Sleep Research Review™

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In this issue:

Abbreviations used in this issue:

ADHD = attention deficit hyperactivity disorder; **AHI** = apnoea-hypopnoea index; **CPAP** = continuous positive airway pressure; **HR** = hazard ratio; **OSA** = obstructive sleep apnoea; **REM** = rapid eye movement.

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Welcome to the latest issue of Sleep Research Review.

In this issue, new guidelines from the American Thoracic Society provide evidence-based recommendations for the management of overweight/obesity in patients with OSA, and an intriguing proof-of-concept study identifies some potential pharmacological treatments for OSA. A study from the well-regarded Boston University research group suggests that a Mediterranean-style diet improves sleep quality, and Norwegian investigators find that adolescents with delayed sleep phase have identifiable risk indicators in childhood. Comments for this issue have been provided by Associate Professor Belinda Miller (Melbourne).

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

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Medical Research Advisor

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The role of weight management in the treatment of adult obstructive sleep apnea. An official American Thoracic Society Clinical Practice Guideline

Authors: Hudgel D et al., on behalf of the American Thoracic Society Assembly on Sleep and Respiratory Neurobiology

Summary: This guideline from the American Thoracic Society provides evidence-based recommendations for the management of overweight/obesity in patients with OSA. The guideline recommends that patients with OSA who are overweight or obese should be initially treated with lifestyle intervention comprising a reduced-calorie diet, exercise or increased physical activity, and behavioural guidance. Pharmacological therapy and bariatric surgery may be suitable for selected patients who need further assistance with weight loss.

Comment: This new guideline from the American Thoracic Society aims to provide an evidence-based and clinically relevant guide to dietary, exercise and bariatric surgery recommendations in patients with OSA and overweight/obesity. The multidisciplinary expert panel assessed the evidence and feasibility surrounding key clinical issues, such as use of reduced-calorie diet and exercise versus comprehensive lifestyle intervention and when to consider referral for bariatric surgery. Evidence is drawn from both OSA and non-OSA literature. For most questions, there is limited supporting evidence, particularly on the impact of interventions on OSA itself. Thus, most recommendations are conditional rather than definitive. The guidelines also include practical advice on a clinician's approach to lifestyle management in this patient group.

Reference: Am J Respir Crit Care Med 2018;198(6):e70-87

Abstract

The combination of atomoxetine and oxybutynin greatly reduces obstructive sleep apnea severity

Authors: Taranto-Montemurro L et al.

Summary: This trial evaluated the effects of an oral combination of atomoxetine (a norepinephrine reuptake inhibitor) and oxybutynin (an antimuscarinic agent) on OSA severity and genioglossus responsiveness in patients with OSA. 20 patients were randomised to receive placebo or atomoxetine 80mg + oxybutynin 5mg prior to sleep for 1 night each in a double-blind, crossover design. Median age was 53 years and body mass index was 34.8 kg/m^2. Atomoxetine + oxybutynin decreased AHI by 63% compared with placebo (7.5 vs 28.5 events/h; p<0.001), and increased genioglossus responsiveness approximately 3-fold (6.3 vs 2.2 %/cmH_2O; p<0.001). Neither atomoxetine nor oxybutynin reduced AHI when administered separately in a subgroup of 9 patients.

Comment: Pathophysiological traits contributing to OSA are now recognised to include increased pharyngeal collapsibility, reduced compensatory pharyngeal dilator muscle activation, reduced ventilatory control stability (elevated loop gain) and reduced respiratory arousal threshold in addition to the well-known traits of obesity and anatomical predisposition. These insights mean that development of personalised-medicine approaches to OSA treatment may be feasible. Sleep-related hypotonia of pharyngeal muscles is mediated by central norepinephrine reduction during sleep and additionally in REM sleep, by inhibitory effects of acetylcholine. This small randomised controlled trial found the combination of a noradrenergic (atomoxetine) and an antimuscarinic (oxybutynin) enhanced genioglossus activity and reduced OSA severity in their subjects with moderate OSA. As a proof-of-concept study it raises very interesting questions, and will undoubtedly be followed by larger longer-term trials including sustainability of response, symptomatic assessment and patient selection.

Reference: Am J Respir Crit Care Med 2018; published online Nov 5

Abstract

Apnea-hypopnea event duration predicts mortality in men and women in the Sleep Heart Health Study

Authors: Butler M et al.

