Compared to women without OSA, women with OSA were more frequently positive at the Berlin questionnaire (P < 0.01), more frequently reported HTA (45.6% vs. 35.5%, P = 0.04), had a greater intake of antidepressants and had a trend to increased use of anxiolytics. Considering anthropometric data, women with OSA had greater BMI (25.6 ± 0.3 vs. 24.2 ± 0.3 Kg/m$^2$, P < 0.01) and a greater neck circumference (OSA women: 34.9 ± 0.2 cm vs. women without OSA: 34.0 ± 0.2 cm, P = 0.02) without differences for waist and hip circumference.

The main findings of our study may be summarized in three points. Firstly, the OSA incidence in our sample decreased compared to middle-aged population, the OSA risk being 1.31 in our group. Secondly, as in middle-aged studies, women reported less frequently the cardinal symptoms of OSA and had a higher risk to have had, or to be treated, for mood and anxiety disorders. Although, depression and anxiety scores were higher in OSA women, comparison of women with and without OSA showed that there were no significant differences between groups for anxiety and depression scores as well as for previous psychiatric treatment, suggesting that these symptoms reflect more a gender phenotype that an OSA consequence. Thirdly, OSA women have increased risk of pathological obesity but comparison of women with and without OSA showed lack of significant differences in anthropometrics and DEXA values, suggesting that obesity and fat distribution do not contribute to OSA risk in elderly women. Finally, analysis of factors associated with OSA shows that hypertension and increased systolic blood pressure are the factors associated with the increased OSA risk in older women that would be exposed more frequently to vascular ischemic risk. This greater risk for hypertension on OSA elderly women may be related to gender differences in endothelial dysfunction,[4] or genetic predisposition[5] and susceptibility[6] to hypertension, as suggested in middle-aged patients.

In conclusion, in a community elderly population, the incidence of undiagnosed OSA in women is similar to that found in men. The atypical clinical spectrum and the fat distribution in OSA women appear to be more gender-related than OSA-dependent. The presence of OSA predisposes women to increased risk of hypertension stressing the need for prompt therapy in these cases.

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**Telemetric CPAP titration at home in patients with sleep apnea-hypopnea syndrome.** Dellacà R, Montserrat JM, Govoni L, Pedotti A, Navajas D, Farré R. *Sleep Med. 2011 Feb;12(2):153-7.*

*What is the feasibility of a telemetric system for home continuous positive airway pressure titration for obstructive sleep apnea?*

| Subjects | Methods | Outcomes |
| --- | --- | --- |
| 20 subjects with SAHS<br>• Age: 56 ± 3 yrs<br>• BMI: 35 ± 2 kg/m² | One-night home telemetric CPAP titration followed one week later by a hospital PSG | Home-titrated CPAP improved:<br>• AHI: from 58.1 ± 5.1 to 3.8 ± 0.6 events per h<br>• $\%SaO_2 < 90\%$: from 19.8 ± 1.1% to 4.4 ± 0.7%,<br><br>Optimal CPAP settings between telemetric home and PSG titrations were similar:<br>• Telemetric home: 9.15 ± 0.47 $cmH_2O$<br>• PSG: 9.20 ± 0.41 $cmH_2O$* |

$\%SaO_2 < 90\%$: percentage of sleep time with arterial oxygen saturation below 90%; AHI: apnea hypopnea index; BMI: body mass index; CPAP: continuous positive airway pressure; PSG: polysomnography; SAHS: sleep apnea-hypopnea syndrome; *mean difference: 0.02 $cmH_2O$, limits of agreement: ± 1.00 $cmH_2O$

*Conclusion*
Optimal continuous positive airway pressure settings for obstructive sleep apnea were similar between polysomnography and telemetric home titration.

*Commentary*
To date, the gold standard for diagnosing sleep apnea and for determining optimal positive airway pressure settings for treatment has been an in-laboratory polysomnography. At times, these sleep studies can take up limited healthcare resources. In addition, some patients find in-laboratory studies uncomfortable and may not sleep well enough to obtain valuable information. To improve patient comfort and as cost-saving measures, there has been a push to diagnose sleep apnea using home sleep testing and to adjust positive airway pressure therapy in the home. Currently, automatic positive airway pressure (auto-PAP) devices are used to help determine effective pressures for treatment of sleep apnea. The pressures delivered by these machines are adjusted based on proprietary algorithms. Stored data from the machine are then downloaded so that optimal pressure settings can be determined retrospectively. Auto-PAP titrations have been successful in determining optimal pressure settings.[1,2] However, titrations using auto-PAP devices are not recommended for patients with significant co-morbidities such as congestive heart failure, patients with significant chronic obstructive pulmonary disease, and central sleep apnea syndromes.[3]

In this study, a continuous positive airway pressure (CPAP) titration was performed in the home of 20 consecutive patients diagnosed with sleep apnea. On average, the sleep apnea was severe based on the in-laboratory polysomnogram. A conventional CPAP device was tested overnight on the patient while

telemetric monitoring was performed. The telemetric unit, which functioned also as an Internet server, was connected to the CPAP device, and transmitted data in real time. Flow, pressure, and leaks were monitored by a sleep technician located remotely. Based on this real-time information, the CPAP pressure was titrated according to protocol.

Similar efficacy was demonstrated for in-home CPAP titration study versus in-laboratory titration. The optimal pressure determined in-home was almost the same as that obtained in-laboratory with significant improvements in AHI in both cases. However, it is important to point out that this was an unblinded study and that the same technician titrated the remote CPAP and the in-laboratory CPAP and was aware of the optimal pressure determined by each. Further studies comparing telemetric titration versus in-laboratory titration targeting groups currently excluded from auto-PAP titrations would be of interest. Furthermore, information regarding oxygen saturation would provide additional valuable data, particularly in selected patients.

Telemedicine is increasingly being used to improve the efficiency and economics of healthcare delivery.[4] This study presents a novel and effective method of adjusting positive airway pressure therapy remotely for treatment of sleep apnea. The telemetric monitoring and adjustment of pressure settings can be used initially to determine an effective CPAP pressure and later to re-evaluate and optimize subsequent CPAP settings. It may be useful in patients who are currently excluded from undergoing an in-home, unmonitored auto-PAP titration and in patients for whom auto-PAP data is confusing or unhelpful. It is efficient by allowing the real-time determination of an effective CPAP setting versus a retrospective review of stored auto-PAP data. This model is also remarkably cost-effective in that the patient remains at home, one technician may monitor and adjust settings in more than one patient at a time, and the telemetric unit functions as its own Internet server. The use of a telemetric unit for CPAP titration shows promise in the real-time determination of effective treatment for sleep apnea.

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**The effect of exercise on obstructive sleep apnea: a randomized and controlled trial.** Sengul YS, Ozalevli S, Oztura I, Itil O, Baklan B. *Sleep Breath. 2011 Jan;15(1):49-56.*

*Does breathing and physical exercise improve pulmonary function, apnea hypopnea index and quality of life of patients with obstructive sleep apnea?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 20 male patients with mild to moderate OSAS<br>• Age: 40-65 yrs | Subjects were randomized to:<br>• Aerobic and breathing exercises (applied for 12 weeks): n=10<br>• Control: n=10<br><br>Assessments (before and after exercise):<br>• Anthropometric data<br>• Exercise testing, PFT, MIP, MEP<br>• QOL (SF-36)<br>• Quality of sleep (FOSQ)<br>• ESS<br>• PSG | Compared to baseline, exercise was associated with:<br>• No change in anthropometric parameters<br>• No change in FVC% and $FEV_1$/FVC<br>• Improved MaxVO$_2$, MET and maximum work load (W)<br>• Improved vitality and mental health domains<br>• Improved activity level<br>• Improved AHI |

AHI: apnea hypopnea index; ESS: Epworth Sleepiness Scale; FEV1/FVC: forced expiratory volume in the first second as a percent of predicted value/forced vital capacity; FOSQ: Functional Outcomes of Sleep Questionnaire; FVC: forced vital capacity as a percent of predicted; MaxVO$_2$: maximal oxygen consumption; MEP: maximal expiratory pressure; MET: metabolic equivalents; MIP: maximal inspiratory pressure; OSA: obstructive sleep apnea; PFT: pulmonary function test; PSG: polysomnography; QOL: quality of life; SF36: Short Form-36

*Conclusion*
Exercise improved apnea hypopna indices, health-related quality of life, quality of sleep and exercise capacity, but not anthropometric characteristics and respiratory function, in persons with mild to moderate obstructive sleep apnea.

*Commentary*
The pathophysiology underlying obstructive sleep apnea (OSA) is unclear and complex.  Thus, treatment options for OSA are confusing. Treatment modalities can be divided into two parts as nonsurgical and surgical methods. Some studies have defined lower airway obstruction although upper airway anatomy is the most important reason for OSA.[1] In addition, the link between systemic metabolic aberrations such as increased plasma concentrations of the cytokines, and upper airway collapse has been suggested in the literature.[2,3] Most studies on exercise training have emphasized improvement in OSA symptoms and quality of life.[4-6] Many physicians recommend an active lifestyle and weight loss for these patients. Research has supported this opinion because physically active patients with OSA experience less severe OSA symptoms compared to those who are less active.[7] Consequently body weight, upper airway dilator

muscles or respiratory instability have been shown as the primary defect. To start to answer this query, we investigated the effects of physical and breathing exercise training on pulmonary function, apnea-hypopnea index (AHI) and quality of life in patients with OSA.

The subjects were randomized to exercise (n = 10) and control (n = 10) groups. The control group was not given any information and/or exercise apart from routine clinical treatment and proposals. The exercise group received breathing and aerobic exercises three times a week for 12 weeks. After breathing exercises, the patients did warm up exercises. Then, they did aerobic exercises, resistance, and duration of which were increased according to their tolerance on bicycle and treadmill. During the treadmill and bicycle exercises, which were applied at sub-maximal intensity at 60–70% of maximal oxygen consumption, it was ensured that the intensity of fatigue that the patients perceived was at the interval of 4–5 according to the Modified Borg scale. Heart rate and peripheral oxygen saturation was measured by pulse oximeter during these exercises. After the bicycle and treadmill exercises, exercise program was finished with a cooling down period. Anthropometric measurements, pulmonary function tests, exercise capacity, quality of sleep and health-related quality of health were repeatedly measured at the end of week 12 in order to describe the effects of exercise treatments in patients with OSA.

The results of our study demonstrated that supervised exercise training reduced the severity of OSA. We determined improvement in quality of life and sleep parameters of mental health, activity level and vitality. Expected results after breathing exercises were improvement in outcomes of pulmonary function tests. When this study was completed, we found that parameters of the pulmonary function tests did not change despite significant improvements in all indices of exercise testing. Supervised aerobic exercises that we took great pains with following heart rates and blood pressure for maintaining submaximal exercise level for each exercise session showed effectiveness in exercise test results. In addition, anthropometric measurements did not change at the end of the exercise period. All these given results were collected from male patients who had mild to moderate OSA. We selected a study sample that consisted of male OSA patients because it's well known that this disorder affects men more frequently than women and is often associated with central obesity and possible deleterious effects of male sex hormones.

In conclusion, exercise training applied to patients with OSA surprisingly decreased AHI despite no changes in breathing function and anthropometric characteristics. The positive effect of aerobic exercises on OSA patients is well known although its underlying mechanism is not known. Exercise may affect sleep by many different mechanisms, but there is not enough research on clinical exercise training to find out these mechanisms. We know that small sample size is a limitation of this study. Further studies are needed to define the role of exercise mechanisms in patients with OSA. If the researchers solve this mystery, clinicians and also patients who are coping with the symptoms of OSA can be guided in the management of this disease.

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# Circadian Rhythm Sleep Disorders

**Phase advance with separate and combined melatonin and light treatment.** Paul MA, Gray GW, Lieberman HR, Love RJ, Miller JC, Trouborst M, Arendt J. *Psychopharmacology (Berl). 2011 Mar;214(2):515-23.*

*Are the effects of properly timed melatonin and light additive or synergistic in phase advancing circadian rhythms?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 11 subjects | Subjects spent from Tuesday evening until Friday afternoon in the laboratory under one of four conditions and three sleep schedules: <br><br> Four conditions: <br> • Melatonin (3 mg) administered at 1600 h on Wednesday <br> • Placebo administered at 1600 h on Wednesday <br> • Light (green light administered between 0700-0800 h on Thursday) <br> • Melatonin plus light (3 mg melatonin at 1600 h on Wednesday and green light treatment between 0600 and 0700 h on Thursday) <br><br> Three sleep schedules: <br> • Night 1: 2345 to 0630 h <br> • Night 2: 1600 to 0530 h <br> • Night 3: 2345 to 0700 h <br><br> Assessments: <br> • Pre- and post-treatment DLMO assessments on Tuesday and Thursday evenings | Changes in phase (advancements) were: <br> • Melatonin at 1600 h: 0.72 h* <br> • Light treatment from 0700 to 0800 h: 0.31 h** <br> • Combined treatment: 1.04 h*** |

DLMO: dim light melatonin onset; *P < 0.005; **non-significant; ***P < 0.0002

*Conclusion*

There was an additive effect on phase advancement from combination afternoon melatonin and next morning light administration.

*Commentary*

Crowley et al. used a combination of intermittent bright light during night shifts, sun glasses for the commute home, and 1.8 mg SR (slow release) melatonin prior to daytime sleep to adapt subjects to simulated night shifts but the effects of light and melatonin were not separated.[1] Wirz-Justice et al. reported that bright light from 2100 to 2400 h caused a phase delay of 0.68 h. They also found that melatonin treatment at 2040 h resulted in a phase advance of 0.40 h. However, when they combined these two treatments, the net phase shift was similar to their placebo condition concluding that the combined effects of light and melatonin are additive.[2] Revell et al. evaluated the phase advancing efficacy of three daily melatonin doses (0.5 mg, taken about 3 h before DLMO and 3 mg , taken about 5 h before DLMO) , along with four daily 30-min light pulses upon awakening with 30–min between adjacent pulses. They found phase advances of 1.7, 2.5, and 2.6 h for each of light only, 0.5 mg melatonin plus light, and 3.0 mg melatonin plus light, respectively, demonstrating that a 0.5 mg dose taken daily 3 h before DLMO is as effective as a 3 mg dose taken 5 h before DLMO. However, since melatonin was not administered without light, the effects of melatonin alone could be determined.[3]

Prior to the work discussed here, we assessed green light at approximately 350 lux (eye-level ) for efficacy in each of phase advance and phase delay.[4] We also assessed 3 melatonin formulations (3 mg regular release (RR), 3 mg sustained release (SR), and 3 mg surge-sustained release (SSR), consisting of 1 mg regular release and 2 mg sustained release for both phase advance and phase delay.[5] In the current study,[6] we wished to determine whether or not the combined effects of melatonin and light are additive or synergistic (i.e., more than the sum of the separate phase shifting effects of each treatment) in terms of net phase shifting efficacy.

The subjects taking part in this study had an average pre-treatment DLMO of 20.97 ± 0.15 h across all 4 treatment conditions (3 mg SR melatonin at 1600 h, placebo at 1600 h, light treatment from 0700 to 0800 h, and the combined condition with 3 mg SR melatonin at 1600 h with next morning light treatment advanced by 1 hr [i.e., 0600 h to 0700 h since we anticipated that the 16 h melatonin dose would advance the DLMO by about 1 hour]) to keep the light treatment at the optimum point on the light phase response curve for phase advance.  We found no synergy in phase shifting efficacy for the combination of 3 mg SR melatonin  (0.72 h) and green light (0.31 h) but if those 2 separate effects are added together (1.03 h), we obtain the same result as combining the 2 effects (1.04 h) confirming that the effects are completely additive. The other significant finding in this study is that melatonin had more than twice the phase shifting efficacy of this specific light treatment.

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**The human circadian system adapts to prior photic history.** Chang AM, Scheer FA, Czeisler CA. *J Physiol. 2011 Mar 1;589(Pt 5):1095-102.*

*Does prior photic history affect light's effects on phase-shifting of endogenous circadian rhythms?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 17 healthy adults<br>• Gender: 40% F<br>• Age: 23.8 ± 2.7 yrs | Randomized, controlled, single blinded, crossover study<br><br>32-day inpatient protocol<br><br>Subjects were assigned to two prior light conditions prior to light exposure (6.5 hrs in duration at the beginning of the subjective night)<br><br>Prior light history:<br>• Very dim light: 1 lux<br>• Typical room light: 90 lux<br><br>Light exposures:<br>• Control light exposure: 1 lux<br>• Experimental light exposure: 90 lux<br><br>Assessments:<br>• Plasma melatonin suppression<br>• Phase resetting | Compared to prior typical room light exposure, prior very dim light history was associated with greater melatonin suppression and greater phase delays in response to subsequent light stimulus |

*Conclusion*
Compared to indoor room light exposure, very dim illuminance increased the phase-shifting response to subsequent photic stimulus.

*Commentary*
The human circadian system organizes and regulates the timing of many biochemical and physiological processes, including the timing of sleep, on a daily basis. Light is the most potent stimulus for synchronizing the endogenous circadian clock to the 24-hour day. Although the timing,[1-3] intensity,[4] duration,[5, 6] and wavelength[7, 8] of light are known to modulate photic resetting of the circadian system and acute suppression of melatonin secretion, the effect of prior photic history on these processes is not well understood. Previous studies in humans have provided evidence of modulation of the sensitivity of the melatonin-suppressing response by prior lighting conditions[9-11] but there were no published reports of the effect of prior light on the phase-resetting response.

