

# Sleep Research Review™



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Issue 8 - 2018

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### Abbreviations used in this issue:

AHI = apnoea-hypopnoea index;  
CBT-I = cognitive behavioural therapy for insomnia;  
CPAP = continuous positive airway pressure; OSA = obstructive sleep apnoea;  
PD = Parkinson disease; PSG = polysomnography;  
REM = rapid eye movement; RSD = REM Sleep Behaviour Disorder.

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## Welcome to the latest issue of Sleep Research Review.

In this issue we report that sodium oxybate may improve sleep disturbance in patients with PD; severe OSA during REM sleep is associated with a higher incidence of cardiovascular disease; and oronasal masks may be less effective than nasal masks in patients with OSA. An analysis of the Icelandic Sleep Apnea Cohort underscores the need for a personalised approach to OSA management, Swedish investigators examine whether uvulopalatopharyngoplasty improves sleep quality in patients with OSA, and Canadian researchers report a potential association between sleep-disordered breathing symptoms and behavioural problems in very young children. 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,

**Dr Janette Tenne**

Medical Research Advisor

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### Sodium oxybate for excessive daytime sleepiness and sleep disturbance in Parkinson disease

**Authors:** Büchele F et al.

**Summary:** This crossover study investigated the effects of sodium oxybate on excessive daytime sleepiness and disturbed night-time sleep in patients with PD. 12 patients with PD and excessive daytime sleepiness (Epworth Sleepiness Scale [ESS] score >10) were randomised 1:1 to receive sodium oxybate followed by placebo, or placebo followed by sodium oxybate; phases were separated by a 2- to 4-week washout period. Sodium oxybate (3–9g per night, individually titrated dosage) was taken at bedtime and 2.5–4h later for 6 weeks. Sodium oxybate significantly improved daytime sleepiness compared with placebo when measured both objectively (mean sleep latency, +2.9 min;  $p=0.002$ ) and subjectively (ESS score, -4.2 points;  $p=0.001$ ). Eight (67%) patients had an electrophysiologically-defined positive treatment response. Sodium oxybate also improved subjective sleep quality and objectively measured slow-wave sleep duration.

**Comment:** In patients with narcolepsy, sodium oxybate can be a very effective treatment for excessive daytime sleepiness, sleep fragmentation and cataplexy. In Australia, it is considered a second-line therapy for narcolepsy for those patients in whom other therapies are not sufficiently effective or not tolerated, and access is very limited. Drawbacks include its short duration of effect on sleep continuity, with two divided doses usually needed overnight; abuse potential (it has been used as a “date rape” and illicit drug); and its potential for respiratory depression and worsening of OSA. PD and narcolepsy may both be associated with debilitating disrupted sleep, RSD features, and excessive daytime sleepiness, although the underlying neurobiology is different. Treatment options in patients with sleep problems related to PD remain limited. In highly selected patients with PD, sodium oxybate may be a potential future treatment option, although more safety and efficacy studies are needed.

**Reference:** *JAMA Neurol* 2018;**75**(1):114-18

[Abstract](#)

### Obstructive sleep apnea during REM sleep and cardiovascular disease

**Authors:** Aurora N et al.

**Summary:** This analysis of data from the Sleep Heart Health study examined the association between REM sleep OSA and cardiovascular disease in a community cohort. 3265 participants with REM sleep OSA (with or without prevalent cardiovascular disease) were evaluated during a mean 9.5-year follow-up. The composite cardiovascular end-point comprised nonfatal or fatal events, including myocardial infarction, coronary artery revascularisation, congestive heart failure, and stroke. The adjusted hazard ratio for a cardiovascular end-point was 1.35 in those with severe REM sleep OSA ( $\geq 30$  AHI events/h) compared with a reference group ( $< 5.0$  AHI events/h). Stratified analyses showed that the association was strongest in those with prevalent cardiovascular disease and severe REM sleep OSA (adjusted hazard ratio, 2.56).

