

Sleep Research Review™

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Issue 5 - 2017

In this issue:

- > Grey matter changes in older patients with OSA
- > Internet-based vs in-person CBTi in military personnel
- > Sodium oxybate for refractory narcolepsy with cataplexy
- > Bariatric surgery may improve OSA
- > CPAP may improve sense of smell
- > Positional therapy vs oral appliance therapy for position-dependent OSA
- > Sleep in schizophrenia
- > Impact of school start time in adolescents
- > Sleep time duration recommendations
- > A 3-herb mixture improves sleep quality

Abbreviations used in this issue:

AHI = apnoea-hypopnoea index
CBTi = cognitive behavioural therapy for insomnia
CPAP = continuous positive airway pressure
OSA = obstructive sleep apnoea

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Welcome to the latest issue of Sleep Research Review.

Highlights of this issue include a report of structural grey matter changes associated with OSA in middle-aged and older individuals, a comparison of internet-based and in-person CBTi for military personnel with insomnia, and promising findings for sodium oxybate in patients with severe refractory narcolepsy with cataplexy. We also report that laparoscopic Roux-en-Y gastric bypass improves OSA, CPAP treatment improves sense of smell, and a herbal mixture (valerian, hop, and jujube) improves sleep quality in patients with insomnia.

We hope you enjoy this issue and look forward to hearing your comments. If you have colleagues or friends within Australia who would like to receive our publication, please send us their contact email and we will include them for the next issue.

Kind Regards,

Dr Peter Solin

peter.solin@researchreview.com.au

Gray matter hypertrophy and thickening with obstructive sleep apnea in middle-aged and older adults

Authors: Baril A-A et al.

Summary: This study investigated the association between grey matter changes and OSA in middle-aged and older individuals. 71 individuals aged 55–76 years (AHI 0.2–96.6 events/h) were evaluated by magnetic resonance imaging. Two techniques were used: voxel-based morphometry (measuring grey matter volume and concentration) and FreeSurfer (a brain imaging software package that estimated the volume of predefined cortical/subcortical regions and cortical thickness). No association was found with voxel-based morphometry, but FreeSurfer revealed increased grey matter with OSA. Higher levels of hypoxaemia correlated with increased volume and thickness of the left lateral prefrontal cortex, and increased thickness of the right frontal pole, the right lateral parietal lobules, and the left posterior cingulate cortex. Respiratory disturbances positively correlated with right amygdala volume. More severe sleep fragmentation was associated with increased thickness of the right inferior frontal gyrus.

Comment: Reductions in various higher mental functioning parameters have been well seen and documented in OSA. What hasn't been clear is whether there are obvious structural changes definable through imaging techniques. Neuroimaging provides a non-invasive tool to determine structural changes or variations with disease states and it appears that structural abnormalities predate symptomatic development of OSA. This study implies that structural abnormalities are present before the symptoms of sleep apnoea emerge, and sleep apnoea may be changing neuroanatomy before obvious symptoms begin. There is a correlation with measurable changes in grey matter, and the severity of hypoxaemia, respiratory disturbances, and broken sleep. One implication is that neuroimaging may be used to classify the severity of sleep apnoea. A question raised by this study is whether neuroimaging helps predict outcomes, such as longevity and accelerated cognitive decline. Also, are there patterns of abnormality which are predictive of better, or worse, outcomes?

Reference: *Am J Respir Crit Care Med* 2017;195(11):1509-18

[Abstract](#)

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References: 1. BELSOMRA Product Information. 2. Herring WJ et al. *J Clin Sleep Med* 2016;12(9):1215–25 & Supplementary Tables. Copyright © 2017 Merck Sharp & Dohme Corp a subsidiary of Merck & Co. Inc., Kenilworth, New Jersey, USA. All rights reserved. Merck Sharp & Dohme (Australia) Pty Limited, Level 1, Building A, 26 Talavera Rd, Macquarie Park, NSW 2113 Australia. NEUR-1207010-0038. First issued June 2017. BEL0011/RR_B.

Internet and in-person cognitive behavioral therapy for insomnia in military personnel

Authors: Taylor D et al.