Data from 13 healthy young adults who participated in a controlled, randomized, single-blinded, crossover study were analyzed to compare the effects of two prior light conditions on the melatonin suppression and phase resetting responses to a subsequent light exposure (LE). Each participant was exposed to four LEs: two experimental LEs and two control LEs. Each LE lasted 6.5 h in duration and was administered during the biological night in order to induce maximal phase delays and melatonin suppression by the experimental LEs. The illuminance of the control LEs was very dim (1 lux) and not expected to produce any significant suppression or phase shift of plasma melatonin levels and enabled control for any effects of the experimental protocol other than the LEs. The illuminance of the experimental LEs (90 lux), a typical indoor room light level, was selected to provide sufficient stimulus for the suppression and phase shifting of melatonin but not to saturate these circadian responses. Each control and experimental LE was preceded by 3 days of either very dim or typical room light (1 lux vs. 90 lux) as a prior light history.

Very dim light history (1 lux) sensitizes the circadian timing system to the melatonin-suppressing (68% increase) and phase-shifting (63% increase) effects of a subsequent light exposure as compared to typical room light history (90 lux). Similarly, the moderately dim room illuminance of 90 lux is sufficient to blunt the efficacy of a sub-saturating light exposure on the circadian system. Taken together, these results provide evidence for dynamic adaptive changes in the sensitivity of circadian ocular photoreception.

These are the first published findings to show the impact of prior photic history on the circadian phase-resetting response to light in humans. While the results of adaptation of the circadian pacemaker by prior photic history are striking, there is much still unknown regarding the effect of prior light exposure. The time course for the dynamic adaptive changes of sensitization and desensitization of circadian ocular photoreception is not precisely known and warrants further investigation. Defining this plasticity and the influence of prior photic history on the timing of the human circadian system has significant implications for application in both scientific and clinical settings. Potentiating the photic sensitivity of the circadian pacemaker would amplify phase shifts in response to light stimuli and may allow the use of lower intensity and/or shorter duration of light stimuli to achieve a similar effect. Ultimately, the clinical implication of such findings may enable the optimization of light therapy in the treatment of circadian phase misalignment. Application for these and other results of studies examining the role of photic history in sensitizing the human circadian system may be most useful in the treatment of shift work sleep disorder with light and/or sleep schedules and thus should be considered in treatment plans.

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# Parasomnias and Movement Disorders

**Efficacy and augmentation during 6 months of double-blind pramipexole for restless legs syndrome.**
Högl B, Garcia-Borreguero D, Trenkwalder C, Ferini-Strambi L, Hening W, Poewe W, Brenner SS, Fraessdorf M, Busse M, Albrecht S, Allen RP. *Sleep Med. 2011 Apr;12(4):351-60.*

*What is the long-term efficacy of pramipexole therapy for restless legs syndrome?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 331 persons with RLS<br><br>• Pretreatment serum ferritin > 30 ng/mL<br><br>234 subjects completed the study | Subjects were randomized to one of the following for 26 weeks:<br>• Pramipexole: 0.125-0.75 mg/d<br>• Placebo<br><br>Assessments:<br>• IRLS score<br>• Global change<br>• Symptoms<br>• QOL<br>• Development of augmentation<br><br>Definitions:<br>• IRLS responder rate: ≥50% score reduction | Compared to placebo, pramipexole was associated with:<br>• Greater change in adjusted mean IRLS score: -13.7 vs. -11.1*<br>• Higher IRLS responder rate: 58.6% vs. 42.8%**<br>• Greater incidence of augmentation: 9.2% vs. 6.0%<br>• More treatment-related adverse events |

IRLS: International RLS Study Group Rating Scale; QOL: quality of life; RLS: restless legs syndrome; *P = 0.0077; **P = 0.0044

### Conclusion

A 6-month therapy using pramipexole was more effective in reducing symptoms of restless legs syndrome but was associated with greater risk of augmentation compared to placebo.

### Commentary

Augmentation is the main complication of dopaminergic drug therapy of restless legs syndrome (RLS). Previous reports, based on retrospective case series and varying definitions of augmentation, reported augmentation rates of higher than 70 % in patients on levodopa treatment, and up to 30 % in patients on dopamine agonist treatment. Only very recently, data on augmentation based on a standardized definition of augmentation, the use of validated instruments for augmentation (such as the Augmentation severity scale of the European RLS Study Group) and data derived from trials which included retrospective or prospective assessment of augmentation with standardized instruments and expert panels under dopaminergic treatment, have become available, for instance, the retrospective analysis of medium- or

long-term open label treatment data, or the prospective assessment of augmentation during a double blind placebo controlled study, such as the present study.

The present study is a phase IV, randomized, double blind, placebo controlled dose titration trial with pramipexole treatment of RLS over 6 months and safety testing that included augmentation. Suspected augmentation cases (from multiple entry points) were reviewed by an expert panel. The confirmed rate of augmentation was 9.2 % for pramipexole and 6.0 % for placebo. The authors concluded, based on the presence of a similar augmentation rate with placebo treatment, that beginning or mild augmentation is difficult to distinguish from natural RLS fluctuations.

This is one of the recent papers, which have assessed the occurrence of augmentation with appropriate methods under treatment with currently used dopamine agonists. Compared to retrospective evaluation of augmentation based on varying definitions, the rates were lower than in previous retrospective case series with pramipexole. However, for the assessment of augmentation, studies longer than 6 months seem to be needed and appropriate.

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**Preferential D2 or preferential D3 dopamine agonists in restless legs syndrome.** Manconi M, Ferri R, Zucconi M, Clemens S, Giarolli L, Bottasini V, Ferini-Strambi L. *Neurology. 2011 Jul 12;77(2):110-7.*

*Which dopamine agonist receptor subtype, D2 or D3, plays the key role in the treatment of restless legs syndrome?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 45 drug-naive persons with idiopathic RLS and PLMS | Placebo-controlled, prospective, single-blind trial<br><br>Subjects were randomized to either:<br>• Bromocriptine (D2 preferential agonist) 2.5 mg<br>• Pramipexole (D3 preferential agonist) 0.25 mg<br>• Placebo<br><br>Assessments:<br>• Two consecutive full night PSGs (one without medication and another with medication or placebo)<br>• Symptoms of restlessness | Improvement in subjective symptoms: pramipexole > bromocriptine > placebo<br><br>Only pramipexole improved SE and reduced WASO<br><br>Efficacy in reducing PLMS: pramipexole > bromocriptine |

PLMI: periodic leg movement index; PLMS: periodic leg movements during sleep; PSG: polysomnography; RLS: restless legs syndrome; SE: sleep efficiency; WASO: wakefulness after sleep onset

*Conclusion*
Dopamine D3 receptor subtype agonists were more effective for restless legs syndrome and periodic limb movements during sleep than preferential D2 receptor subtype agents.

*Commentary*
Non-ergot dopamine-agonists (DA) such as pramipexole (PRA), ropinirole and rotigotine represent the first line treatment for restless legs syndrome (RLS) and periodic limb movement during sleep (PLMS).[1] DA is extremely effective since their first administration and even at very low dosages.[2, 3] Although DA have been used in RLS for more than 20 years, we still ignore why and how they are beneficial in RLS, and overall which dopamine receptor subtype is the target of DA in RLS. Dopamine receptors have been classified into two families: D1-like, including D1 and D5 receptors, and D2-like, including D2, D3 and D4 receptors. Current drug treatments for RLS focus on the D2-like receptor family.[4]

The purpose of the study was to understand which DA receptor subtype plays the main role in the treatment of RLS with PLMS. In order to address this issue, we compared the efficacy of equivalent low dosages of the dopamine D3 receptor subtype-preferring agonist PRA with the D2 receptor subtype-preferring agonist bromocriptine (BRO) in a placebo-controlled, prospective single-blind investigation on

45 drug naïve patients with idiopathic RLS. PRA is approximately 24-fold more selective for D3 receptors than BRO, and BRO is about 2-fold more selective for D2 receptors than PRA.[5]

Each patient underwent two consecutive full night polysomnographic studies. The first night was performed without pre-medication. Prior to the second night, one group received a single oral dose of 0.25 mg PRA while a second group received a single oral dose of 2.5 mg BRO, and the remaining patients received placebo. Additional subjective evaluation of the severity of RLS symptoms by a visual analogue scale (VAS) was also assessed in the morning.

After treatment, VAS score was improved by both PRA (mean 1.5, 1.56 SD) and BRO (mean 3.3, 1.72 SD); however, the amelioration after PRA medication was considered to be more evident. A significant improvement of sleep efficiency and a reduction of the percentage of wakefulness after sleep onset were observed in the group treated with PRA, whereas both BRO and placebo caused a mild worsening of the same parameters. PLMS strongly decreased after BRO and PRA medication compared to placebo. However, PRA exerted a more stable and strong suppression effect than BRO; this was particularly evident for patients with higher PLMS index, for PLMS occurring during the first half of the night, and for the leg movements with the highest periodicity with the typical intermovement-interval around 10-30 seconds.[6] For instance, in patients with a PLMS index over 80, PRA suppressed more than 80% of events, while the effect of BRO did not exceed 50%.

These results point to the D3 receptor subtype as a possible preferential target of DA in RLS, supporting the theory of a dysfunction in the dopaminergic hypothalamic-spinal inhibitory descending pathways. Following this hypothesis, RLS could result from a hyperexcitability of the lower spinal cord circuits (both sensori-motor and autonomic), due to a failure or a reduction of the inhibitory control exerted by the hypothalamic A11 nucleus on the dorsal and on the intermedio-lateral columns.[7] Understanding which is the subtype receptor target of DA in RLS/PLMS might prove to be very important for creating more selective drugs and for avoiding selective subtype receptor antagonists in RLS comorbidity, such as psychiatric disorders. Moreover, these results might shed light on the still unclear etiopathogenetic basis of RLS.

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**Restless legs syndrome and near-infrared light: An alternative treatment option.** Mitchell UH, Myrer JW, Johnson AW, Hilton SC. *Physiother Theory Pract. 2011 Jul;27(5):345-51.*

*Does near-infrared light therapy reduce symtoms of restless legs syndrome?*

| Subjects | Methods | Outcomes |
| --- | --- | --- |
| 34 persons with RLS | Subjects were randomly assigned over a 4-week period to either:<br>• Monochromatic near-infrared light treatment (twelve 30-min treatments to their lower legs)<br>• Control<br><br>Assessments at baseline, weeks 1-4, and posttreatment<br>• IRLS score | Compared to controls, near-infrared light treatment was associated with:<br>• Decrease in RLS symptoms at 4 weeks of treament* *Note*: Significant improvement persisted after 4 weeks posttreatment compared to baseline**<br>• Lower IRLS scores |

IRLS: International RLS rating; RLS: restless legs syndrome; *P < 0.001; **P < 0.001

### Conclusion
Near-infrared light treatment was effective in decreasing symptoms associated with restless legs syndrome.

### Commentary
There are few treatment options in managing restless legs syndrome (RLS); the most frequently used are dopaminergic drugs, which may have side effects, and exercise. By definition, RLS symptoms are lessened by movement.[1] Therefore, exercise is considered an effective management alternative, but it loses its attraction when the patient wants to sleep. No one knows the mechanism behind the success of exercise, but it is conceivable that the increase in blood flow induced by movement[2] plays a role. Other blood flow enhancing treatment alternatives should, therefore, also successfully decrease RLS symptoms. This study evaluated the effectiveness of monochromatic near-infrared light (NIR) treatment, a FDA approved device for increasing local blood flow, in decreasing symptoms associated with RLS.

In the 1940s and 1950s, it was hypothesized that decreased blood flow lead to the symptoms associated with RLS.[3] Ekbom[1] believed that vasodilators given to RLS sufferers would decrease the symptoms. The vascular hypothesis was later neglected until 2005, when a study dealing with increased vascular blood flow with enhanced external counter pulsation was shown to significantly decrease RLS symptoms in six patients.[3] Another study[4] showed a high prevalence (36%) of RLS in patients presenting with chronic venous disorder.

Based on anecdotal evidence of clinical success, this study examined the effectiveness of a device that delivers monochromatic near-infrared light (NIR). The Anodyne® therapy system is a non-invasive, drug-free device that delivers light (with a wavelength of 890 nm) through diodes.[5] The proposed mechanism of near infra-red light therapy lies in its ability to generates nitric oxide (NO) in the endothelium.[6] NO is

able to initiate and maintain vasodilation[7,8] and it has influence on neurotransmission (as it is a neurotransmitter itself).[8]

Subjects had to meet the 4 minimal criteria established by the International Restless Legs Syndrome Study Group (IRLSSG) for the diagnosis of RLS[9] in order to be admitted to the study. The patients' symptoms were tracked using a validated 10-question RLS rating scale (IRLS).[10] The subjects underwent 12 treatments with NIR (the control group did not receive any actual treatment) 3 times a week for 4 weeks. No other treatment was given. The subjects were encouraged to maintain their level of medication and to make changes only after confirming with their doctor. RLS related drug intake was similar in both groups. All subjects were asked to complete the 10-question IRLS[10] on six occasions: one week prior to treatment (baseline), at the end of each week of treatment (weeks 1-4), and one week after cessation of treatment. In addition to these six weeks of data collection, the NIR treatment group was also asked to complete the IRLS at four weeks post treatment. After four weeks of treatment, the treatment group had a significantly greater improvement in RLS symptoms than the control group (P < 0.001). Improvement was still significant after 4 weeks post treatment when compared to baseline (P < 0.001).

Treatment with NIR decreases symptoms associated with RLS as demonstrated in lower IRLS scores. This non-invasive, drug-free method of treating RLS might become a valuable new management option. This study also demonstrates once again that RLS is, at least in part, a vascular disorder. More research is needed to determine the mechanism(s) behind NIR treatment and RLS.

Since this study was published, I have received several emails inquiring about NIR or offering valuable insight into other research and hypotheses. One person told me that his RLS symptoms disappear while in a hyperbaric chamber and that they are exacerbated when he takes blood pressure reducing medication. A research group in Sweden contacted me because they too found evidence that hypoxia might be involved in the etiology of RLS. They found altered microvascularization in the anterior tibialis muscle in RLS sufferers, which could be caused by local hypoxia.[11] They also showed an upregulation of the vascular endothelial growth factor in RLS patients; again, possibly imposed by local hypoxia.[12]

These are exciting times. I believe that we are close to finding the cause of RLS and as a result we'll be able to recommend additional and possibly more efficient treatment options. Let's keep searching!

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**The effect of magnesium infusion on rest cramps: randomized controlled trial.** Garrison SR, Birmingham CL, Koehler BE, McCollom RA, Khan KM. *J Gerontol A Biol Sci Med Sci. 2011 Jun;66(6):661-6.*

*Is magnesium therapy effective in reducing the frequency of nocturnal leg cramps?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 46 community-dwelling older adult with complaints of leg cramps<br>• Age: 69.3 ± 7.7 yrs<br>• Averaged number of leg cramps at baseline: 8 per week | Double blind, placebo controlled RCT<br><br>Subjects were randomized to either:<br>• IV magnesium sulfate (5 consecutive days infusion of 20-mmol (5 g))<br>• Placebo<br><br>Assessments:<br>• Number of leg cramps per week in the 30 days immediately pre and post infusions<br>• Magnesium retention (measured by 24-hour urinary magnesium excretion) | Compared to placebo, magnesium therapy was associated with a greater mean change in cramps per week: -2.4 vs. -1.7*<br><br>There was no correlation between treatment response and magnesium retention |

IV: intravenous; RCT: randomized controlled trial; *P = .51, 95% CI -3.1 to 1.7

*Conclusion*
Intravenous magnesium sulfate did not significantly reduce the number of leg cramps per week among community-dwelling older adults suffering from frequent legs cramps.

*Commentary*
The only therapy with established efficacy for the prophylaxis of nocturnal leg cramps (quinine)[1] is actively discouraged by multiple drug regulatory bodies (such as the FDA)[2] based on safety concerns. In the absence of solid evidence to guide them, physicians and patients have no choice but to turn to less established interventions. One such cramp therapy, widely available in health food stores and pharmacies and marketed directly to consumers over the Internet for the prophylaxis of skeletal muscle cramps, is oral magnesium supplementation.

While one study in pregnant women found magnesium to have benefit for nocturnal leg cramp prophylaxis,[3] the two published trials of oral magnesium for cramp prophylaxis in older adults[4, 5] (who constitute the majority of nocturnal leg cramp sufferers) have failed to find benefit. However, oral magnesium supplements have limited bioavailability, in large part because a substantial portion of the magnesium absorbed by the gut occurs via a saturable transport mechanism.[6] To better determine the efficacy of magnesium as a cramp prophylactic we performed an RCT of 46 nocturnal leg cramp sufferers

in which magnesium was given intravenously according to an infusion protocol similar to what would be carried out in our health authority for the treatment of hospital inpatients with recognized magnesium deficiency. We also determined the percentage retention of the infused magnesium load on the first day of infusions since this has been shown to correlate well with the change in tissue magnesium on skeletal muscle biopsy following repletion.[7]

Regardless of the degree of magnesium retention, we found no benefit to a series of magnesium infusions on the frequency of nocturnal leg cramps. Given this presumably more bioavailable method of drug delivery failed to provide benefit, it seems unlikely that oral magnesium would be efficacious for this indication in older adults.