**Comment:** A recent systematic review and meta-analysis of the association of CPAP with cardiovascular disease and death in adults concluded that CPAP use did not reduce the risk of these events, although multiple cross-sectional studies and observational trials have suggested otherwise. This current study is a large long-term observational trial of subjects with REM sleep-isolated OSA, selected from the Sleep Heart Health Study cohort. The conclusion was that there was an association with recurrent cardiovascular events and severe REM sleep-isolated OSA, but only in subjects with pre-existing cardiovascular disease. Those subjects were also older, had a higher body mass index and were more likely to be male and ex-smokers; these factors may in part explain the results. The interactions between OSA and cardiovascular disease remain of concern and we will need to develop a ‘personalised medicine’ approach to OSA risk stratification over time.

**Reference:** *Am J Respir Crit Care Med* 2018;**197**(5):653-60

[Abstract](#)



## Nasal vs oronasal CPAP for OSA treatment

**Authors:** Andrade R et al.

**Summary:** This meta-analysis compared the use of nasal vs oronasal CPAP masks in patients with OSA. A search of Cochrane Central Register of Controlled Trials, Medline, and Web of Science identified 5 randomised and 8 non-randomised trials (n=4,563) that were suitable for inclusion. Random-effects meta-analysis revealed that oronasal masks were associated with a significantly higher mean CPAP level (+1.5 cmH<sub>2</sub>O; p<0.001), higher residual AHI (+2.8 events/h; p<0.001), and poorer adherence (-48 min/night; p=0.001) than nasal masks.

**Comment:** Finding a comfortable mask interface is arguably the most important and difficult task when commencing and maintaining a patient on CPAP therapy. CPAP was initially designed for use with a nasal interface. However, oronasal masks are now also frequently used, particularly in patients with nasal obstruction. Concerns with use of oronasal masks relate to potential induction of upper airway narrowing by posterior displacement of the chin, tongue and soft palate, by a combination of the physical pressure of the mask and anatomical change caused by mouth opening. This meta-analysis concluded that oronasal masks were less effective than nasal masks, with poorer adherence and higher AHI. However, this should be balanced against individual patient preference and symptoms; oronasal mask use is still much better than no use if a nasal mask is not tolerated.

**Reference:** *Chest* 2018;153(3):665-74

[Abstract](#)

## Changing faces of obstructive sleep apnea: treatment effects by cluster designation in the Icelandic Sleep Apnea Cohort

**Authors:** Pien G et al.

**Summary:** This study compared the responses of three OSA phenotypes (Disturbed Sleep, Minimally Symptomatic, and Sleepy) to CPAP therapy. 706 patients in the Icelandic Sleep Apnea Cohort who had moderate to severe OSA and were prescribed CPAP were evaluated over a 2-year period. Overall, effect sizes were moderate to large when comparing sleepiness, insomnia-related, and apnoeic symptom changes in the Sleepy group with changes in the other two groups. Within the Disturbed Sleep group, CPAP users and nonusers showed similar changes in insomnia-related symptoms. The Minimally Symptomatic group remained relatively asymptomatic during follow-up, but reported significant decreases in daytime sleepiness and physical fatigue (CPAP users generally had greater improvements). The Sleepy group had reductions in nearly all measured symptoms, including drowsy driving; almost all of the improvements were greater among CPAP users than nonusers.

**Comment:** Personalised medicine is a move from a 'one size fits all' approach to the management of patients with a particular condition, to one which uses new approaches to better target therapies to achieve the best outcomes. Key to this approach is identifying patient phenotypes, which may be based on pathogenetic (including airway collapsibility, loop gain, arousal threshold), biomarker, symptoms or other features, that relate to treatment responses. This study from Iceland used symptoms of patients with moderate to severe OSA to group them into three clinical phenotypes (Disturbed Sleep, Minimally Symptomatic, and Sleepy) and assessed their responses to CPAP therapy. CPAP therapy benefitted all groups, but the type and magnitude of benefit differed. The main benefit is that such studies help in advancing personalised sleep apnoea management, matching patients to treatment with CPAP and/or other treatments. Many important questions remain, including the relationship of symptom-based phenotypes to other phenotypes, stability over time and cardiovascular risk.