Summary: This analysis of data from the Sleep Heart Health Study investigated whether apnoea-hypopnea event duration predicts mortality. Among 5712 participants, 1290 deaths occurred over 11 years of follow-up. After adjusting for confounding factors, Cox proportional hazards models showed that individuals with the shortest apnoea-hypopnoea event duration were at significant risk for all-cause mortality (HR, 1.31). The relationship was observed in both men and women and was strongest in those with moderate sleep apnoea (HR, 1.59).

Comment: AHI, the current metric of OSA assessment, is known to be an imperfect tool. While there is a clear association of OSA severity as measured by AHI with mortality, the AHI does not capture important variables such as degree of hypoxaemia and sleep fragmentation. The authors investigated whether respiratory event duration, which is related to arousal threshold and considered a heritable trait, is predictive of all-cause mortality. Short event duration was significantly associated with increased mortality, with the association strongest in those with moderate OSA. Mechanistically, this may reflect an increased "arousability" state and excess sympathetic tone. This study suggests that consideration of this easily measured sleep study metric may aid in phenotyping and risk assessment of people with OSA.

Reference: Am J Respir Crit Care Med 2018; published online Oct 19
Abstract

Mediterranean diet pattern and sleep duration and insomnia symptoms in the Multi-Ethnic Study of Atherosclerosis

Authors: Castro-Diehl C et al.

Summary: This analysis of the Multi-Ethnic Study of Atherosclerosis assessed the associations of sleep duration and insomnia symptoms with current Mediterranean-style diet. Actigraphy-measured sleep duration and self-reported insomnia symptoms were obtained from 2068 individuals. A 10-point Mediterranean-style diet (aMed) score, derived from a self-report food frequency questionnaire, was collected at the same time as the sleep assessment and 10 years before. Compared with individuals with a low aMed score, those with a moderate-high aMed score were more likely to sleep 6–7 vs <6 h/night ($p<0.01$) and less likely to report insomnia symptoms. An increase in aMed score in the preceding 10 years was not associated with sleep duration or insomnia symptoms, but individuals with an unchanging score reported fewer insomnia symptoms than those with a decreasing aMed score ($p\leq0.01$).

Comment: This study, from the well-regarded Boston University research group, examined whether a Mediterranean-style diet is related to sleep duration and sleep quality. Sleep duration and quality are both recognised as predictors of risk for cardiovascular disease, with diet being a potential link. The results suggest that individuals with a Mediterranean-style diet were more likely to have adequate sleep duration and less likely to have insomnia. An intriguing question is the potential mechanism(s); proposals include anti-inflammatory effects on neurons, improved glucose and lipid homeostasis leading to improved brain function and mood, and effects of specific dietary components containing serotonin and melatonin. A generally healthy lifestyle in addition to a healthy diet may also play a role.

Reference: Sleep 2018;41(11):zsy158
Abstract

RESEARCH REVIEW
The Australian Perspective Since 2007

Precursors of delayed sleep phase in adolescence

Authors: Hysing M et al.

Summary: This population-based longitudinal study in Norway assessed sleep behaviour, sleep problems and mental health in childhood as possible precursors for the development of delayed sleep phase (DSP) during adolescence. 2200 children were assessed at age 7–9 years, 11–13 years, and 16–19 years. Sleeping <9 h/night at age 11–13 years was significantly associated with DSP at age 16–19 years (adjusted odds ratio, 3.37). Sleep problems at 11–13 years were more frequent in children who developed DSP compared with those who did not (20% vs 12%) but the results were not significant after adjustment for early mental health problems. Sleep problems and mental health at age 7–9 years were not related to later DSP.

Comment: Sleep/wake timing usually shifts later in adolescence, likely due to a combination of biological, social, behavioural and psychological factors. For some adolescents, the circadian delay will be quite pronounced and have negative functional impacts and thus fulfil the diagnostic criteria for Delayed Sleep Phase Syndrome. Adolescents with DSP have a higher rate of mental health problems than their peers in terms of depressive, anxiety and ADHD-symptoms. This longitudinal study found that mental health issues and shorter sleep hours at 11–13 years, but not at 7–9 years, were associated with DSP later in adolescence. From a prevention perspective, it seems that early adolescence may be an important intervention time to prevent the development of DSP. Both mental health problems and sleep problems are possible targets for such interventions.

Reference: Sleep 2018;41(11):zsy163
Abstract

Neighborhood disadvantage is associated with actigraphy-assessed sleep continuity and short sleep duration

Authors: Troxel W et al.