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**Usefulness of the SINBAR electromyographic montage to detect the motor and vocal manifestations occurring in REM sleep behavior disorder.** Iranzo A, Frauscher B, Santos H, Gschliesser V, Ratti L, Falkenstetter T, Stürner C, Salamero M, Tolosa E, Poewe W, Santamaria J, Högl B; SINBAR (Sleep Innsbruck Barcelona) Group. *Sleep Med. 2011 Mar;12(3):284-8.*

*Is the SINBAR electromyographic montage useful to detect the motor and vocal manifestations displayed by patients with the idiopathic form of rapid eye movement sleep behavior disorder (RBD)?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 11 persons with idiopathic RBD<br>• Gender: 36% F<br>• Age: 67.7 ± 5.5 yrs<br>• Mean reported RBD duration: 5.4 ± 4.4 yrs<br><br>17,818 REM sleep 3-second mini-epochs free of artifacts were scored | PSG with synchronized audiovisual monitoring<br><br>Phasic EMG activity in REM sleep was scored and quantified in 3-s mini-epochs using using the SINBAR EMG montage (simultaneous EMG recording of mentalis, flexor digitorum superficialis and extensor digitorum brevis) | SINBAR EMG montage detected most (94.4%) of the motor and vocal manifestations occurring in RBD<br>• Sensitivity of 94.4%, specificity of 47.2%, NPP of 95.4% and PPN of 41.9%<br>• Isolated EMG of mentalis failed to show phasic EMG activity in 35.5% of behavioral events<br>• 64.8% of all mini-epochs contained phasic EMG activity<br>• 28.8% of mini epochs contained movements or vocalizations |

EMG: electromyographic; NPV: negative predictive value; PPV: positive predictive value; PSG: polysomnography; RBD: REM sleep behavior disorder; REM: rapid eye movement

***Conclusion***
The SINBAR electromyographic montage detected 94.4% of motor and vocal manifestations occurring in rapid eye movement sleep behavior disorder.

***Commentary***
REM sleep behavior disorder (RBD) is a parasomnia characterized by dream-enacting behavior associated with loss of normal REM sleep muscle atonia. Correct diagnosis of RBD is important because patients with the idiopathic form have an increased risk for developing a neurodegenerative disease, it may lead to serious injury, and it is a well treatable disorder.[1] The International Classification of Sleep Disorders (ICSD-2) established in 2005 that the diagnosis of RBD requires demonstration of REM sleep without atonia by polysomnography mainly because other sleep disorders can mimic the clinical features of RBD.[2,3] The ICSD-2 defined REM sleep without atonia as the "electromyographic (EMG) finding of excessive amounts of sustained or intermittent elevation of submental EMG tone or excessive phasic submental or (upper or lower) limb EMG twitching". This definition has several limitations. Firstly, it is unclear which muscle or combination of muscles of the body provides the highest rates of abnormal REM sleep EMG activity in RBD. Secondly, it is not stated how the tonic and phasic EMG activity have to be measured. And thirdly, a

precise definition of "excessive amounts of tonic and phasic EMG activity" was not provided since normal values of these measures are unknown. To solve these limitations, the SINBAR (sleep Innsbruck and Barcelona) have published a set of three papers.

In the first study, it was determined which muscle or combination of muscles provides the highest rates of REM sleep phasic EMG activity in patients with RBD.[4] Seventeen patients with idiopathic RBD (n = 8) and RBD secondary to Parkinson disease (n = 9) underwent polysomnography including EMG recording of 13 different muscles. Phasic EMG activity in REM sleep was quantified for each muscle separately. It was found that simultaneous recording of the mentalis, flexor digitorum superficialis in the upper limbs and extensor digitorum brevis in the lower limbs muscles provided the highest rates of REM sleep phasic EMG activity in subjects with RBD. This combination of muscles (which we called the SINBAR EMG montage) detected 82% of all 3-second mini-epochs containing phasic EMG activity.

In a second study, we evaluated the usefulness of the SINBAR EMG montage to detect the movements and vocalizations occurring in RBD.[5] Polysomnographic studies with synchronized audiovisual monitoring of eleven patients with idiopathic RBD were analyzed. Phasic EMG activity in REM sleep was scored and quantified in 3-second mini-epochs while the video was reviewed to detect motor events and vocalizations. A total of 64.8% (11,562 out of 17,848) mini-epochs contained phasic EMG activity whereas 28.8% (5,135 out of 17,848) contained movements or vocalizations. Using the SINBAR EMG montage, 94.4% of the mini-epochs containing behavioral events were linked to phasic EMG activity. The sensitivity of the SINBAR EMG montage was 94.4%, specificity was 47.2%, negative predictive value was 95.4% and positive predictive value was 41.9%. Isolated EMG recording of the mentalis did not show phasic EMG activity in 35.5% of the behavioral events detected in the video. We concluded that the SINBAR EMG montage is a useful approach for the diagnosis of RBD showing that it detects the majority (94.4%) of the motor and vocal manifestations occurring in RBD.

In a third study, we evaluated the EMG activity in the SINBAR montage (mentalis, flexor digitorum superficialis, extensor digitorum brevis) and other muscles to obtain normative values for the correct diagnosis of RBD in clinical practice.[6] Thirty RBD patients (15 with the idiopathic form and 15 linked to Parkinson disease) and 30 matched controls were evaluated. Participants underwent video-polysomnography with registration of 11 body muscles including those from the SINBAR EMG montage. Tonic, phasic and "any" (either tonic or phasic) EMG activity were blindly quantified for each muscle. When choosing a specificity of 100%, the 3-second mini-epoch cut-off for a diagnosis of RBD was 18% for "any" EMG activity in the mentalis (AUC 0.990). Discriminative power was higher in upper limbs (100% specificity, AUC 0.987–9.997) than in lower limb muscles (100% specificity, AUC 0.813-0.852). We combined "any" EMG activity in the mentalis with left and right phasic flexor digitorum superficialis muscles and found a cut-off of 32% (AUC 0.998) for both subjects with idiopathic RBD and Parkinson disease. Thus, we concluded that for the diagnosis of idiopathic RBD and RBD associated with Parkinson disease, it is a great value using a polysomnographic montage quantifying "any" (either tonic or phasic) EMG activity in the mentalis and phasic EMG activity in the right and left flexor digitorum superficialis in the upper limbs with a cut-off of 32%, when using 3-second mini-epochs.

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# Medical, Neurological and Psychiatric Disorders

**Decreasing sleep-time blood pressure determined by ambulatory monitoring reduces cardiovascular risk.** Hermida RC, Ayala DE, Mojón A, Fernández JR. *J Am Coll Cardiol. 2011 Sep 6;58(11):1165-73.*

*Which is a better predictor of cardiovascular risk – wake or sleep blood pressure?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 3,344 persons<br>• Gender: 48% F<br>• Age: 52.6 ± 14.5 yrs | Prospective study (median follow-up of 5.6 yrs)<br><br>Subjects with HTN at baseline were asked to take their HTN medications either at awakening or bedtime<br><br>Assessments: BP | At follow-up, only sleep BP was a significant predictor of outcomes<br>• Each 5-mm Hg decrease in sleep mean systolic BP was associated with a 17% reduction in CVS risk* |

BP: blood pressure; CVS: cardiovascular; DM: diabetes mellitus; HTN: hypertension; *P < 0.001

## Conclusion
Sleep blood pressure was a significant predictor of cardiovascular outcomes.

## Commentary
The correlation between blood pressure (BP) level and target organ damage, cardiovascular disease (CVD) risk, and long-term prognosis is greater for ambulatory BP monitoring (ABPM) than clinical BP measurements. Nevertheless, the latter continue to be the "gold standard" to diagnose hypertension, assess CVD risk, and evaluate hypertension treatment. Independent ABPM studies have found that elevated sleep-time BP is a better predictor of CVD risk than either the awake or 24h BP means. A major limitation of all previous ABPM-based prognostic studies is reliance upon a single baseline profile only from each participant at the time of inclusion, without accounting for potential changes in the level and pattern of ambulatory BP thereafter during follow-up, as a consequence of BP-lowering therapy, aging, and/or development of target organ damage and concomitant diseases. Thus, the results of studies so far reported pertaining to the prognostic value of ABPM for CVD risk is based on the assumption that the features of the 24h ABPM pattern do not change over time during the years of follow-up. In other words, it is assumed that event-subjects with an elevated sleep-time BP mean at the time of baseline evaluation, many years before the event, continued to have an elevated sleep-time BP mean during the entire follow-up span. Furthermore, due to the lack of periodic multiple evaluations with ABPM in all previous reported studies, the potential reduction in CVD risk associated with modification of prognostic ABPM parameters (i.e., either increase of the sleep-time relative BP decline towards a more normal dipping pattern or reduction of the asleep BP mean), has never before been evaluated.

The MAPEC (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares, i.e., Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events) study was specifically designed to prospectively investigate whether specific changes in the circadian BP profile results in reduced CVD risk.[1]

Participants with baseline BP ranging from normotension to sustained hypertension were systematically evaluated by periodic, at least annually, 48-h ABPM. In particular, we evaluated the comparative prognostic value of: (i) clinic and ambulatory BP; (ii) different ABPM-derived characteristics, e.g., asleep vs. awake BP mean; and (iii) specific changes in ABPM characteristic during follow-up, mainly whether reduced CVD risk is more related to the progressive decrease of asleep or awake BP.[2]

We prospectively studied 3344 subjects (1718 men/1626 women), 52.6 ± 14.5 yrs of age, during a median follow-up of 5.6 years. Those with hypertension at baseline were randomized to ingest all their prescribed hypertension medications upon awakening or one or more of them at bedtime.[3-5] At baseline, BP was measured at 20-min intervals from 07:00 to 23:00h and at 30-minute intervals at night for 48 consecutive hours, and physical activity was simultaneously monitored every minute by wrist actigraphy to accurately derive the awake and asleep BP means. Identical assessment was scheduled annually and more frequently (quarterly) if treatment adjustment was required to improve ambulatory BP control.

Data collected either at baseline or at the last ABPM evaluation per participant showed that sleep systolic BP mean was the most significant predictor of both total CVD events and major events (a composite of CVD death, myocardial infarction and stroke). Moreover, when the asleep BP mean was adjusted by the awake mean, only the former was a significant independent predictor of outcome in a Cox proportional-hazard model adjusted for sex, age, diabetes, anemia and chronic kidney disease.[2] Analyses of changes in ambulatory BP during follow-up revealed a 17% reduction in CVD risk for each 5 mmHg decrease in the asleep systolic BP mean (P < 0.001), independently of changes in any other clinic or ambulatory BP parameter. The increased event-free survival associated with the progressive reduction in the asleep systolic BP mean during follow-up was significant for subjects with either normal or elevated BP at baseline.

In conclusion, the ABPM-derived asleep BP mean is the most significant independent prognostic marker of CVD morbidity and mortality. Most important, the progressive decrease in asleep BP mean, a now validated novel therapeutic target[6] that requires proper patient evaluation by ABPM and best achieved by the ingestion of at least one hypertension medication at bedtime,[3-5] is the most significant predictor of event-free survival, nor only in the general hypertensive population, but also in high-risk patients, such as those with chronic kidney disease or diabetes.[7]

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**Effect of daily sedative interruption on sleep stages of mechanically ventilated patients receiving midazolam by infusion.** Oto J, Yamamoto K, Koike S, Imanaka H, Nishimura M. *Anaesth Intensive Care. 2011 May;39(3):392-400.*

*Does daily sedative interruption affect sleep characteristics in mechanically ventilated patients?*

| *Subjects* | *Methods* | *Outcomes* |
|---|---|---|
| 22 mechanically ventilated ICU patients who received midazolam<br>• Age: 70 ± 10 yrs<br>• Gender: 27% F<br>• BMI: 22 ± 4<br>• APACHE II score: 15 ± 4<br>• Days of mechanical ventilation prior to the study: 4 ± 2 days | Randomized controlled trial<br><br>Subjects were randomized to either:<br>• DSI: Sedation interrupted (6:00–21:00) and administered (21:00–6:00) – n = 11<br>• CS: Sedation administered continuously the whole day – n = 11<br><br>Assessments:<br>• PSG for 24 hrs (TST, SWS, REM, arousal index)<br>• Amount of midazolam use<br>• Sedation range (RSS) | Sleep characteristics:<br>• SWS (21:00–6:00): DSI > CS (6 vs. 0 min)*<br>• REM (21:00–6:00): DSI > CS (54 vs. 0 min)**<br>• TST (21:00–6:00): DSI < CS (7.3 vs. 8.7 hr)***<br>• Arousal index (21:00–6:00): DSI > CS (4.4 vs. 2.2 per hr)#<br><br>Midazolam use (whole day):<br>• DSI < CS (0.6 vs. 2.6 mg/kg)<br><br>Sedation range (21:00–6:00):<br>• DSI=CS (4.7 vs. 5.0) |

APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: body mass index; CS: continuous sedation; DSI: daily sedative interruption; ICU: intensive care unit; MV: mechanical ventilation; PSG: polysomnography; REM: rapid eye movement; RSS: Ramsay sedation scale; SWS: stage 3 and 4 non-rapid eye movement sleep (slow wave sleep); TST: total sleep time; *P = 0.04; **P = 0.02; ***P = 0.047; #P = 0.03

### Conclusion
Compared with continuous sedation, daily sedative interruption was associated with increased slow-wave sleep and rapid eye movement sleep in mechanically ventilated patients.

### Commentary
In intensive care units (ICUs), mechanically ventilated patients often exhibit sleep fragmentation and a suppression of both rapid eye movement (REM) sleep and slow wave sleep (SWS).[1,2] These sleep disturbances are considered to be associated with long-term outcomes. The importance of improving the quality and quantity of sleep for critically ill patients is increasingly recognized.[1,2] To devise an adequate sleep-promotion strategy, one must avoid oversedation and minimize the use of agents that inhibit the patient's ability to achieve normal sleep.

Critically ill patients are often given sedatives and analgesics to increase comfort, decrease anxiety, and promote amnesia and sleep. Although gamma-aminobutyric acid (GABA) agonists, including

benzodiazepine and propofol, are the medications recommended as first-line sedation in the ICU, pharmacological sedation with GABA agonists does not equal to physiological sleep. In addition, it may even induce significant disturbance in sleep architecture including suppression SWS and REM sleep.[1-3] To minimize the potential of oversedation with the use of continuous sedation (CS), the daily sedative interruption (DSI) has been explored.[4, 5] DSI allows better assessment of patient's sedative needs, reduces drug accumulation, and the duration of mechanical ventilation and ICU stay compared with CS.[4] It is also known that DSI reduces incidence of posttraumatic stress disorder and complication of critical illness;[5] however, we hardly know how DSI affects sleep characteristics. In this study, we investigated the effects of DSI on sleep architecture in comparison with CS. The results revealed DSI reduced 78% of total amount of midazolam use and increased the duration of SWS and REM sleep compared with CS. The less amount of midazolam could have contributed to more SWS and REM sleep in DSI than those in CS. In normal subjects, as a factor in the homeostatic need for sleep, SWS during nighttime is strongly related to wakefulness on the day before. DSI may benefit mechanically ventilated patients both because of promoting restorative sleep related to awakening in daytime and reducing the total amount of sedatives.

The sleep architecture of mechanically ventilated patients was severely disturbed compared with normal people of the same age range; however, our results revealed DSI was effective sedation strategy to preserve sleep quality and quantity in mechanically ventilated patients. Many factors interfere with normal sleep, and DSI is not enough to improve sleep quality of mechanically ventilated patients. Integrated strategy, including minimal environmental disturbance, optimized ventilation mode, or use of sleep-promoting agents to promote restorative sleep, is needed for better sleep architecture of mechanically ventilated patients. Further research is required to evaluate the effects of different sedative agents on better sleep architecture in ICU.

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**Evaluating nocturnal oxygen desaturation in COPD--revised.** Lacasse Y, Sériès F, Vujovic-Zotovic N, Goldstein R, Bourbeau J, Lecours R, Aaron SD, Maltais F. *Respir Med. 2011 Sep;105(9):1331-7.*

*What is the prevalence of nocturnal oxygen desaturation in persons with stable chronic obstructive pulmonary disease with and without sleep apnea?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 128 persons with stable COPD<br>• $FEV_1$ (mean): 37% predicted<br>• Daytime $PaO_2$: 56-69 mmHg | Cross-sectional study<br><br>Assessments: Home oximetry (on 2 occasions over a 2-week period) | Excellent test-retest reliability between the 2 oximetries<br><br>Patients were classified as:<br>• Significant NOD without SA: 38% (could not be predicted by any patient characteristic or physiological measure)<br>• Significant NOD with SA: 16% |

COPD: chronic obstructive pulmonary disease; NOD: nocturnal oxygen desaturation; SA: sleep apnea

***Conclusion***
About 38% of persons with stable chronic obstructive pulmonary disease without sleep apnea had evidence of nocturnal oxygen desaturation.

***Commentary***
The rationale of assessing for nocturnal desaturation in COPD is that it may decrease survival[1], and its treatment with supplemental oxygen may prolong survival. This comes from an indirect comparison of the British Medical Research Council Study[2] and the National Heart Lung and Blood Institute's trial[3] suggesting that patients receiving 12 hours of oxygen/day (most of which was provided at night) was associated with better survival than those receiving no oxygen therapy. However, these were severely hypoxemic patients with a daytime $PaO_2 \leq 55$ mmHg who would qualify for LTOT. To date, only two randomized trials directly addressed the issue of nocturnal oxygen therapy in patients with COPD with significant nocturnal oxygen desaturation who would not qualify for LTOT.[4-5] The meta-analysis of these two studies concluded that nocturnal oxygen therapy had no effect on survival (pooled odds ratio: 0.97; 95% CI: 0.41 – 2.31).[6] However, the number of patients randomized in these 2 trials was small and the issue remains unresolved.