**Reference:** *Sleep* 2018;41(3):zsx201

[Abstract](#)

## Sleep quality after modified uvulopalatopharyngoplasty

**Authors:** Joar S et al.

**Summary:** The randomised controlled SKUP3 trial evaluated the impact of uvulopalatopharyngoplasty (UPPP) on sleep quality in patients with OSA. 65 patients with OSA were randomised to the UPPP group or a control group. Outcomes were assessed using the Functional Outcomes of Sleep Questionnaire (FOSQ) and the Karolinska Sleep Questionnaire (KSQ). In 8 of 9 scales, significant differences were observed between the intervention and control groups in favour of UPPP. At the 6- and 24-month postoperative follow-ups, 8 of 9 scales were significantly improved from baseline.

**Comment:** CPAP adherence remains a major issue in the management of patients with OSA, with estimates of about 30–80% of patients nonadherent (mean use <4 h/night) to therapy. Thus, other treatments such as UPPP continue to be pursued, although previous studies have questioned its use due to lack of efficacy and potential side effects. This Swedish study is a randomised controlled trial of patients with moderate to severe OSA (mean AHI 53), intolerant of CPAP therapy, who were randomised to have UPPP or no surgery, and followed for 24 months. A previous study from this research group reported on PSG outcomes pre- and post-surgery; this report is of subjective sleep quality measures only. The results suggested a sustained improvement in sleep quality with UPPP. However, lacking a larger number of randomised controlled trials in other patient cohorts, my impression is that UPPP remains a treatment only for highly selected patients with moderate to severe OSA.

**Reference:** *Sleep* 2018;41(1):zsx180

[Abstract](#)

## Parent-reported symptoms of sleep-disordered breathing are associated with increased behavioral problems at 2 years of age

**Authors:** Tamana S et al.

**Summary:** This analysis of data from the Canadian Healthy Infant Longitudinal Development Birth Cohort Study examined the association between sleep-disordered breathing (SDB) and behavioural problems at age 2. Parent-reported SDB symptoms were assessed quarterly between 3 months and 2 years of age for 583 participants. Four phenotypes were identified: no SDB (64.7%), early-onset SDB (15.7%, peak symptoms at 9 months), late-onset SDB (14.2%, peak symptoms at 18 months), and persistent SDB (5.3%). Persistent SDB predicted the greatest magnitude of behavioural problems at age 2 years compared with children without SDB. Children with early-onset SDB or late-onset SDB also had more behavioural problems than children without SDB.

**Comment:** SDB in children has peak prevalence between the ages of 2 and 8 years. Consequences associated with SDB in children include behaviour problems, poor learning and poor executive function. Tonsil and adenoidectomy in preschool and school-aged children has had mixed results on improvements in behaviour and executive function, suggesting some consequences may be irreversible. This longitudinal study evaluated very young children, from 3 months to 2 years, and used parent-reported symptoms of SDB as the primary variable. Level 3 home PSG was performed at the single time point of the 1-year study visit. An association between SDB symptoms and increased behaviour problems was found, with the most marked effects seen in children with the longest duration of symptoms. This raises the possibility that very early screening for SDB and offering intervention might be beneficial. However, no PSG-derived measures of SDB were associated with parent-reported behaviour problems, a potential point of concern for result interpretation. As always, more research is needed.