Summary: This study examined the association between neighbourhood characteristics and actigraphy-assessed sleep continuity and duration in an urban community. 788 predominantly African American adults (mean 55 years; 77% female) living in two low-income neighbourhoods were included. Greater perceived safety of the neighbourhood was associated with higher sleep efficiency and shorter wakefulness after sleep onset (WASO). Greater neighbourhood disorder and street lighting were associated with poorer sleep efficiency, longer WASO, and greater likelihood of short sleep duration. Higher levels of crime were associated with poorer sleep efficiency and longer WASO.

Comment: Urbanisation and Westernised lifestyles have profound impacts on sleep, with insomnia and inadequate sleep duration highly prevalent. Living in socially disadvantaged neighbourhoods is recognised to be associated with poorer self-reported sleep quality. This detailed study included assessment of perceived neighbourhood safety as well as objective measures, both of the neighbourhood itself, including disorder (graffiti, litter), crime rates and lighting, and of sleep duration. Both perceived and objective measures of neighbourhood disadvantage were associated with poorer sleep efficiency. Noise levels and pollutants were not assessed. Such studies may alert urban planners and public health policy-makers to address modifiable neighbourhood factors that could contribute to the burden of poor sleep health of those living in disadvantaged areas.

Reference: Sleep 2018;41(10):zsy140
Abstract

Independent commentary by Associate Professor Belinda Miller

Associate Professor Belinda Miller is a consultant physician in respiratory and sleep disorders, with over 25 years' experience. She has a PhD in respiratory physiology during sleep, and ongoing research interests in sleep, ventilatory failure and COPD. She is medical lead for oxygen therapy at Alfred Health, and a clinical advisor on oxygen therapy for the Victorian Health Service, as well as maintaining an active role in training of medical students, basic and advanced trainees.

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References: 1. CIRCADIN® Product Information, 9 June 2016. **2.** Zisapel N. Sleep and sleep disturbances: biological basis and clinical implications *Cell Mol Life Sci* 2007;64:1174-1186. **3.** http://search.tga.gov.au/s/search.html?collection=tga-artg&profile=record&meta_i=153959 (Accessed 30th April 2018) **4.** EPAR. Assessment report for Circadin. *Procedure No EMEA/H/C/695* 2014.

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Sleep duration and remaining teeth among older people

Authors: Koyama S et al.

Summary: This study analysed data from the Japan Gerontological Evaluation Study (2010) to determine the association between sleep disturbance and the number of remaining teeth in older adults. 169,215 adults with a mean age of 73.7 years were included. 28.1% of them reported sleep duration of approximately 7h, while 2.7% reported short (≤4h) sleep duration and 4.7% reported long (≥10h) sleep duration. 14.7% of participants had none of their own teeth. Compared with adults with 20 or more teeth, those with no teeth or 1–9 teeth were at a significantly higher risk for both short sleep (relative risk ratio [RRR], 1.43 and 1.29, respectively) and long sleep duration (RRR, 1.75 and 1.48, respectively).

Comment: An association between tooth loss and sleep disturbance is not intuitively obvious! Previous studies have shown that both longer (>9h) and shorter (<6h) sleep duration is associated with increased all-cause mortality in older people. The authors of this study, part of a large long-term study of health in people >65 years, hypothesised there is a relationship between tooth loss and sleep disturbance as indicated by self-reported sleep duration. Their findings support this, with those with fewer teeth having higher risks for both long and short sleep duration, and thus potentially for worse health outcomes. As it is a cross-sectional study no causality can be inferred, although the authors suggest that OSA may be the linking factor, as a cause of sleep disturbance and as loss of teeth may be associated with change in tongue and jaw position. More reason perhaps for attention to dental health?

Reference: Sleep Med 2018;52:18-22
Abstract

Pulmonary rehabilitation and oropharyngeal exercises as an adjunct therapy in obstructive sleep apnea

Authors: Neumannova K et al.

Summary: This open-label study investigated the benefits of pulmonary rehabilitation (PR) and oropharyngeal exercises when used in conjunction with CPAP therapy in patients with OSA. 40 patients with OSA (mean 54.2 years) with moderate to severe OSA were randomised to receive CPAP therapy alone or in conjunction with PR and oropharyngeal exercises. Those in the CPAP + PR group received a 60-min individual PR session twice a week for 6 weeks. At study end, OSA severity was controlled by CPAP treatment in both groups. However, only those in the CPAP + PR group had a significant reduction in neck, waist, and hip circumferences, body mass index, and an improvement in pulmonary function.