Also, determination of nocturnal desaturation may be important because it may impact sleep quality and/or health-related quality of life. This hypothesis is not supported by Lewis' findings who could not demonstrate any association between nocturnal desaturation and impairment of health-related quality of life, sleep quality or daytime function.[7] The effect of nocturnal oxygen therapy on quality of life and sleep quality was directly addressed in a single randomized, placebo-controlled cross-over trial involving 19 daytime normoxemic COPD patients with nocturnal oxygen desaturation.[8] The authors observed significant differences only in the sleep dimension of the Nottingham Health Profile. All the other dimensions of the Nottingham Health Profile, SF-36 and St-George's Respiratory Questionnaire showed no difference between nocturnal oxygen and placebo. The interpretation of results of both Lewis' and Orth's

studies are limited by their small sample size.

Our finding of a high prevalence of nocturnal oxygen desaturation in patients with moderate-to-severe COPD not qualifying for LTOT may be an indication of the need for regular screening of this patient population using home oximetry, although the benefits of administering nocturnal oxygen to this population remains to be established. In this regard, an international, randomized, placebo-controlled trial of nocturnal oxygen in COPD is currently underway (ClinicalTrtials.gov id: NCT01044628).

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**Excessive daytime sleepiness in multiple system atrophy (SLEEMSA study).** Moreno-López C, Santamaría J, Salamero M, Del Sorbo F, Albanese A, Pellecchia MT, Barone P, Overeem S, Bloem B, Aarden W, Canesi M, Antonini A, Duerr S, Wenning GK, Poewe W, Rubino A, Meco G, Schneider SA, Bhatia KP, Djaldetti R, Coelho M, Sampaio C, Cochen V, Hellriegel H, Deuschl G, Colosimo C, Marsili L, Gasser T, Tolosa E. *Arch Neurol. 2011 Feb;68(2):223-30.*

*What is the prevalence and risk factor/s of excessive daytime sleepiness in persons with multiple system atrophy and Parkinson disease?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 86 persons with MSA<br><br>86 persons with PD<br><br>86 healthy persons matched for age and gender | Survey of EDS<br><br>Assessments:<br>• ESS<br>• Modified ESS<br>• SOSS<br>• TSS<br>• PSQI<br>• Disease severity<br>• Amount of dopaminergic treatment<br>• Presence of RLS | ESS scores (mean [SD]):<br>• MSA: 7.72 [5.05]<br>• PD: 8.23 [4.62]<br>• Healthy subjects: 4.52 [2.98]*<br><br>EDS (ESS score >10) was present in:<br>• MSA: 28%<br>• PD: 29%<br>• Healthy subjects: 2%**<br><br>Correlations with EDS:<br>• Dopaminergic treatment in PD but not MSA<br>• Disease severity (weak correlation) in MSA and PD<br><br>Presence of RLS:<br>• MSA: 28%<br>• PD: 14%<br>• Healthy subjects: 7%***<br><br>Predictors of EDS:<br>• MSA – SDB and SE<br>• PD – RLS and amount of dopaminergic treatment |

EDS: excessive daytime sleepiness; ESS: Epworth Sleepiness Scale; MSA: multiple system atrophy; PD: Parkinson disease; PSQI: Pittsburgh Sleep Quality Index; RLS: restless legs syndrome; SDB: sleep disordered breathing; SE: sleep efficiency; SOSS: Sudden Onset of Sleep Scale; TSS: Tandberg Sleepiness Scale; *P < .001; **P < .001; ***P < .001

## Conclusion

Excessive daytime sleepiness was present in about one-quarter each of persons with multiple system atrophy and Parkinson disease.

## Commentary

Sleep disorders are common in neurodegenerative disorders and particularly in synucleinopathies. The three main sleep complaints - insomnia/sleep fragmentation, excessive daytime sleepiness (EDS) and parasomnias - have all been described. For example, in Parkinson's disease (PD), hypersomnia and "sleep attacks" were brought into prime time with the report of Frucht et al[1] and several studies since then have recognized its relevance in PD. In Multiple System Atrophy (MSA), a synucleinopathy that may also present with parkinsonism, the frequency and characteristics of excessive daytime sleepiness is not well known. The goal of this multicenter study was to assess the prevalence, characteristics and associations of EDS in MSA and to compare them with those occurring in patients with PD and healthy individuals. To that end, we recruited in 13 tertiary referral centers across Europe and Israel 86 MSA patients, 86 PD patients, matched for age, gender and disease severity, and 86 healthy control subjects matched for age and gender.

We evaluated nocturnal sleep quality (Pittsburgh Sleep Quality Index), daytime sleepiness (modified Epworth Sleepiness Scale, Tandberg sleepiness scale), restless legs presence (IRLS group questionnaire) as well as standard motor, cognitive and mood scales. PSG recordings were not done. Because patients with limited physical mobility cannot perform some of the activities described in the Epworth Sleepiness Scale, we also assessed sleepiness using the Tandberg Sleepiness Scale (completed with the help of the caregiver). This scale simply asks about the amount of time a patient spends sleeping during the day, and it has been used often to assess sleepiness in PD.

We found that EDS is equally frequent in MSA (28%) as in PD (29%), and more common in both conditions than in a healthy control group (2%). However, in each of the two disorders, EDS appeared to be related with different findings. Whereas in PD, amount of dopaminergic treatment and RLS symptoms were associated with EDS, in MSA, the associated factors were presence of sleep breathing disorders (by clinical history) and sleep efficiency. An unexpected finding was a high percentage of RLS in MSA - twice as much as in PD, and 4 times more often than in controls.

Our findings suggest that EDS is common in MSA, occurring as often as in PD. Improving sleep disordered breathing and increasing sleep efficiency may be of help to solve this symptom.

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**Increasing walking and bright light exposure to improve sleep in community-dwelling persons with Alzheimer's disease: results of a randomized, controlled trial.** McCurry SM, Pike KC, Vitiello MV, Logsdon RG, Larson EB, Teri L. *J Am Geriatr Soc. 2011 Aug;59(8):1393-402.*

*Are non-pharmacologic interventions (walking, bright light exposure, and the combination) effective for treating sleep and nocturnal disturbances in community-dwelling persons with dementia?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 132 persons with probable or possible AD | Parallel-group, randomized, single blind trial<br><br>Subjects were assigned to either (all 6 weeks):<br>• Walking only<br>• Light exposure only<br>• Combination walking + light exposure + guided sleep education (NITE-AD)<br>• Educational contact control<br><br>Assessments<br>• Wrist actigraphy<br>• SDI<br>• Cornell Scale<br>• Self-Administered Comorbidity Questionnaire<br>• SDQ, Sleep apnea subscale<br>• MMSE | Compared to controls, active treatment at two-months was associated with actigraphically-measured:<br>• Decrease in TWT*<br>• Improvement in sleep percent**<br>• Reduced number of nighttime awakenings***<br><br>Improvements were not sustained at 6-month follow-up<br><br>Better adherence ($\geq 4$ days/week) to walking and light exposure recommendations was associated with significantly less TWT and better sleep percent<br><br>No differences in caregiver subjective reports of patient sleep on the SDI |

AD: Alzheimer disease; MMSE: Mini-Mental State Examination; SDI: Sleep Disorders Inventory; SDQ: Sleep Disorders Questionnaire; TST: total sleep time; TWT: total wake time; *P=.05 (effect size .51), .04 (effect size .53), and 01 (effect size .63), respectively, for walking, light, and NITE-AD; **P=.07 (effect size .45), .07 (effect size .48), and .02 (effect size=.63), respectively, for walking, light, and NITE-AD; ***P=.07 (effect size .46) walking

*Conclusion*
Walking, light exposure and their combination were effective treatments for improving sleep in community-dwelling persons with Alzheimer disease.

*Commentary*
Treating sleep disturbances in dementia has proved challenging. Given the significant side effect risks of sedating medications and the lack of empirical evidence supporting their use for cognitively impaired individuals, behavioral and somatic interventions, such as walking and bright light exposure, are potential alternatives to pharmacotherapy. This study was the largest community-based randomized trial to date

examining their efficacy of behavioral interventions on the objective and subjective (caregiver report) sleep of persons with Alzheimer's disease. All three active conditions showed moderate effect size improvements in actigraphic sleep (reductions in TWT between 33-40 minutes/night) compared to an attention-control condition. However, none were associated with improvements in caregiver subjective reports about patient sleep, a finding that was surprising because subjective sleep outcomes often show more robust response to treatment than actigraphic outcomes. What lessons can we take from these mixed results?

One lesson concerns the reliability of the subjective sleep reports. Unlike typical insomnia studies where subjective ratings are self-reported, studies of persons with memory loss must rely on caregiver *proxy* reports about the patient's sleep. Our prior research has shown that caregiver ratings of sleep disturbances are not always congruent with actigraphy measurements, particularly among caregivers who are physically and emotionally strained or prone to use a more critical style of dealing with patient behavioral disturbances.[1] Since the current study was published, we have also conducted data analyses comparing actigraphic sleep "improvers" (reductions in total wake time of 40 minutes or greater) to "improvements" on patient sleep ratings on an exploratory proxy sleep outcome (the Pittsburgh Sleep Quality Index; improvement = decrease to a total PSQI score of < 5 or a drop in 5+ points from baseline value). Results showed that all cases where there was congruence between actigraphic and PSQI-based sleep improvement had a minimum patient objective TWT decrease of 66 minutes per night.[2] Furthermore, in 67% of cases where actigraphic TWT improved but caregivers did *not* report improvements on the PSQI, caregivers slept in a different room. These findings suggest that large changes in TWT and close sleeping proximity are necessary for caregivers to recognize patient sleep improvements.

A second lesson concerns individual preferences and life circumstances of patient-caregiver dyads who are coping with sleep and nocturnal behavioral disturbances. In the current study, people who practiced the behavioral interventions consistently had better treatment outcomes. Our experience in the field, however, was that study participants varied widely in their willingness to walk or use a light box on a regular basis. Implementation of non-pharmacological treatments to improve sleep in persons with dementia requires caregiver oversight to ensure that they are carried out consistently and safely, and can add to the burden caregivers feel in an already difficult situation. Patients with higher levels of depression and behavioral disturbances, and stressed non-spousal caregivers were less likely to walk.[3] Inclement weather conditions; neighborhood walkability; caregiver or patient physical limitations; and patient resistance to being asked to walk every day all also interfered. Common complaints about the light box were: its size was unwieldy in smaller homes; patients found the light too bright/irritating; having to use the light box at the same time every evening was disruptive to family routines; and it was difficult for caregivers to keep the patient engaged (and awake, seated and properly oriented) for the full recommended hour. Changing nighttime sleep and daytime napping routines can interfere with precious caregiver respite time and increase conflict between caregiver and care-recipient. Thus, behavioral treatments for sleep, particularly when delivered without being personalized to the unique sleep problem and patient/caregiver dyadic situation, are not always effective, and may actually worsen patient mood and behavior. Better tools for evaluating what patient/caregiver personal characteristics and aspects of their living environments are most influential in dyads' acceptance of, and response to, behavioral treatment are needed in order to improve both the short and longer term efficacy of these interventions and permit their effective use in community settings.

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**Melatonin versus placebo in children with autism spectrum conditions and severe sleep problems not amenable to behaviour management strategies: a randomised controlled crossover trial.** Wright B, Sims D, Smart S, Alwazeer A, Alderson-Day B, Allgar V, Whitton C, Tomlinson H, Bennett S, Jardine J, McCaffrey N, Leyland C, Jakeman C, Miles J. *J Autism Dev Disord. 2011 Feb;41(2):175-84.*

*Does melatonin affect sleep of children with autism spectrum disorders and severe dysomnias?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 22 children with autism spectrum disorders unresponsive to behavior management for severe dysomnias<br><br>17 children completed the study | Double blind, crossover RCT<br><br>Subjects were randomized to (3 months):<br>• Placebo<br>• Melatonin (maximum dose of 10 mg) | Compared to placebo, melatonin was associated with:<br>• Improved SOL (by an average of 47 min)<br>• Improved TST (by an average of 52 min)<br>• No difference in night awakenings<br>• No significant difference in side effect profile |

ASD: autism spectrum disorder; RCT: randomized controlled trial; SOL: sleep onset latency; TST: total sleep time

*Conclusion*
Melatonin improved both sleep onset latency and total sleep time in children with autism spectrum disorders.

*Commentary*
High rates of sleep problems are reported by parents of children with autism.[1] Studies report between 44% and 83% of children with autism having sleep difficulties,[2] in comparison to 10-20% of typically developing young children.[3] Behaviour therapy is effective for sleep problems in children with autism,[4] but there are some children in whom it does not work. This has a significant impact on the child and the family.

Since Phillips and Appleton's[5] review showing only three randomized controlled trials with a total of 35 children with developmental disorders, one further RCT has been published in children with learning disabilities.[6] Only one published trial with a randomized controlled methodology has been conducted to date with children who have autism.[7] This study had to be halted after only seven children had completed.[7] At the time of our study, melatonin was becoming more commonly used in clinical practice with children on the autism spectrum with little evidence to support its prescription and no license for this use.[8] Our study sought to fill a gap in research literature for autism.

Twenty-two children with autism spectrum disorders who had not responded to supported behaviour management strategies for severe dysomnias entered a double blind, randomized, controlled, crossover trial involving three months of placebo versus three months of melatonin to a maximum dose of 10mg. Seventeen children completed the study. There were no significant differences in age [*M (SD)* group A: 8.9 (3.0), group B: 8.5 (2.3), *t* (15) = 0.328, P = .747] or gender (*chi* (1) = 0.565, P = .452) between the two

groups. There were no significant differences between sleep variables at baseline. Melatonin significantly improved sleep latency (by approximately 50 minutes) and total sleep (by the same amount) compared to placebo, but not number of night awakenings. The side effect profile was low and not significantly different between the two arms.

The children entered for study were those with the most severe difficulties as evidenced by the fact that their sleep had not improved despite behavior management support (in some instances with intensive support). This suggests that melatonin is a useful adjunctive treatment for serious sleep problems in children with autism, and further research should be commissioned to bolster this literature.

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**Predicting nocturnal hypoventilation in hypercapnic chronic obstructive pulmonary disease patients undergoing long-term oxygen therapy.** Tarrega J, Anton A, Guell R, Mayos M, Samolski D, Marti S, Farrero E, Prats E, Sanchis J. *Respiration. 2011;82(1):4-9.*

*What is the prevalence and risk factor/s of nocturnal hypoventilation in persons with hypercapnic chronic obstructive pulmonary disease?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 80 persons with clinically stable COPD with hypercapnic respiratory failure requiring LTOT | Prospective multicenter study<br><br>Assessments:<br>• PFT<br>• ABG (wake and sleep)<br>• Respiratory polygraphy<br><br>Definition:<br>• NHV: increase in $PaCO_2$ >10 mmHg during sleep compared to wake | 21% of subjects met criteria for NHV<br><br>Variables that best discriminated NHV were BMI* and diurnal increase of $PaO_2$ after $O_2$**<br>• Sensitivity: 82%<br>• Specificity: 78% |

ABG: arterial blood gas analysis; BMI: body mass index; COPD: chronic obstructive pulmonary disease; LTOT: long-term oxygen therapy; NHV: nocturnal hypoventilation; $O_2$: oxygen; $PaO_2$: partial pressure of oxygen in arterial blood; PFT: pulmonary function testing; *OR 1.26, 95% CI 1.068-1.481; P = 0.006; **OR 0.89, 95% CI 0.807-0.972; P = 0.010

### *Conclusion*
Nocturnal hypoventilation developed in 21% of persons with stable hypercapnic chronic obstructive pulmonary disease undergoing long-term oxygen therapy, and was related to higher body mass indices and lower $PaO_2$ after oxygen administration.

### *Commentary*
Continuous oxygen therapy has been shown to increase survival in patients with chronic respiratory failure (CRF)[1,2] and may have a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity and mental state. However, it may also cause carbon dioxide retention that can be worse during sleep due to changes in ventilation.[3] Diurnal hypercapnia has been considered a sign of poor prognosis in COPD patients undergoing long-term oxygen therapy (LTOT).[4-6] Therefore, we can expect that nocturnal hypercapnia in COPD patients undergoing LTOT may have a negative influence on the course of the illness. However, the consequences of this phenomenon are largely unknown. Although it is widely accepted that oxygen-induced hypercapnia may develop during COPD exacerbations, few studies have analyzed this phenomenon in stable COPD patients or during sleep.[7,8]

As a conclusion of our study, we consider that oxygen-induced nocturnal hypercapnia – NHV (nocturnal hypoventilation): $PaCO_2$ > 10 mmHg above awake values[9] in stable COPD patients with conventional criteria for LTOT is a more frequent phenomenon than generally expected, occurring in 21% of our study population. NHV is best predicted by a higher BMI together with a lower awake $PaO_2$ breathing oxygen. The NHV group also had higher levels of hemoglobin concentration, hematocrit and $D_LCO$ than the non-

NHV group. Although not validated, this multivariate model proposed showed sensitivity of 82% and specificity of 78%. Furthermore, it included variables that are simple to obtain in everyday clinical practice. It facilitates identification of patients with NHV and allows us to optimize treatment for chronic respiratory failure. Therefore, clinicians should be aware of this phenomenon in order to evaluate alternative treatments such as noninvasive ventilation in this subgroup of patients.[10,11]

However, as variability in NHV prevalence seems to be related to the inclusion criteria and the form of measurement, a clear definition of NHV is needed; also prospective studies are required to establish the clinical significance of this phenomenon.