**Reference:** *Sleep* 2018;41(1):zsx177

[Abstract](#)

## Characteristics and correlates of sleep duration, daytime napping, snoring and insomnia symptoms among 0.5 million Chinese men and women

**Authors:** Chen Y et al., on behalf of the China Kadoorie Biobank Study Investigators

**Summary:** This cross-sectional study evaluated the impact of inadequate sleep duration and insomnia on physical and mental health. 512,891 adults aged 30–79 years from ten diverse areas in China recorded detailed information on sleep patterns (duration, daytime napping and snoring) and insomnia symptoms. Overall, mean sleep duration was 7.38 h/night, with 23% reporting short (<6h) and 16% reporting long (≥9h) sleep duration, 21% taking daytime naps and 22% having frequent snoring. 17% of participants reported insomnia symptoms. Logistic regression analysis showed that the adjusted odds ratios of having insomnia symptoms were increased in people with major depressive episodes (6.10), generalised anxiety disorders (7.46) and any chronic diseases (1.46), but were decreased in those reporting napping (0.77) and frequent snoring (0.86).

**Comment:** Insomnia and inadequate sleep duration are highly prevalent in Westernised populations, and lifestyle factors including shift work and electronic device use are likely contributing to poor sleep. Systematic reviews have shown that those with either short sleep (<6h) or long sleep (>9h) duration have higher risks of cardiovascular disease and all-cause mortality. Depression and anxiety both contribute to and are aggravated by poor sleep. Previous cross-sectional studies in high-income countries have found both short and long sleep duration are associated with older age, women and socioeconomic status. This very large-scale study reports that sleep issues are also very common in China (a low- to middle-income country), both in urban and rural populations. Mean sleep duration was longer and prevalence of insomnia was lower than in US population studies. However, these issues were similarly strongly associated with poor mental health, particularly depression, and poor physical health status. Other associations of insomnia with older age, women, lower household income and education were also present, indicating these factors are potent drivers of poor sleep in diverse populations.

**Reference:** *Sleep Med* 2018;44:67-75

[Abstract](#)



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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](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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## The effect of light exposure on insomnia and nocturnal movement in Parkinson's disease

**Authors:** Martino J et al.

**Summary:** This retrospective longitudinal study evaluated the use of light therapy in patients with PD. Outcomes for PD patients who had been undergoing light therapy (using polychromatic light) for 15 years were reviewed. It was found that 1h of exposure to light just prior to bed significantly improved insomnia and reduced RSD within 1 month after commencing treatment. In addition, the improvement was maintained as long as light therapy was continued.

**Comment:** PD affects about 2% of those over the age of 65, and is the second most common neurodegenerative disorder, ranking behind Alzheimer disease. Patients may experience both dopamine-responsive motor disturbance and debilitating non-motor disturbance including cognitive impairment, autonomic nervous system disturbance and sleep disturbance. Of these, sleep disturbance is the most consistently reported. It is probably multifactorial, with factors including motor disturbance, central degeneration and abnormal cerebral metabolism. RSD may predate other symptoms of PD, at times by many years, and there is evidence from cross-sectional and longitudinal studies that RSD may be a risk factor and predictor of PD-mild cognitive impairment and PD-dementia. This small retrospective study suggests that light therapy improves RSD and insomnia symptoms in both the short and long term. Melatonin has also been shown to be helpful in reducing RSD symptoms, suggesting an associated mechanism. However, much larger, prospective controlled studies are needed to further evaluate this treatment.

**Reference:** *Sleep Med* 2018;44:24-31

[Abstract](#)

## Continuous positive airway pressure treatment with nasal pillows in obstructive sleep apnea

**Authors:** Lanza A et al.

**Summary:** This study evaluated the use of a CPAP nasal pillows mask in patients with OSA. 144 consecutive CPAP-naïve patients were included. After an initial mask fitting session all patients were allowed to choose the type of nasal interface they preferred: 70.8% chose the nasal pillows mask and 29.2% chose the nasal mask. Patients were offered the option of switching to an alternative mask if needed. Clinical and polygraphic features and CPAP pressure levels were similar in both groups at baseline and at 12 months. Both groups had good adherence to treatment (5.5 h/night in the nasal pillows group and 5.3 h/night in the nasal mask group). 53% of patients reported at least one side effect during the study period, but no significant between-group differences were observed. Nostril pain was the most common side effect in the nasal pillows mask group.