Comment: A number of patients newly diagnosed with OSA ask whether upper airway exercises will improve their condition. This paper unfortunately does not answer that question, although it showed overall health benefits from an exercise programme. Previous small studies and a meta-analysis suggest that oropharyngeal exercises may decrease AHI in adults with moderate OSA but the effects appear inconsistent (and the exercises need to be done on an ongoing basis). In this study, all subjects were treated with CPAP and half were also randomised to PR plus oropharyngeal exercises. Those on the exercise programme lost weight and body fat, and had less nocturnal hypoxaemia when reassessed on CPAP therapy, as compared to the control group. The results suggest that patients with OSA may benefit from a multidisciplinary approach to health management. However, more focussed studies evaluating oropharyngeal exercises independently are still required to assess whether those techniques are of value to patients.

Reference: Sleep Med 2018;52:92-97
Abstract

Pharmacological agents for improving sleep quality at high altitude

Authors: Kong F et al.

Summary: This systematic review and meta-analysis evaluated the safety and efficacy of drugs prescribed for improving sleep quality in patients with acute exposure to high altitudes. A search of various electronic databases identified 8 randomised controlled trials (n=152) that compared drug treatments (acetazolamide, temazepam, zolpidem, zaleplon, and theophylline) with placebo or no-treatment that were suitable for inclusion. The non-benzodiazepines were generally superior with regard to improving sleep quality. Patients taking zaleplon or zolpidem reported a significant improvement in subjective sleep quality, and both agents improved total sleep time, sleep efficiency index, and stage 4 sleep duration on polysomnography. Temazepam was similar to placebo for sleep onset and sleep quality. Both acetazolamide and theophylline reduced the sleep efficiency index.

Comment: Altitude-related health problems have become a major medical issue as both tourists and job-seekers travel from the lowlands to high altitude regions during the sightseeing periods. Fragmented and unrefreshing sleep is highly prevalent among non-natives at altitude and leads to reduced cognition and daytime performance. Hypoxaemia and periodic breathing are major contributors to poor-quality sleep. This meta-analysis evaluated the effects of respiratory stimulants (acetazolamide, theophylline) and sedatives (temazepam, GABA receptor agents – "z-drugs") on sleep. The conclusion was that the GABA receptor agents were more effective at improving sleep quality without impairing ventilation. Respiratory stimulants appear to improve nocturnal hypoxaemia and periodic breathing although not sleep continuity, while sedatives appear to improve sleep fragmentation and subjective sleep quality without consistent change in ventilation; maybe a combination approach is needed?

Reference: Sleep Med 2018;51:105-14
Abstract

Does armodafinil improve driving task performance and weight loss in sleep apnea?

Authors: Chapman J et al.

Summary: This Australian study investigated the impact of the wakefulness-promoter armodafinil on driving performance in overweight OSA patients undergoing weight loss. Overweight patients with OSA who had rejected standard treatment and suffered daytime sleepiness were randomised in a double-blind design to receive armodafinil 150mg or placebo daily for 6 months. Patients were also randomised to one of two diets for 6 months with follow-up at 1 year. Armodafinil improved driving task performance (assessed by steering deviation in the final 30 min of a 90-min afternoon driving task) compared with placebo at 3 months (p=0.004), but not at 6 months (p=NS). Patients in the armodafinil group lost 2.4kg more body fat than those in the placebo group at 6 months (p=0.002).

Comment: The clinical scenario of patients with symptomatic OSA who are intolerant of usual treatments is distressingly common. Alternate options are limited, and weight loss, while potentially helpful, is slow and often difficult. Thus many clinicians would be interested to see if a wakefulness-promoting agent improves patients' daytime performance impairment. The study was negative for the primary end-point of driving performance improvement at 6 months with armodafinil, although there was improvement at 3 months. Patients in the armodafinil arm did have greater weight and fat loss and modest increase in activity levels as compared to placebo, although with an increased side effect burden. The study was underpowered and the armodafinil dose was not titrated up from 150mg. However, at present there is not a clear rationale for armodafinil therapy in patients with sleep apnoea not currently on CPAP.

Reference: Am J Respir Crit Care Med 2018;198(7):941-50
Abstract