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**Sleep disturbance in dementia with Lewy bodies and Alzheimer's disease: a multicenter analysis.** Bliwise DL, Mercaldo ND, Avidan AY, Boeve BF, Greer SA, Kukull WA. *Dement Geriatr Cogn Disord. 2011;31(3):239-46.*

*Does the prevalence of nighttime sleep disturbance differ between persons with Alzheimer disease versus demetia with Lewy bodies?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 4,531 persons | Assessments:<br>• NSD (NPIQ)<br>• Dementia diagnosis (DLB and probable AD) | NSD was more common in subjects with DLB than AD*<br>• Results were independent of severity of dementia, depressive symptoms and measures of hallucinations, delusions, agitation and apathy<br><br>Comorbidity of NSD with hallucinations, agitation and apathy was higher in DLB than AD<br><br>NSD was associated with more advanced disease in AD but not in DLB |

AD: Alzheimer disease; DLB: dementia with Lewy bodies; NPIQ: Neuropsychiatric Inventory Questionnaire; NSD: nocturnal sleep disturbance; *OR = 2.93, 95% CI = 2.22-3.86

*Conclusion*
Persons with dementia with Lewy bodies were more likely to have nocturnal sleep disturbance than those with Alzheimer disease.

*Commentary*
The purpose of this study was to compare disturbed sleep in the two most common forms of dementia, Alzheimer's disease (AD) and Dementia with Lewy Bodies (DLB). Why compare sleep in AD and DLB? Beyond answering the practical question of who is more likely to come to the attention of sleep medicine specialists, this question begets a host of mechanistic issues involving how these disorders and their associated neuropathophysiology influence systems impacting control of sleep. AD has been the focus of many studies of sleep over the years.[1,2] Many of the features of sleep in AD have been well described, and although many issues remain unsolved (e.g., sleep apnea in dementia),[3] there can be little doubt that sleep problems, including phenomena like sundowning,[4] daytime sleepiness[5] and wandering,[6] are all common in AD.[7,8] It is only within the last decade that researchers, led by Brad Boeve and colleagues[9] followed up the prescient observations of Carlos Schenck and Mark Mahowald[10,11] and began to systematically compare disturbed sleep in AD to sleep in another common form of dementia, DLB. DLB is differentiated from AD neuropathologically by deposition of the degraded protein alpha-synuclein, rather

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than the proteins beta-amyloid and tau, the two key neuropathologic hallmarks of AD. A key, early observation was that patients with synucleinopathies typically showed REM behavior disorder (RBD), often years before a diagnosis of dementia was established. It has always remained unclear whether AD patients also demonstrated RBD, but the general speculation (based on the Boeve et al data) was that they were, as a diagnostic group, less likely to demonstrate this. The neurobiological substrates for the suspension of REM atonia in synucleinopathies are beyond the scope of this brief summary and the reader is directed elsewhere for a more complete description.[12] These facts set the backdrop for the analyses reported in the current study.

Our study used the single, largest source of rigorously characterized patients with both disorders (AD and DLB) anywhere in the world, the Uniform Data Set (UDS) established the National Alzheimer's Coordinating Center (NACC), collected under the auspices of the federally funded National Institute of Aging AD Research Centers. All NIA-funded Centers follow rigorous criteria for defining disease and inclusion and exclusion criteria. This is a very important feature of the data; one can be reasonably certain that, although the diagnoses are made clinically ante-mortem, they represent the most accurate and reliable rendering of the patient's condition possible, made by a variety of experts across the United States.  On a regular basis, each NIA Center reports not only their diagnostic data to the NACC (located at the University of Washington), but also data derived from specific scales mandated for use as a part of the UDS. In our analyses, we relied upon caregiver-derived data from a widely used questionnaire used in dementia research, the Neuropsychiatric Inventory-Questionnaire (NPI-Q). The NPI-Q data used in this study are all publically accessible and can be obtained (with permission) from the NACC Website.

Results confirmed our suspicion that caregivers of DLB patients were far more likely (in fact, over twice as likely) to report that the patient under their care suffered from sleep problems, relative to caregivers of AD patients. Interestingly, it did not make any difference if the patient was a man or a woman or the caregiver was a man or woman. Nor did it not matter if the caregiver lived with the patient, or did it matter how educated the caregiver was. Apparently, knowledge about sleep problems (which we speculate included dream enactment) becomes commonly known to those who care for dementia patients. It was a robust finding. One interesting difference between NPI-Q reported sleep disturbance in the AD and the DLB patients was that in the former sleep disturbance appeared to be a late stage accompaniment, whereas, in DLB, it appeared much earlier in the disorder. This was completely compatible with the early data of Schenck, Mahowald, Boeve and colleagues. Other points made in the paper include our speculations about what the results may or may not mean for the ways in which various centers take information about sleep disturbance into account in making diagnoses. The interested reader is directed back to the primary paper for this discussion, as well as for describing some of weaknesses with using the NPI-Q as the sole vehicle of information about sleep.

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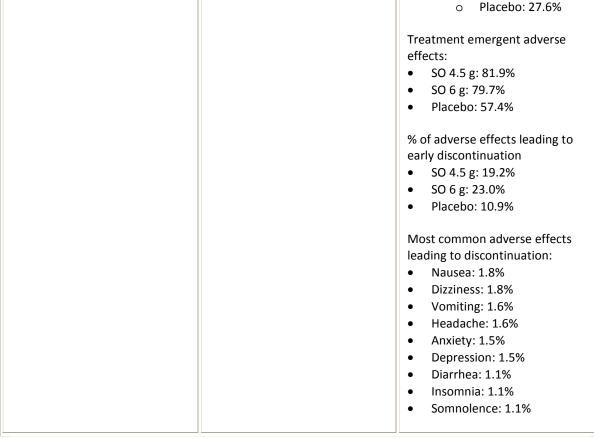Emory University School of Medicine
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**Sodium oxybate reduces pain, fatigue, and sleep disturbance and improves functionality in fibromyalgia: results from a 14-week, randomized, double-blind, placebo-controlled study.** Russell IJ, Holman AJ, Swick TJ, Alvarez-Horine S, Wang YG, Guinta D; Sodium Oxybate 06-008 FM Study Group. *Pain. 2011 May;152(5):1007-17.*

*Does sodium oxybate improve sleep, fatigue and pain in persons with fibromyalgia?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 1853 screened subjects<br><br>548 enrolled subjects with FM<br>• Age: > 18 yrs<br>• BMI: < 40 kg/m2<br>• Pain VAS: > 50/100 mm<br>• No inflammatory rheumatic disease, and major depressive or other significant psychiatric disorder<br><br>334 (61%) subjects completed the study | Double-blind, randomized, placebo-controlled, parallel-group 14-week trial<br><br>Subjects were randomized to:<br>• Placebo: n = 183<br>• SO 4.5 g: n = 182<br>• SO 6 g: n = 183<br><br>Assessments:<br>• Pain VAS<br>• Fatigue VAS<br>• FIQ<br>• JSS<br>• PGIC<br>• SF36<br>• Pain Composite criteria: > 30% reduction in pain VAS *plus* >30% improvement on FIQ *plus* much better or very much better on PGIC<br>• Safety | Compared to placebo, both doses of SO were associated with significantly greater improvements in:<br>• % with ≥ 30% reduction in pain VAS scores:<br>  o SO 4.5 g: 54.2%<br>  o SO 6 g: 58.5%<br>  o Placebo: 35.2%<br>• Reduction in fatigue VAS (LS Mean +/- SE)<br>  o SO 4.5 g: -27.9 +/- 2.1<br>  o SO 6 g: -30.0 +/- 2.1<br>  o Placebo: -17.6 +/- 2.2<br>• Reduction in sleep disturbance (JSS; LS Mean +/- SE)<br>  o SO 4.5 g: -6.1 +/- 0.5<br>  o SO 6 g: -6.2 +/- 0.5<br>  o Placebo: -2.9 +/- 0.5<br>• % with ≥ 30% reduction in FIQ<br>  o SO 4.5 g: 55.3%<br>  o SO 6 g: 56.0%<br>  o Placebo: 38.8%<br>• % Reporting much better or very much better on PGIC<br>  o SO 4.5 g : 48.3%<br>  o SO 6 g: 45.4%<br>  o Placebo: 27.2%<br>• % Meeting Pain Composite criteria<br>  o SO 4.5 g: 42.9%<br>  o SO 6 g: 49.6% |

<table>
<tr><td></td><td></td><td>o     Placebo: 27.6%<br><br>Treatment emergent adverse effects:<br>• SO 4.5 g: 81.9%<br>• SO 6 g: 79.7%<br>• Placebo: 57.4%<br><br>% of adverse effects leading to early discontinuation<br>• SO 4.5 g: 19.2%<br>• SO 6 g: 23.0%<br>• Placebo: 10.9%<br><br>Most common adverse effects leading to discontinuation:<br>• Nausea: 1.8%<br>• Dizziness: 1.8%<br>• Vomiting: 1.6%<br>• Headache: 1.6%<br>• Anxiety: 1.5%<br>• Depression: 1.5%<br>• Diarrhea: 1.1%<br>• Insomnia: 1.1%<br>• Somnolence: 1.1%</td></tr>
</table>

FIQ: Fibromaylgia Impact Questionnaire; FM: fibromyalgia; JSS: Jenkins Sleep Scale; PGIC: Patient Global Impression of Change; SF36: Short Form 36 Health Survey; SO: sodium oxybate; VAS: 100-mm Visual Analog Scale

### Conclusion
Sodium oxybate significantly improved pain, fatigue, sleep disturbance and functionality in persons with fibromyalgia.

### Commentary
Fibromyalgia syndrome (FMS) is a relatively common disorder that is manifested by signs and symptoms encompassing both physical and psychologic spheres. The most common patient complaints are chronic pain, overwhelming fatigue, non-refreshing nocturnal sleep and a variety of mood disorders. Treatment of FMS has been geared to the modulation of the CNS nociceptive system that in a best-case scenario provides some degree of pain relief. However, it is clear the sleep complaints of FMS patients are severe and play a significant part of the underlying CNS mechanisms demonstrated by studies that corroborated the bi-directionality of pain/sleep pathologic interaction.

SXB is the sodium salt of gamma-hydroxybuterate (GHB), an endogenous metabolite of gamma-aminobutyric acid (GABA). It is approved by the FDA to treat excessive daytime sleepiness and cataplexy

in patients with narcolepsy. (N.B., SXB is NOT approved for the treatment of fibromyalgia.) SXB is a unique pharmacologic agent whose exact mechanism of action has not been fully ascertained. It is known to bind to both GABAB receptors as well as specific GHB receptors in the CNS (both receptors are G-protein coupled). In addition, there is evidence that points to SXB's ability to modulate the signaling of CNS monoaminergic transmitters (DA, 5-HT and NE) and endogenous opioids, and increase GH concentrations. SXB has been shown to decrease sleep fragmentation and increase slow wave sleep.

There has long been known a bi-directional relationship between sleep and pain, i.e. pain disturbs sleep and disturbed sleep (fragmented or shortened sleep) enhances and/or changes the perception of pain. Sleep loss of 4 hours (specifically REM sleep) is hyperalgestic the following day as measured by finger-withdrawal to a painful stimulus. Conversely, the application of noxious stimuli during sleep causes a decrease in SWS and an increase in alpha and beta frequencies consistent with lighter and more fragmented sleep. Moldofsky et al. found that noxious stimulation used to disrupt SWS in normal individuals during the night resulted in complaints the following morning by the subjects that their sleep was unrefreshing and they developed daytime fatigue, body aches and increased tender points in many of the same areas as patients with FMS. Hakkionen et al. found that restoration of SWS increases next day mechanical pain thresholds suggesting that improvement in SWS induces an independent analgesic effect.

Sleep abnormalities in patients with FMS have been well described. These include the finding of alpha frequency waves over-riding slower background rhythms during non-REM sleep (referred to as alpha-delta or A-D sleep). It has been postulated that A-D sleep is associated with a "hypervigilent" state of sleep resulting in the subjective feeling of non-refreshing or nonrestorative sleep. A newer method of looking at sleep over extended periods as opposed to the classic 30-second epoch on polysomnography has utilized computer-aided analysis looking at what has been termed the "cyclic alternating pattern" (CAP). A low frequency pattern is associated with stable and consolidated sleep whereas higher frequency patterns are associated with more fragmented and disruptive sleep. Patients with FMS typically exhibit high CAP frequencies.

The results of a large study of FMS patients who met the 1990 ACR criteria for tenderpoints were reported in two papers. In 2009, Russell et al reported on the safety and efficacy of SXB in a randomized, double-blind, placebo controlled, multicenter clinical trial (SXB-26). In 2010, Moldofsky et al reported results based on the same SXB-26 study, looking at sleep physiology and sleep/wake symptoms in this group of FMS patients. Moldofsky et al reported on 304 patients of whom 195 were randomized to an 8-week evaluation of SXB 4.5 g, SXB 6 g and placebo. The enrollees were washed out of their prestudy medications prior to the 8-week treatment period. The randomized population was 94% women and had a mean age of 46.5 years. 192 (98%) patients were treated and 151 (77%) of the randomized population completed the protocol. SXB is always given in two divided doses; the first dose (50% of the total nightly dose) is taken at bedtime and the second dose is taken 2.5-4 hours later. The primary outcome variable (POV) was a composite of change from baseline in 3 self-reported measures: pain rating on a visual analog scale (Pain VAS), the Fibromyalgia Impact Questionnaire (FIQ), and the Patient Global Impression of Change (PGI-C). Secondary measures included the Jenkins Sleep Scale (JSS), Epworth Sleepiness Scale (ESS), fatigue VAS, and quality of life measures (Short Form-36 Health Survey [SF-36] and Functional Outcome of Sleep Questionnaire (FOSQ)). As in the Sodium Oxybate 06-008 study, significant benefit was observed with both trial doses of SXB (4.5 and 6 g/night).

The SXB-26 FMS study was the first to assess objective and subjective measures of disrupted sleep in a large number of patients with FMS. Polysomnographic interpretation using visual scoring rules was

performed on 209 screened patients and 181 randomized patients of whom 138 completed the study and computer aided CAP analysis was performed on 88 randomized patients of whom 47 completed the entire study.

Screening polysomnographic data corroborated previous findings that FMS patients exhibited a high prevalence of alpha-delta (A-D) sleep with maximum alpha EEG intrusion > 24 min/hr of sleep in 66% of patients as well as showing significant non-REM sleep disruptions, e.g., elevated CAP frequency, periodic limb movements of sleep (20% exhibiting > 5/hr) and moderate to severe obstructive sleep apnea (15%). The baseline subjective scales and scores for randomized patients revealed significant sleep complaints with shortened sleep duration in 74%(< 6 hrs of sleep/nt), 66% having multiple nocturnal awakenings (> 3/nt) and light or very light sleep in 78% of the patients. The ESS was elevated at 11. JSS, FOSQ and SF-36 scores all indicated significant daytime fatigue with worsening symptoms as the day progressed. Based on a completers analysis, treatment with SXB resulted in a dose dependent decrease in fatigue measured by Fatigue VAS with significant reductions compared to placebo throughout the day with SXB 6 g and for morning only with SXB 4.5 g dose. Dose dependent improvements were seen in JSS and ESS scores (statistically significantly better than placebo for both SXB doses). Polysomnographic findings revealed that SXB 6 g dose significantly increased stages N2 and N3 individually, and collectively, there was an increase in total non-REM sleep. Both SXB 4.5 g and SXB 6 g significantly reduced total REM sleep compared to placebo. Total sleep time and sleep efficiency increased with SXB 6 g by an amount that fell just short of statistical significance. A statistically significant decrease was seen in WASO for the SXB 6 g dose. A1 CAP rate (indicating a more stable sleep state) showed improvement for both doses of SXB but the increase was not statistically significant; however, decreases in the phase A2/A3 CAP rates (indicating more fragmented sleep) for both doses of SXB were seen with statistical significance being demonstrated for the SXB 6 g dose only.

Treatment-emergent AEs were reported in all 3 treatment groups (placebo - 60%; SXB 4.5 g/night - 68% and SXB 6 g/night - 78%). Most AEs were mild-moderate and dose dependent. Adverse events affecting ≥ 2% of the patients and that differed significantly in frequency between sodium oxybate and placebo included: nausea, pain in extremity, nervous system disorders (including dizziness, headache, paresthesias, somnolence), dizziness (individually), restlessness, renal and urinary incontinence (individually). Ten patients (5%) reported experiencing either anxiety (2%) and/or depression (3%).