**Comment:** Nasal pillow style masks seem to be increasingly popular in patients commencing CPAP therapy. Certainly I find it is often much easier to convince a patient to consider a CPAP trial if I show them a small nasal pillow mask rather than a large oronasal mask. Self-image and claustrophobia issues are often less with a smaller mask than a larger one, although not banished entirely. This study, although retrospective and observational, does suggest that many patients prefer nasal pillow over standard nasal masks. Nasal pain was a side effect, but this did not appear to impact on efficacy or adherence. There has been concern of displacement of nasal pillow masks at higher CPAP pressures. However in this study, while mean CPAP pressures were 11–12 cmH<sub>2</sub>O, CPAP pressures up to 15 cmH<sub>2</sub>O were used without apparent problem.

**Reference:** *Sleep Med* 2018;41:94-99

[Abstract](#)

## The effectiveness of behavioural and cognitive behavioural therapies for insomnia on depressive and fatigue symptoms

**Authors:** Ballesio A et al.

**Summary:** This systematic review and meta-analysis assessed the impact of CBT-I on depressive and fatigue symptoms. A search of PubMed, Scopus and Web of Science identified 47 studies that were suitable for inclusion; 11 classes of treatment or control conditions were identified. Meta-analysis of the data showed that individual face-to-face CBT-I significantly improved depressive symptoms but not fatigue symptoms compared with controls. There was high heterogeneity between studies.

**Comment:** Chronic insomnia affects about 10% of adults, and is associated with poor physical and mental health. Treatment of insomnia includes both non-pharmacological psychotherapies and hypnotic medications. CBT-I is considered the preferred therapy for chronic insomnia, with little evidence for long-term hypnotic medication use. This meta-analysis confirms that CBT-I is an effective treatment for sleep onset and sleep maintenance insomnia, but has minimal effect on increasing total sleep time. Face-to-face CBT-I was more helpful than self-help measures, and impact was greater with five or more sessions, as compared to four or fewer. A greater response was seen in patients with concurrent psychiatric disorders and insomnia, which is helpful given the large amount of overlap between these conditions. The accompanying editorial highlighted the shortage of therapists in this area; the next challenge may be to find how to teach more practitioners effective CBT-I skills.

**Reference:** *Sleep Med Rev* 2018;37:114-29

[Abstract](#)

## Effects of school start time on students' sleep duration, daytime sleepiness, and attendance

**Authors:** Bowers J & Moyer A

**Summary:** This meta-analysis examined the impact of school start time on students' sleep patterns and attendance. Analysis of data from 5 longitudinal studies and 15 cross-sectional comparison group studies indicated that later school start times were associated with longer sleep duration, less daytime sleepiness and less tardiness to school.

**Comment:** Mental alertness, concentration and memory retention are all impaired by sleep deprivation. Many recent studies show that sleep deprivation in teenagers is common and is associated with impaired school performance. While adults need approximately 7–8 hours of sleep each night, children aged 12–13 years need about 9–11 hours and adolescents aged 14–17 years need about 8–10 hours for optimal functioning. During puberty, sleep-wake cycles shift to a more delayed sleep pattern; how much is intrinsic versus behavioural is a matter of debate. This meta-analysis of cross-sectional and longitudinal studies concluded that a delayed school start time is beneficial for teenagers, with delays in school start time resulting in an increase in sleep duration. Data on the impact of this increase on students' performance is limited; some included studies suggested reduced sleepiness and less late school arrival. However, to put the data in context, a "late" school start was generally about 8.30am, not mid-morning.

**Reference:** *Sleep Health* 2017;3(6):423-31

[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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