The 06-008 and the SXB-26 studies show remarkably similar profiles in terms of results and AEs. The SXB-26 study is significant for demonstrating statistically significant improvement in both objective and subjective sleep parameters in patients with FMS. The 06-008 study further demonstrated statistically significant improvement in pain, fatigue, sleep disturbance and functionality in a larger number of patients with FMS. The AE's have been similar in all trials and indicate SXB is safe when used as directed. SXB carries a black-box warning for the treatment of narcolepsy patients with excessive daytime sleepiness and/or cataplexy. It is a potent CNS depressant and care needs to be taken when prescribing it. As stated previously, SXB is not approved for the treatment of fibromyalgia.[1-29]

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**The improvement of movement and speech during rapid eye movement sleep behaviour disorder in multiple system atrophy.** De Cock VC, Debs R, Oudiette D, Leu S, Radji F, Tiberge M, Yu H, Bayard S, Roze E, Vidailhet M, Dauvilliers Y, Rascol O, Arnulf I. *Brain. 2011 Mar;134(Pt 3):856-62.*

*Are movement, speech and facial expression improved during rapid eye movement sleep behavior disorder in multiple system atrophy?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 49 persons with MSA<br><br>49 persons with idiopathic PD<br><br>98 bed partners | Assessments:<br>• Structured questionnaire (bed partners) to determine improvement in movement (speed, smoothness and strength), facial expression and the quality of speech<br>• Video-PSG: 22 subjects with MSA and 19 subjects with PD | RBD was noted in 88% of subjects with MSA<br>• 81% showed some improvement during RBD<br>• 73% had improvement in movement*<br>• 59% had improvement in speech**<br>• 50% had improvement in facial expression<br><br>Rate of improvement in PD > MSA |

MSA: multiple system atrophy; PD: Parkinson disease; PSG: polysomnography; RBD: REM sleep behavior disorder; REM: rapid eye movement sleep; *faster, 67%; stronger, 52%; and smoother, 26%; **louder, 55%; more intelligible, 17%; and better articulated, 36%

*Conclusion*
Movement and speech were improved during rapid eye movement sleep behavior disorder in persons with multiple system atrophy.

*Commentary*
Multiple system atrophy (MSA) is an atypical parkinsonism characterized by severe motor disabilities that are poorly levodopa-responsive. Most patients with MSA[1] develop rapid eye movement sleep behavior disorders, enacting their dreams during REM sleep because of impaired REM sleep atonia.[2] We have recently reported that parkinsonism disappears during RBD movements in patients with Parkinson's disease. The bed partners of these patients noticed faster, stronger and smoother movements, as well as louder and more articulated speech in these patients during sleep, which sharply contrasts with their movements when awake. The restoration of motor control was confirmed by video surveillance. No bradykinesia, tremor or hypertonia was observed during these REM sleep-associated movements. We hypothesize that these improvements derive from either a transient re-establishment of dopamine transmission (as suspected in other paradoxical kinesias) or a transient bypass of the basal ganglia.[3] The aim of this study was to determine if this REM sleep associated motor improvement could also be observed in MSA because of a loss of both presynaptic nigrostriatal neurons but also putaminal post synaptic neurons.[4]

This study proved transient restored motor control during RBD in patients with MSA. Indeed, 81 % of patients improved their movements (73% of the patients), speech (59%) or facial expression (50%) during REM sleep, compared to movements performed during the wake state. REM sleep movements were faster (67% of the patients ), smoother (26%) and stronger (52%) but they had a broken and jerky aspect. We observed no difference in the percentage of REM-related motor improved between patients affected with MSA-P and MSA-C. The rate of improvement was higher in Parkinson's disease than in multiple system atrophy, but no further difference was observed between the two forms of multiple system atrophy (predominant parkinsonism versus cerebellar syndrome). Video-monitored movements during rapid eye movement sleep in patients with multiple system atrophy revealed more expressive faces, and movements that were faster and more ample in comparison with facial expression and movements during wakefulness. These movements were still somewhat jerky but lacked any visible parkinsonism. Cerebellar signs were not assessable. We conclude that parkinsonism also disappears during rapid eye movement sleep behavior disorder in patients with multiple system atrophy, but this improvement is not due to enhanced dopamine transmission because these patients are not levodopa-sensitive. These data suggest that extrapyramidal regions do not influence these movements; however, the influence of abnormal cerebellar control remains unclear. The transient disappearance of parkinsonism here is all the more surprising since no treatment (even dopaminergic) provides a real benefit in this disabling disease. By specifying motor control during REM sleep, this study shows that there are still functional pathway to use to improve motor disability during wake for MSA, but perhaps also for other movement disorders.

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# Pediatric Sleep Medicine

**An hour less sleep is a risk factor for childhood conduct problems.** Holley S, Hill CM, Stevenson J. *Child Care Health Dev. 2011 Jul;37(4):563-70.*

*Does sleep duration affect the risk of behavioral problems among school-aged children?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 91 children aged 6-11 years | Assessments:<br>• ACT for an average of 6 nights in the child's own home.<br>• SDQ completed by parents<br><br>Note: SDQ is a brief screening questionnaire for childhood psychopathology that is comprised of 5 sub-scales, namely emotional symptoms, conduct problems, hyperactivity, peer problems and pro-social scale | Sleep duration was not predictive of emotional symptoms or hyperactivity, but accounted for some of the variance in conduct problems |

ACT: actigraphy; SDQ: Strengths and Difficulties Questionnaire

## *Conclusion*
Decreased sleep duration in children aged 6 to 11 years increased the likelihood of conduct problems, but not emotional symptoms or hyperactivity.

## *Commentary*
Sleep problems affect an estimated 20-30% of all children. Secular trends in children's sleep suggest that contemporary children sleep less than their parents' and grandparents' generations. These are important observations as healthy sleep underpins healthy neurodevelopment.[1]

Several studies have shown associations between parent reports of sleep problems and childhood behaviour difficulties including: conduct problems, hyperactivity,[2] inattention and internalizing symptoms.[3] These studies relied on parental or child self-reports of sleep. Such reports may be subject to bias and, therefore, inaccurate.[4] Wrist worn accelerometers (actigraphs) provide a reliable measure of sleep including aspects not easily observed by a parent, such as night wakings.[5] Previous actigraphic studies have demonstrated a relationship between sleep problems and behavior difficulties including externalizing problems,[6] delinquency and thought disorder.[7] Despite the growing number of studies demonstrating such relationships, findings are inconsistent. Specifically it is unclear what dimensions of sleep quality (sleep duration, sleep efficiency or both) are associated with daytime behavioral difficulties. We aimed to identify which behavioral symptoms are best predicted by objective sleep measures in a population sample of 91 healthy, typically-developing school children aged 6-11 years. Our data

demonstrated that absolute minutes of recorded sleep predict the risk of conduct problems, supporting previous research.[6] However, in contrast to previous parent reports, sleep variables did not predict either hyperactivity or emotional symptoms. This may reflect the objective methodology used to measure sleep. However, the direction of the association between sleep time and conduct problems is unknown. Does less sleep cause conduct problems? Or are the conduct difficulties disrupting sleep? A growing body of research suggests that a lack of sleep has a detrimental effect on prefrontal cortical functions that may underpin behavioural regulation[8] but, conversely, conduct difficulties may also be associated with prefrontal cortical dysfunction.[9] Further research is needed to identify the mechanisms underpinning this association and whether it reflects acute or chronic sleep loss. However, irrespective of direction of causality, sleep problems are readily amenable to behavioral management approaches and should be prioritized as part of any treatment goal in childhood conduct disorder.

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**Delaying school starting time by one hour: some effects on attention levels in adolescents.** Lufi D, Tzischinsky O, Hadar S. *J Clin Sleep Med. 2011 Apr 15;7(2):137-43.*

*What are the effects, if any, of delaying school start times of middle-school students on their attention level?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 47 students | Subjects were entered into either:<br>• Experimental protocol (n = 26): School start time was delayed for 1 hr for 1 week and returned to regular schedules on the 2nd week<br>• Control protocol (n = 21): School start time remained on the regular schedule for 2 weeks.<br><br>Assessments:<br>• Tests of attention (MCPT, TOA) | Delaying school start time was associated with:<br>• Longer nighttime sleep (average of 55 minutes more each night)<br>• Better performance in measures of attention, impulsivity and rate of performance |

MCPT: Mathematics Continuous Performance Test; TOA: d2 Test of Attention

***Conclusion***
Delaying school start time of middle-school students by one hour resulted in longer duration of nighttime sleep and improved levels of attention.

***Commentary***
In 2008, the American National Sleep Foundation recommended 8-9 hours sleep every night for adolescents. Surveys showed that in many countries, adolescents sleep less than eight hours; this happens in the USA,[1] in the Far East,[2] and in Israel.[3] In the last decade, sleep deprivation has been reaching epidemic proportions;[4] its negative effect is more conspicuous among adolescents as compared to adults. During adolescence, a physiological shift to a later sleep phase is a major reason for their later bedtimes, and schooling is the cause of their early wake-up times, and short periods of sleep during week days. However, during the weekend, we notice later bedtimes, later wake-up times, and longer periods of sleep.

The effect of partial sleep deprivation upon cognitive functioning has been well documented and can be described as 'devastating.' Sleep loss may reduce motivation, decrease speed of functioning, degrade accuracy, impair the ability to maintain wakefulness, demean cognitive performance, and increase subjective sleepiness.[5] A few more of the cognitive functions where sleep deprivation causes difficulties are: memory, learning, logical thinking, mathematical ability, alertness, reaction time, attention and vigilance. Dinges, Maislin, Mullington and Van Dongen[6] summarized their study by saying that chronic

sleep restriction, in normal adults, to no more than six hours or less may be equivalent to two nights of total sleep deprivation. Dinges and Van Dongen[5] went further and discovered that recovery from sleep loss can improve cognitive functioning.

When one considers the physiological and the environmental factors which affect adolescents, making them sleep more seems like an impossible task. The combination of homework, social activities, participating in various leisure activities such as sport, music, dance and art are other reasons for missing sleep. The most obvious reasons for missing sleep time are the mobile phone, television and computer (MTC). These three 'screen oriented' activities are major leisure activities of adolescents today.

Combining the above factors one can understand that increasing sleep time is essential for improving cognitive functioning and learning among adolescents. Lufi, Tzischinsky and Hadar[7] found that a specific group of adolescents, as compared to a control group, who obtained 55 minutes more sleep following the delay in their school start time, perform better on tests requiring attention. The main results of this study were found the using a computerized test (MATH-CPT), and a paper and pencil test (d2 Test of Attention).

It seems that changing the school's starting time can help to reach this goal better as compared to other options, such as explaining the importance of sleep, forcing adolescents to go to sleep earlier, preventing adolescents from social and leisure activities, and not allowing adolescents to use the screen oriented activities (MTC). Delaying school starting time will go with the natural biological tendency and with the wish of the adolescents to stay up late. It needs bureaucratic changes, which are easier to reach and cost less in a long run.

The authors strongly suggest that high schools consider a change in the time at which school starts, i.e. at least one hour later. Such a change should improve the attention level of the students, reduce impulsivity, and increase the rate of performance, possibly without harming other daily functions of the adolescents.

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**Does an intervention that improves infant sleep also improve overweight at age 6? Follow-up of a randomised trial.** Wake M, Price A, Clifford S, Ukoumunne OC, Hiscock H. *Arch Dis Child. 2011 Jun;96(6):526-32.*

*Does a brief primary care behavioral intervention that successfully reduced parent-reported infant sleep problems also reduce adiposity at age 6?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 328 children with parent-reported sleep problems at age 7-8 months<br><br>193 children were followed up at age 6 years<br>• Gender: 45% F<br>• Retention: 59% (equal attrition between groups) | Follow-up study at age 6 years (5 years post-intervention) of a population-based cluster randomised trial comparing usual care vs. behavioral sleep strategies delivered from 8-10 months<br><br>Assessments (at age 6 years):<br>• BMI<br>• % Overweight/obese<br>• Waist circumference<br>• Sleep measures<br>• Severity of parent-reported child sleep problems<br>• Parent-reported usual child sleep and wake times, SOL and number/duration of wakings | During infancy, compared to controls, intervention was associated with:<br>• Fewer parent-reported sleep problems and night wakings<br>• No difference in total sleep duration<br><br>At 6 years, control and intervention did not differ in:<br>• BMI z-score*<br>• Rates of overweight: 20% vs. 17%**<br>• Waist circumference***<br>• Sleep outcomes |

BMI: body mass index; SOL: sleep onset latency; *adjusted mean difference 0.2, 95% CI -0.1 to 0.4; **adjusted OR 1.4, 95% CI 0.7 to 2.8; ***adjusted mean difference -0.3, 95% CI -1.6 to 1.1

*Conclusion*
The brief infant sleep intervention failed to reduce obesity at 6 years.

*Commentary*
The current obesity epidemic is tipped to ravage both the health and health care costs of the next generation. Since community-based lifestyle and clinical interventions have had very limited success in reducing or preventing childhood obesity, alternative intervention avenues hold great appeal. Sleep is one such possibility that is currently generating intense interest.

Systematic reviews suggest that shorter sleep duration may play a causal role in the genesis of obesity, in both adults and children.[1] Proposed mechanisms for a sleep/obesity relationship include (i) fatigue leading to reduced physical activity, (ii) increased intake of calorie-dense foods, (iii) lower nocturnal leptin and higher ghrelin production, thus increasing daytime appetite, and (iv) lower nocturnal growth hormone production, resulting in decreased lypolysis.[1]

Therefore, trials are already under way to investigate whether improving sleep duration can prevent or reduce obesity in children or adults.[2-4] The rationale for these trials, however, is based on predominantly cross-sectional or short-term longitudinal studies that found an association between reduced sleep duration and overweight/obesity. Relatively little attention has been paid to the specific components of sleep that could, in turn, impact on total sleep duration and BMI through the mechanisms above. These include sleep quality, day-to-day variation in sleep patterns (including 'catch-up' sleep) and sleep timing.

In a long-term follow-up to a randomized controlled trial - the gold standard for assessing causality[5] - we seized a unique opportunity to examine whether population-based strategies known to improve infant sleep might also play a role in reducing overweight in children at 6 years of age. We hoped this would provide the first evidence that a sustainable, cost-effective primary care infant sleep strategy could also impact, in the longer term, on the childhood obesity epidemic.

In Melbourne, Australia, maternal and child health nurses provide a universal well-child care service from 0-6 years over a series of standardized visits at key ages. Via this service, we used a population-based secondary prevention framework in which we first recruited a large, population-based cohort of 4-month-old infants and screened them all for parent-reported sleep problems at age 7-8 months. We systematically offered a primary care intervention at age 8-10 months to all infants thus identified with a sleep problem and subsequently randomized to the intervention arm. Every nurse in the participating communities was trained to deliver behavioral sleep strategies over one to three structured individual consultations with the parent. Compared to usual care, the intervention reduced parent-reported sleep problems as well as improved parent mental health, and was highly cost-effective.

Unfortunately, this brief infant sleep intervention did not reduce overweight/obesity at 6 years. Nor did it increase infant sleep duration. However, this did not explain the lack of effect because, in post-hoc analyses, neither infant nor childhood sleep duration predicted anthropometric outcomes – suggesting that it was not simply the intervention's low intensity or brevity that was at fault. Whatever the place of sleep intervention in established obesity, it, therefore, seems unlikely that population-based primary care infant sleep interventions will lessen rates of early childhood obesity.

Studies published since have continued to produce conflicting findings as to sleep-adiposity relationships in children. Childhood sleep quality and BMI were cross-sectionally associated in pre-adolescents,[6] and in a small longitudinal study longer sleep duration at ages 3-5 years predicted lower BMI and less obesity at age 7 years.[7] In contrast, sleep duration did not predict BMI across multiple time points from birth to child age 7 years[8] or in a clinical sample of adolescents.[9]

Also of interest are two new studies shining a spotlight on whether secular trends in sleep duration have truly paralleled the upswing in obesity. Repeated nationally representative cross-sectional time-diary surveys show that the average adult Australian slept as long (if anything, slightly longer) in 2006 as in 1992,[10] while a study of secular trends in sleep duration for nearly 700,000 children from 20 countries found that children globally sleep about an hour less per night than a hundred years ago – but sleep may have actually increased in Australia and the UK, two countries with marked obesity increases.[11] This makes sleep duration a questionable driver of the population obesity epidemic, but leaves open considerations of sleep quality and fragmentation.

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**Nocturnal hypoventilation: predictors and outcomes in childhood progressive neuromuscular disease.**
Katz SL, Gaboury I, Keilty K, Banwell B, Vajsar J, Anderson P, Ni A, Maclusky I. *Arch Dis Child. 2010 Dec;95(12):998-1003.*

*What are the prevalence, predictive factor/s, presentation and course of nocturnal hypoventilation in children with progressive neuromuscular disease?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 46 children with progressive NMD without neurocognitive impairment<br>• Age: 6-17 yrs | Prospective cohort study<br><br>Assessments:<br>• PSG<br>• PFT<br>• Manual muscle strength<br>• QOL<br>• Conners questionnaire | Prevalence of NH: 14.8%*<br><br>Maximal sensitivity and specificity for NH were achieved with thresholds of FVC < 70%** and $FEV_1$ < 65%*** predicted<br><br>Scoliosis also predicted NH[#]<br><br>Over a period of 1 yr, children with NH had:<br>• Greater increase in RV/TLC[##]<br>• Decline in muscle strength[###]<br>• Worsened perception of health status |

$FEV_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; NH: nocturnal hypoventilation; NMD: neuromuscular disease; PFT: pulmonary function test; PSG: polysomnography; QOL: quality of life [CHQ-PF50]; RV: residual volume; TLC: total lung capacity; *95% CI 8.0-25.7%; **sensitivity 71.4; specificity 64.1; ***sensitivity 71.4; specificity 79.5; [#]sensitivity 88.9; specificity 80.4; [##]0.075 (-0.003 to 0.168) vs -0.03 (-0.065 to 0.028); [###]-0.67 (-0.90 to 0.10) vs 0.53 (-0.05 to 0.90)

### Conclusion
Nocturnal hypoventilation was noted in 15% of children with progressive neuromuscular disease, and was associated with greater gas trapping, decreased muscle strength and worse perception of health status over a one year period despite non-invasive positive pressure ventilation.

### Commentary
In children with progressive neuromuscular diseases, nocturnal hypoventilation will eventually occur due to respiratory muscle involvement. It often has an insidious onset and is frequently difficult to diagnose on clinical grounds.[1] Polysomnography (PSG) is the gold standard for its diagnosis, but pediatric sleep laboratories are in short supply. Moreover, the optimal timing and indications for testing are not known. Recent guidelines on respiratory management of patients with Duchenne Muscular Dystrophy state the need to screen for nocturnal hypoventilation, but do not provide guidance as to either specific indications or frequency of PSG in these children.[2,3] They do acknowledge that this is an area of controversy, requiring further study.[2] Identification of isolated nocturnal hypoventilation is important, however, as intervention with noninvasive ventilation early in this process can improve quality of life and survival.[4-6]

The aims of this study were to (1) determine the prevalence of nocturnal hypoventilation in an asymptomatic clinic population of children with progressive neuromuscular disease, (2) to identify daytime predictors of nocturnal hypoventilation and finally (3) to determine the impact of treatment with noninvasive ventilation over a one-year period. A cross-sectional study of 46 children aged 6-17 years, recruited from two tertiary care pediatric neuromuscular clinics in Canada was conducted, including polysomnography, pulmonary function testing, manual muscle strength testing, quality of life and neurocognitive testing. This was followed by a one-year cohort study over one year to evaluate changes in these parameters, and to compare changes between those with and without nocturnal hypoventilation.

The prevalence of previously undetected nocturnal hypoventilation was 15.2%. Symptoms of sleep disturbance and daytime fatigue were rare and were not predictive of sleep-disordered breathing. Pulmonary function tests were predictive of the presence of NH. Thresholds of forced vital capacity (FVC) < 70% (sensitivity 71.4; specificity 64.1) and forced expiratory volume in one second ($FEV_1$) < 65% predicted (sensitivity 71.4; specificity 79.5) were identified. These were much higher than previously identified thresholds of FVC < 40%,[4] and inspiratory vital capacity (IVC) < 60%,[7] in studies of adults with more advanced disease. The only other pediatric study identified a threshold of IVC < 40%,[8] but was smaller. In an asymptomatic population of children with progressive neuromuscular disease, screening for nocturnal hypoventilation should, therefore, occur in individuals with less impaired pulmonary function than previously indicated by the literature. The presence of scoliosis was an additional predictor of NH, likely due to its contribution to chest wall restriction, although body mass index was surprisingly not predictive of the presence of NH.

Individuals with NH had a trend towards more rapid decline in pulmonary function, with increased gas trapping (increased residual volume to total lung capacity ratio), indicative of weakening expiratory muscles. Those with NH also perceived a greater decline in health status, highlighting the significance children and families place on the introduction of this therapy.

Sleep disordered breathing and nocturnal hypoventilation are common in this patient population, and, if untreated, lead to significant morbidity and mortality.[9] Although noninvasive ventilation has benefit, early intervention before the onset of actual hypoventilation has not been shown to be beneficial, and may actually be harmful.[10] Early and accurate diagnosis is therefore imperative. PSG, unfortunately, remains the primary diagnostic test,[9] but its limited availability and costs are a barrier to its use as a screening tool. This study identifies and highlights the need, however, for early screening for NH in children with progressive neuromuscular conditions regardless of symptoms of sleep-disordered breathing as the prevalence of NH is high. Clinical predictors of NH, including, FVC < 70%, FEV1 < 65% and/or the presence of scoliosis can be used to prioritize individuals for screening with polysomnography, where resources are scarce. This study, therefore, provides guidance for clinicians as to predictors of hypoventilation and the need for screening for identification of NH. It also describes, albeit in a small sample, a trend towards more rapid worsening of pulmonary function over time and poorer perception of general health status in those with NH, as compared to those without NH. This population may, therefore, require closer vigilance for other pulmonary complications of neuromuscular disease.

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**Normative values of polysomnographic parameters in childhood and adolescence: quantitative sleep parameters.** Scholle S, Beyer U, Bernhard M, Eichholz S, Erler T, Graness P, Goldmann-Schnalke B, Heisch K, Kirchhoff F, Klementz K, Koch G, Kramer A, Schmidtlein C, Schneider B, Walther B, Wiater A, Scholle HC. *Sleep Med. 2011 Jun;12(6):542-9.*

*How does age, Tanner pubertal stage and gender affect the sleep architecture of healthy children?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 209 healthy children | Assessment: One-night PSG during habitual bedtime | Sleep parameters that increased with age: AI, RL, SE (TST/SPT; TST/TIB), N2, mean SCD and number of stage shifts<br><br>Sleep parameters that decreased with age: TST, SPT, WASO, N3, stage R, MT and number of sleep cycles<br><br>Sleep parameters that were dependent on Tanner stages and age: TST, SPT, AI, RL, N2, N3, MT, number of sleep cycles and mean SCD<br><br>No difference between genders was noted |

AI: awakening index; MT: movement time; N2: stage 2; N3: stage 3; PSG: polysomnography; RL: REM latency; SCD: sleep cycle duration; SE: sleep efficiency; SPT: sleep period time; TIB: time in bed; TST: total sleep time; WASO: wake after sleep onset

***Conclusion***
Among healthy children one to eighteen years of age, certain sleep parameters (awakening index, sleep efficiency, REM latency and stage N2) increase with age, whereas others (total sleep time, wake after sleep onset, stage N3 and REM, and movement time) decrease with age.

***Commentary***
In the literature, normative data on the evolution of sleep architecture across childhood are limited.[1-11] Also, most studies include too wide of an age spectrum and the number of subjects was usually too small to give precise, significant statements. This study aimed to describe age-related changes in the macrostructure of normal sleep during childhood and adolescence regarding AASM guidelines in performing and scoring polysomnographies.[12] For the first time, the study shows the development of sleep in the full age range from 1 to 18 years of age. Age groups are narrowly defined for precision so it should be possible to show the dependency of sleep data on gender, age, and maturity in more detail than in previous studies.

In a prospective, multicenter study, one-night polysomnography was performed at the subjects' habitual bedtimes in 16 laboratories on 209 healthy German children of Caucasian ancestry. Subjects were grouped by gender (112 females, 97 males), age and Tanner stage. All 8 investigated age groups consisted of a statistically relevant number of normal subjects, who were carefully screened. Exclusion criteria included significant medical conditions, use of any medications, and any indication of a sleep related breathing disturbances or other sleep disorders. Children's habitual bedtimes were maintained and, despite the number of sleep labs involved, conditions such as subject selection criteria, instrumentation and measurement techniques, sleep scoring were consistent. The examinations were conducted in accordance with AASM rules for technical performance and scoring of sleep.[12]

To exclude interscorer variability the same expert sleep researcher throughout the entire investigation scored polysomnographies.

Normal values of sleep macrostructure showed significant age dependencies:
- Increasing with age: awakening index, R latency, sleep efficiency (SE; total sleep time TST/ sleep period time SPT) and SE* (TST/ time in bed), stage N2, mean sleep cycle duration and number of stage shifts
- Decreasing with age: TST, SPT, wake after sleep onset, stage N3, stage R and number of sleep cycles.

As Ohayon et al[13] outlined, changes in sleep patterns across childhood and adolescence are related not only to chronological age, but also to maturation stage. So we considered the chronological age, and in adolescents the physiological age characterized by Tanner stages as well. It is interesting that significant correlations of Tanner stages to sleep parameters were also reflected in significant correlations of age to the same parameters.

The following sleep parameters showed a significant dependency on Tanner stage as well as age: TST, SPT, awakening index, R latency, stage N2, stage N3, MT, MT index, number of sleep cycles, mean sleep cycle duration and number of stage shifts. No gender dependencies were found to the above parameters.

Results of previous studies regarding normal values of sleep architecture in sleep[1-11] are not directly comparable with our results. Differences in criteria and methodology for selecting participants, grouping ages, polysomnography technique, or in scoring of sleep pattern according to the rules of Rechtschaffen and Kales[14] or the AASM rules,[12] and in interpreting these rules, limits comparison. Conflicting results demonstrates the necessity to consider the same rules for technical performance of polysomnography and interpretation of polysomnographic patterns. AASM guidelines[12] are helpful in this way, but there are several points that have to be regarded, including racial differences and age typical sleep schedule, as well as other factors that may influence sleep quality.

Because all of the subjects in this study were Caucasian German, the given data may not be directly applicable to other racial ethnic groups, but results should require only minor adjustments.

The prospective study demonstrates new normative data of sleep architecture parameters in German children of Caucasian ancestry from 1 year to 18 years of age. Presented data of age and maturation dependent sleep architecture provide the possibility to correlate polysomnographic data in children with disturbed sleep to data of healthy children in comparable age groups. This study demonstrates that it is helpful to consider more precisely the age of pediatric patients in describing deviations from normal measures.

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**Prolonged-release melatonin for children with neurodevelopmental disorders.** De Leersnyder H, Zisapel N, Laudon M. *Pediatr Neurol. 2011 Jul;45(1):23-6.*

*Does prolonged-release melatonin improve sleep in children with neurodevelopmental disorders?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 88 children with neurodevelopmental disorders<br>• Gender: 47% F | Subjects are given prolonged-release melatonin*<br>• Dose: 4-6 mg<br>• Treatment duration: 6-72 months<br><br>Assessments (questionnaire for parents):<br>• Sleep onset/offset<br>• Sleep quality<br>• Mood | Administration of prolonged-release melatonin was associated with (within 3 months):<br>• Decrease in SOL by 44.0%**<br>• Increase in sleep duration by 10.1%**<br>• Decrease in number of awakenings by 75%**<br>• Improved sleep quality by 75%**<br>• No serious adverse events |

NDD: neurodevelopmental disorder; SOL: sleep onset latency; *Drug: Circadin (2 mg; Neurim Pharmaceuticals, Tel Aviv, Israel); **P < 0.001

### Conclusion
Prolonged-release melatonin improved several sleep parameters, and was safe to use, in children with neurodevelopmental disorders.

### Commentary
Pediatric insomnia in children and adolescents is a widespread problem. The prevalence of pediatric insomnia in children that goes beyond bedtime refusal and night awakenings ranges from 1% to 6% in the general population and is as high as 50–75% in children with neurodevelopmental or psychiatric comorbidities.[1] New studies continue to demonstrate the negative consequences of sleep disorders in children and adolescents, including hyperactivity, irritability, restlessness, poor concentration, impulsiveness and poor memory. Families of children with sleep disturbances also suffer, exhibiting negative effects on daytime function and well-being, as well as elevated levels of family stress.[2] Good sleep practices and proven behavioral strategies, such as extinction programs or bedtime fading are the first lines of treatment. Intervention is based on the effect of changing the parents' behaviour towards the child at bedtime and during the sleeping period. However, sleep disorders have a profound impact on the physical and mental health of children with neurodevelopmental disorders and medications are commonly prescribed such as antihistamines, alpha-adrenergic agonists, antidepressants, antipsychotics, benzodiazepines and non-benzodiazepines. Several exploratory studies have reported the strong beneficial of treatment with melatonin for chronic sleep disturbances with minor side effects. In these cases, inadequate regulation and secretion of melatonin[3-5] may contribute to the impairment of both the initiation of sleep and sleep maintenance and, thus, it is both the circadian phase regulating activity and the sleep regulating activity of melatonin that might be responsible for the clinical benefit in children. Hence, melatonin substitution therapy might be effective for insomnia in children with impaired endogenous melatonin levels. Indeed, fast-release melatonin had been tried in these pediatric

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populations[6] demonstrating improvement in some parameters of sleep quality but not in others (especially sleep maintenance), for which prolonged-release melatonin may be advantageous over fast-release formulations.[7,8]

Circadin® is a prolonged-release formulation of melatonin that was approved in Europe by the EMA in 2007 for the treatment of elderly patients with primary insomnia. Circadin® was also found safe in younger patients over 18[9] and in children 6 to 12 years old with neurodevelopmental disorders.[10] Prolonged-release melatonin mimics the physiological secretion profile of melatonin, inducing sustained blood levels through the night and promotes sleep for 8-10 hours. Hence, melatonin replacement therapy is proposed to be effective for insomnia in children with impaired endogenous melatonin levels. A special access program for Circadin® was established in France since 2001 (ATU of the Agence du Medicament). In the present retrospective study,[10] the long-term efficacy and safety of Circadin® treatment were assessed in 88 children aged 3-18 yrs, 42 females and 46 males, with neurodevelopmental disorders. Patients with Smith Magenis syndrome, a genetic disorder involving mental retardation and extremely severe sleep disorder with severe phase shift of circadian melatonin rhythm, were well represented in this study. The study was conducted by means of a structured questionnaire for the parents consisting of a combination of multiple choice, numeric questions addressed at sleep onset/offset, quality problems and mood. The dose of melatonin ranged from 4 to 6 milligrams and treatment duration ranged from 6 to 72 months. Within 3 months, sleep latency with prolonged-release melatonin decreased by 44.0% ($P < 0.001$), sleep duration increased by 10.1% ($P < 0.001$), number of awakenings decreased by 75% ($P < 0.001$) and sleep quality improved by 75% compared with baseline ($P < 0.001$). A constant and lasting improvement of the patient's sleep disorder was observed and consequently family sleep habits also improved. No serious adverse events or treatment related co-morbidities were reported. It was concluded that prolonged-release melatonin remains a safe and effective therapy in the long-term treatment of sleep disorders in children with neurodevelopmental disorders.

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**The effects of napping on cognitive function in preschoolers.** Lam JC, Mahone EM, Mason T, Scharf SM. *J Dev Behav Pediatr. 2011 Feb-Mar;32(2):90-7.*

*What is the relationship between cognitive function and napping in preschool-aged children?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 59 children enrolled in full-time childcare<br>• Age: 3 -5 yrs | Assessments:<br>• Actigraphy (for 7 days)<br>• NPT (attention, response control and vocabulary)<br>• Behavior ratings and sleep logs (completed by parents) | Weekday napping was:<br>• Inversely correlated with nighttime sleep<br>• Significantly correlated (negatively) with vocabulary and auditory attention span<br><br>Weekday nighttime sleep was correlated:<br>• Positively with vocabulary<br>• Negatively with performance |

NPT: neuropsychological testing

### Conclusion
Daytime napping among preschoolers was associated with worse neurocognitive function.

### Commentary
Napping declines between the ages of 2 and 5 years as sleep is consolidated from a biphasic sleep pattern to a single rest period at night.[1-3] The consolidation of sleep correlates to maturation of the brain.[4] Factors related to nap cessation include cultural/parental choices, biological brain maturation or temperament. There are no studies that have directly examined the relationship between neurocognitive performance and napping for this age group. In adults, sleep deprivation has profound detrimental effects on cognitive functioning and naps are restorative. Since there are no evidence-based guidelines for when naps are critical, some early childhood centers have eliminated napping to increase educational time. In a national survey of the States' Board of Education, 28% have napping policies for pre-kindergarten and kindergarten and 3 states (Alabama, Georgia, Arizona) actually restrict napping.[5] This topic is of great public health importance given that the largest increase in enrollment is in this age group. If the effect of nap deprivation is similar to sleep deprivation, children who miss their naps may have difficulty with tasks that require attention and cognitive control.[6]

We studied 59 healthy, typically developing preschoolers (aged 3-5 years) who attended full-time childcare. Prior to entry into the study, they were screened for development delays using the Peabody Picture Vocabulary Test. We monitored their sleep patterns for a week (Monday to Monday) with actigraphy watches and parent logs. They completed a brief 10-minute battery of neuropsychological tests designed to assess attention and memory. These tests included Number Recall (Kaufman Assessment Battery for Children, Second Edition), Statue (Developmental Neuropsychological Assessment, Second Edition) and the Auditory Continuous Performance Test for Preschoolers.

Most adults and older children who are sleep deprived during the weekdays compensate by increasing sleep on the weekends. We hypothesized that children who did not nap on weekdays would sleep more on weekends, but that was not the case. These children did not increase their sleep on weekends. Conversely, children who napped more on weekdays also napped more on weekends. We also found that the total amount of sleep (i.e., naps + nighttime sleep) in these children remained the same regardless of whether the children napped more or less. The proportion of nighttime versus daytime sleep, however, was different (i.e., children who napped more slept less at night while children who napped less slept more at night).

We also found that napping was associated with cognitive function; but not in the way we expected. We found that children who napped more during the week actually had poorer cognitive performance, specifically with number recall and vocabulary, while children who slept more at night had better cognitive performance in the area of vocabulary and made fewer impulsive errors on the continuous performance test.

The results of this study were novel and unanticipated. Children who napped less did not show signs of sleep deprivation and did not necessarily perform poorly on cognitive tests. There are a number of possible explanations for this finding:  1) Children who nap less have more advanced brain development and are able to consolidate sleep and perform better on cognitive tests; 2) nighttime sleep facilitates performance and decreases the sleep drive for naps; and, 3) less nighttime sleep results in a partially sleep deprived state which negatively affects performance and requires compensation with a nap. Due to the observational nature of this study, a cause-effect relationship between napping and cognitive function cannot be determined. The next logical step would be a randomized trial of nap restriction.

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# Aging

**Zolpidem and zopiclone impair similarly monotonous driving performance after a single nighttime intake in aged subjects.** Bocca ML, Marie S, Lelong-Boulouard V, Bertran F, Couque C, Desfemmes T, Berthelon C, Amato JN, Moessinger M, Paillet-Loilier M, Coquerel A, Denise P. *Psychopharmacology (Berl). 2011 Apr;214(3):699-706.*

*Does zolpidem and zopiclone have residual effects on driving performance in the ageing population?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 16 persons<br>• Age: 55-65 yrs | Double-blind, balanced, cross-over study<br><br>Subjects were randomized (11 pm) to:<br>• ZOP: 7.5 mg<br>• ZOLP: 10 mg<br>• FLUN: 1 mg<br>• Placebo<br><br>Assessments:<br>• Simulated driving (monotonous environment) for 1 h the next morning at 9 am<br>• Blood samples<br>• Subjective alertness | Compared to placebo, both ZOLP and ZOP significantly impaired SD of lateral position, SD of speed and number of road exits<br><br>Detectable blood levels were noted with ZOLP at 8:30 am and 1:30 pm in 11 subjects<br><br>ZOLP significantly impaired subjective alertness |

FLUN: flunitrazepam; SD: standard deviation; ZOLP: zolpidem; ZOP: zopiclone

### Conclusion
Both zolpidem and zopiclone significantly and equivalently impaired driving performance of older drivers.

### Commentary
Zolpidem (Zp) and zopiclone (Zc) are two hypnotic compounds that have been developed by pharmaceutical companies with the aim of reducing the impairments, also called residual effects, of various cognitive functions and driving ability the day after bedtime administration of hypnotic benzodiazepines. Information on the residual effects of Zp and Zc are derived from experimental studies in healthy young subjects or middle-aged patients with insomnia, and results have shown that Zc had residual effects on driving unlike Zp, which did not.[1-3]

Ageing is associated with changes in sleep–wake patterns in terms of sleep induction or sleep maintenance, leading to occasional or constant sleep problems that affect more than 30% of adults over 50 years of age,[4] leading to an increase in hypnotic drug use with increasing age. With age, the driving

abilities or skills, which depend on cognitive, psychomotor and sensory–perceptual functions, decline. Moreover, ageing people may be more likely to be affected by drugs than they were when they were younger due to age-related changes in pharmacokinetics and pharmacodynamics, such as reduced clearance and increased sensitivity[5] that may modify response to medications. Each of these factors may increase the risk of car accidents with age after prescription drug use. The objective of this study was, thus, to assess and compare, in the same study, the residual effects of two of the most commonly prescribed hypnotics, Zp and Zc, on driving performance during the following morning in an ageing population.

Subjects completed a monotonous driving test 60 min duration and the driving parameters analyzed were the standard deviation of the lateral position (SDLP), which is considered as the "gold standard" measure of safe driving, the standard deviation of speed (SDS) and the number of road exits (RE). The subjects also completed self-rating scales reflecting alertness. To tempt to rely driving performance to residual concentrations of hypnotics, two blood samples were collected at 8.30 am and at 1.30 pm.

Surprisingly, our study showed that Zp and Zc significantly impaired the three driving parameters similarly in comparison to placebo. The increased SDLP ($P < 0.00001$), SDS ($P <0.01$) and RE ($P < 0.05$) revealed that subjects had difficulty maintaining trajectory, speed. Subjects felt also less alert after Zp at awakening ($P = 0.0002$) and before the driving test ($P = 0.05$).

While the residual effects of Zc were anticipated in the present study, those found with Zp were not because according to previous studies.[1,3,6] Zp was, to date, considered to be devoid of any residual effects. Nevertheless, two types of data published in recent years are in accord with the present results and indicate that Zp could lead to risks. Indeed, we found that in urban driving tests with accident scenarios, Zp tends to produce more risky behavior compared to placebo.[7] Moreover, two pharmaco-epidemiological studies exploring the risk of accidents associated with Zp use reported an increase in risk with this drug.[8-9] Our study showed that Zp, at the therapeutic dose in older middle-aged subjects, impaired driving performance the morning after a night of sleep at a similar level to that of Zc, which is considered to be equivalent to slightly greater than 0.5 g/L of BAC. Consequently, we can hypothesize that the residual effects of Zp could be at a similar level, which is considered at risk for driving safety. Interestingly, the subjective feelings indicated that subjects were aware of being affected by Zp.

This study also reveals that after 8 h of sleep, subjects had blood concentrations of Zp above the detectable level in 11 of 16 subjects, with values near or above the theoretical maximal concentration (Cmax) of 120 µg/L[10] in four subjects. Our data may not been compared with previous ones as no available residual concentration values of Zp were published. Although no correlations were found between driving parameters and blood concentrations, probably due to the low number of subjects, the pharmacokinetic modifications observed with age for Zp revealed that high concentrations could be found in the morning after 8 h of sleep.

This study is the first to reveal residual effects of the most prescribed hypnotic, i.e., Zp, on monotonous driving performance the morning after bedtime intake in older middle-aged subjects. All parameters studied converge to show that after nighttime intake of Zp, subjects felt less alert and drove worse, perhaps due to residual blood concentrations. This study also shows that the effects observed in young subjects should not be extrapolated to all age ranges, as age-related changes could interact to modify the sensitivity of the drugs.

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# Miscellaneous

**Does timing of alcohol administration affect sleep?** Van Reen E, Tarokh L, Rupp TL, Seifer R, Carskadon MA. *Sleep. 2011 Feb 1;34(2):195-205.*

*Does the timing of alcohol use during the day affect sleep?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 26 healthy young adults<br>• Age: 21-25 yrs | After sleeping 2300-0800 for ≥ 12 nights, subjects were randomized to either placebo or alcohol (vodka tonic targeting 0.05g% concentration) at different times (0400, 1600, 1000 or 2200) during a 20-hr FD protocol and at differet homeostatic loads:<br>• Low (2.24 hrs awake)<br>• Medium (6.25 hrs awake)<br>• High (10.25 hrs awake)<br><br>Assessments:<br>• BAC<br>• Sleep staging and spectral analysis | BAC levels at bedtime:<br>• Low and medium homeostatic load: zero<br>• High homeostatic load: still measurable<br><br>Alcohol use was associated with:<br>• No changes in sleep spectral characteristics<br>• Few changes in sleep stages except for increase in wake when alcohol was given at 0400 at high homeostatic load |

BAC: Breath Alcohol Concentration; FD: 20-hr forced desynchrony protocol

### Conclusion
Except for an increase in wake, alcohol administration had minimal effects on sleep.

### Commentary
An association between sleep and alcohol has been recognized for centuries; however, the exact nature of this association is not clear. A common anecdotal belief is that alcohol facilitates sleep; however, in contrast to this notion are data showing chronic alcohol use and abuse disrupts sleep.[1] Several factors complicate our understanding of the association between alcohol and sleep including sleep schedule prior to laboratory examination, alcohol dose, time of alcohol administration both relative to sleep/wake and time of day/circadian time.

This study examined the effects of a moderate dose of alcohol compared to placebo given at four different circadian phases and at three different homeostatic loads on sleep stage and spectral EEG characteristics using a 20-hour forced desynchrony (FD) protocol. Spectral characteristics were unaffected with alcohol at any time of day. Few alcohol related changes were seen for sleep stages; however, with alcohol given at 0400 at a high homeostatic load, we observed an increase in minutes of wake during the subsequent sleep episode.

Our findings indicate that, with a moderate dose of alcohol administered close to bed (alcohol still on board at bedtime), alcohol disrupts sleep when administered at a time that is near the circadian trough. Our findings are not consistent with notion that alcohol is a useful sleep aid, since stage parameters associated with improved sleep (decreased SOL, increased SWS, etc) were unaffected. These data also suggest that alcohol is not a useful sleep aid when attempting to sleep at adverse circadian phases. Alcohol use may be a pitfall for night shift workers or individuals with jet lag who drink to improve "day sleep." Our data indicate that alcohol consumption near one's circadian trough and when awake for at least 13.33 hours was the worst time to consume alcohol in regards to disrupting sleep in this study.

These data were collected in healthy young adults free of alcohol use/abuse disorders; however, these findings may have implications in the context of alcohol use/abuse. Several studies have shown associations between sleep problems and alcohol consumption.[2,3,4] Drinking at a circadian phase that results in increased sleep disruptions could perpetuate a cycle of using alcohol to self-medicate sleep problems, which in turn disrupts sleep and so on in vulnerable individuals.

Our study had several limitations that complicate interpretation. We had a small sample size that limits power to detect subtle changes in sleep architecture with alcohol. In addition, the alcohol dose was moderate (to achieve .05 breath alcohol concentration) and BrAC was low at bedtime even in the condition when alcohol was administered closest to sleep. The 20-hour FD limited homeostatic load below a normal waking day. Thus, our high homeostatic load condition is only high relative to our other conditions in this study.

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**Effect of night smoking, sleep disturbance, and their co-occurrence on smoking outcomes.** Peters EN, Fucito LM, Novosad C, Toll BA, O'Malley SS. *Psychol Addict Behav. 2011 Jun;25(2):312-9.*

*Does smoking during the night affect sleep quality and outcomes of smoking cessation?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 385 smokers | Double-blind RCT (6 weeks)<br><br>Assessments:<br>• PSQI<br>• Smoking status | Compared to non-night smokers, subjects that smoked during the night had greater sleep disturbance<br><br>Comorbid night smoking and sleep disturbance was associated with greater risk for smoking |

PSQI: Pittsburgh Sleep Quality Index; RCT: randomized controlled trial

*Conclusion*
Night smoking was associated with greater sleep disturbance and increased risk for smoking than non-night smoking.

*Commentary*
Although effective treatments for tobacco smoking exist, the prevalence of smoking in the U.S. has remained mostly stagnant in recent years.[1] One strategy for decreasing smoking prevalence focuses on identifying smokers with risk factors associated with poor smoking cessation outcomes and providing them with tailored or intensified interventions. Sleep disturbance and night smoking are two such risk factors.

Sleep disturbance has numerous physical and psychological sequelae[2] and is prevalent among tobacco smokers.[3-5] Sleep disturbance that occurs either before or immediately after quitting tobacco is associated with poor smoking treatment outcomes.[6-7] One potential cause of sleep disturbance among smokers is night smoking, i.e., waking during the night and smoking. Night smoking appears to be common among smokers (up to 51%[8]) and is also associated with poor smoking treatment outcomes. Although waking during the night and smoking would seem to represent an intrusion to the sleep cycle, the prevalence of clinically important sleep disturbance among night smokers is unknown. Furthermore, it is unknown how the presence of these two risk factors – sleep disturbance and night smoking - might combine to predict even poorer smoking outcomes.

To examine the prevalence of sleep disturbance among night smokers and evaluate the effects of both night smoking and sleep disturbance on smoking cessation outcomes, we examined treatment-seeking smokers in a 6-week randomized controlled trial of naltrexone plus nicotine patch to stop smoking.[9] Participants were 385 adults (48% female; average age = 45.9 years) who smoked an average of 26.4 cigarettes daily. The Pittsburgh Sleep Quality Index (PSQI[10]) and a single item of night smoking ("Do you wake up at night and smoke?") collected pre-treatment information on sleep disturbance and night smoking, respectively. Consistent with the recommendations of Buysse et al,[10] smokers with a global PSQI

score of > 5 were categorized as "poor sleepers." Smokers who responded "yes" to the item on night smoking were categorized as "night smokers."

Among the 385 smokers, 135 (35%) reported waking at night and smoking. Sleep disturbance among these 135 night smokers was common. In comparison to non-night smokers, night smokers reported significantly greater global PSQI scores, as well as greater scores on 6 of the 7 PSQI components, indicating poorer subjective sleep quality, sleep efficiency and daytime dysfunction; longer sleep latency; shorter sleep duration; and greater sleep disturbances.

Among the 135 night smokers, 62 reported a global PSQI score of > 5 and were classified as being "both night smokers and poor sleepers," while 69 did not report a global PSQI score of > 5 and were, thus, classified as "night smokers only." Among the non-night smokers, 63 were classified as "poor sleepers only" and 179 were classified as "neither night smokers nor poor sleepers." In adjusted logistic regression models with smokers who were neither night smokers nor poor sleepers as the comparator group, those who were both night smokers and poor sleepers had significantly greater odds of continuing to smoke at the end of smoking cessation treatment as well as at 6- and 12-month follow-up assessments. Additionally, in comparison to poor sleepers only, those who were both night smokers and poor sleepers had significantly greater odds of continuing to smoke at the end of smoking cessation treatment, although they did not differ during follow-up.

This study indicates that sleep disturbance is prominent among a subgroup of smokers – those who wake during the night and smoke. The fact that the co-occurrence of night smoking and sleep disturbance predicted smoking cessation failure suggests that night smokers with sleep disturbance represent a high-risk group of smokers who may need tailored interventions targeting both risk factors. Future interventions for these high-risk smokers may provide overnight nicotine replacement therapy or incorporate sleep-related interventions into existing smoking cessation treatments. Ongoing work in our research group is testing the benefit of adding a cognitive-behavioral intervention addressing sleep to smoking cessation treatment for smokers with sleep disturbance.

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**Sleep after vaccination boosts immunological memory.** Lange T, Dimitrov S, Bollinger T, Diekelmann S, Born J. *J Immunol. 2011 Jul 1;187(1):283-90.*

*Does sleep affect immunological memory formation?*

| Subjects | Methods | Outcomes |
|---|---|---|
| 27 healthy men | Subjects were vaccinated against hepatitis A (at weeks 0, 8, and 16) followed by a night of sleep or wakefulness<br><br>Assessments:<br>• PSG<br>• Hormone levels (throughout the night)<br>• Vaccination-induced Th cell and Ab responses | Compared with wakefulness, postvaccination sleep was associated with:<br>• Doubling of frequency of Ag-specific Th cells<br>• Greater fraction of Th1 cytokine-producing cells<br>• Increased Ag-specific IgG1<br>• High slow-wave sleep activity<br>• Increased GH and prolactin<br>• Decreased cortisol release |

GH: growth hormone; PSG: polysomnography; SWA: slow-wave activity

*Conclusion*
Postvaccination sleep enhanced human Th1 immune response compared to the wake condition.

*Commentary*
Anecdotal and experimental evidence indicates that sleep supports immune functions.[1,2] So, preliminary studies in humans showed that regular sleep compared to partial or total sleep deprivation enhances the antibody response after vaccination in the early expansion phase.[3,4] However, production of antibodies by B cells critically depends on support by T helper (Th) cells and in the clinical setting long-term protective immunity determines the efficacy of a vaccine. We, therefore, aimed to elucidate if an adjuvant-like action of sleep after vaccination holds true also for the T helper (Th) cell response and for later stages of immunological memory, i.e., in the contraction and maintenance phase of the immune response. 27 healthy young men with a mean (± SEM) age of 26.1 (± 0.7) yrs and BMI of 24.5 (± 0.5) were vaccinated against hepatitis A (Twinrix®, GlaxoSmithKline Biologicals, Rixensart, Belgium) at 8 am at weeks 0, 8 and 16. They were randomized to conditions of 'sleep' or 'wake' and accordingly were either allowed to sleep from 11 pm to 6:30 am in the first night following each of the three inoculations or had to stay awake until 8 pm the next evening. The immune response was monitored immediately before, as well as 1, 2, and 4 weeks after each vaccination, and in 12 subjects again one year after the first inoculation (i.e., at weeks 0, 1, 2, 4, 8, 9, 10, 12, 16, 17, 18, 20, and 52). The frequency and cytokine profile (Th1: IL-2, IFN-gamma, TNF-alpha; Th2: IL-4) of hepatitis A virus (HAV)-specific Th cells were assessed after in vitro stimulation with overlapping viral peptides by flow cytometry. ELISA determined hAV-specific antibodies of the subtypes IgG1, IgG2, IgG3 and IgG4.

Vaccinations were well tolerated and induced a strong Th1 response with high frequencies of IL-2 and IFN-gamma producing HAV-specific Th cells and increases in HAV-specific IgG1 and IgG3 antibodies that are known to be regulated by Th1 cells in humans.[5] Compared to subjects of the wake condition, subjects

with regular sleep after vaccination showed a stronger Th1 response in the expansion, contraction and maintenance phase and this effect became evident already after the first inoculation but was most pronounced after the second and third shot, with still a doubling of HAV-specific Th cells at week 52. This adjuvant-like action of sleep was detectable also for the HAV-specific IgG1 antibody response.

We, then, tested by regression analyses if certain sleep and hormonal parameters that were assessed during the experimental nights could serve as predictors for the Th cell response later on. Interestingly, duration of slow wave sleep stage 4 and slow wave activity, as well as accompanying changes in immunoregulatory hormones, with increases in growth hormone and prolactin and decreases in cortisol, showed high correlations with the frequency of HAV-specific Th cells at weeks 18-20 and 52. Hence, slow wave sleep during very early stages of the immune response, i.e., within 24 hours after inoculation, determines subsequent immunological memory formation, most likely by impacting the immunological synapse between antigen-presenting cell and Th cell that starts to form at this time period in lymphoid tissues. Several lines of evidence indicate that slow wave sleep, by driving the release of endogenous adjuvants like growth hormone and prolactin concomitant with reducing effects on immunosuppressive cortisol, fosters the transfer of antigenic information from antigen-presenting cells into long-term storage in HAV-specific Th cells and at the same time supports differentiation of these cells to the Th1 lineage.[2]

Such a concept bears striking parallels to the memory function of sleep in the neurobehavioral domain with slow wave sleep promoting the transfer of episodic information encoded during prior wakefulness from a temporary to a long-term store.[6] Hence, both the nervous system and the immune system benefit from slow wave sleep to form stable long-term memories.

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Selected from among thousands of journal articles in Medicine, Neurology, Psychiatry, Surgery and Dental Science, this compendium represents some of the finest scientific literature on Sleep Medicine published in 2011. Assembled in this textbook are topics that cover the entire spectrum of adult and pediatric sleep sciences. Concise summaries of notable works are accompanied by commentaries written by major international authorities in Sleep Medicine.

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