Summary: This randomised clinical trial compared in-person and internet-delivered CBTi in military personnel. 100 active duty US Army personnel at Fort Hood, Texas were randomised to undergo internet-based CBTi, in-person CBTi or a control condition (phone call assessments). Internet and in-person CBTi were comparable, except for the delivery format. Internet and in-person CBTi performed significantly better than the control condition for diary-assessed sleep efficiency, sleep onset latency, number of awakenings, wake time after sleep onset, the Insomnia Severity Index, and the Dysfunctional Beliefs and Attitudes About Sleep scale. In-person treatment was better than internet treatment for self-reported sleep quality and dysfunctional beliefs and attitudes about sleep. There were no differences in self-reported daytime sleepiness.

Comment: Cognitive behavioural therapy for insomnia is the standard psychological approach for sleep disorders of which insomnia would be the most important and prevalent. But not everyone can access a therapist in a timely manner, can afford it, can follow up at convenient times, or commit to a treatment course. Some individuals dislike the therapist-patient interaction, or find it confronting. So what else can be done? Delivery of this CBTi through internet or web-based portals has been on the agenda for the last 5 years. This study looks at a more captive group of individuals i.e. military individuals, who may be a bit more disciplined and amenable to therapies via an internet-based approach, and it appears to be a useful alternative to one-on-one therapy. This supports the concept of CBTi through internet portals for individuals as an alternative to one-on-one therapy models. Applicability in the less well-disciplined general population needs to be proven.

Reference: *Sleep* 2017; published online Jun 1
[Abstract](#)

Safety and efficacy of long-term use of sodium oxybate for narcolepsy with cataplexy in routine clinical practice

Authors: Drakatos P et al.

Summary: This retrospective study assessed the efficacy and safety of sodium oxybate in clinical practice in patients with refractory narcolepsy and cataplexy. 90 patients with severe narcolepsy with cataplexy refractory to other treatments who were treated with sodium oxybate at a single centre in 2009–2015 were included. Patients were allowed to take other stimulants and/or anti-cataplectic agents. The Epworth Sleepiness Scale (ESS) score and the number of weekly cataplexy events were both significantly reduced by sodium oxybate for all patients ($p < 0.0001$). The required maintenance dosage could not be predicted. 60% of patients were able to reduce or stop other medications. Nausea, mood swings and enuresis were the most commonly reported adverse events. 26.6% of sodium oxybate recipients discontinued treatment because of adverse events. Events that led to discontinuation of the drug (particularly psychosis) were associated with increasing age and were observed soon after starting treatment.

Comment: This study addressed a simple question in a complex group of patients. Is sodium oxybate a worthy treatment for severe narcoleptics not controlled on standard treatment? The answer is yes. Sodium oxybate improved alertness and reduced sleepiness and cataplectic episodes in individuals refractory to control by standard treatments. However a large proportion of patients desisted with treatment due to unacceptable side effects. Therefore sodium oxybate should be considered in all those with severe narcolepsy, on the understanding that one-quarter will have unacceptable side effects.

Reference: *Sleep Med* 2017;35:80-84
[Abstract](#)

Obstructive sleep apnea: the effect of bariatric surgery after 12 months

Authors: Peromaa-Haavisto P et al.

Summary: This prospective multicentre study investigated the effect of laparoscopic Roux-en-Y gastric bypass (LRYGB) surgery on OSA. A standard overnight cardiorespiratory assessment was undertaken 1 year after bariatric surgery in 132 patients who had OSA prior to the operation. Total AHI decreased from 27.8 events/h prior to the operation to 9.9 events/h after 12 months ($p < 0.001$), and the prevalence of OSA decreased from 71% to 44% ($p < 0.001$). OSA was cured in 45% of patients and cured or improved in 78%, but 20% of patients still had moderate or severe OSA after the operation. De novo OSA occurred in 8% of patients.

Comment: In clinical sleep medicine, weight reduction is the single most important factor to target in about three-quarters of patients. Observational studies have confirmed excellent weight loss with bariatric bands around the top of the stomach (lap band surgery) and more recently gastric sleeve reduction surgery. Pleasingly, weight reduction can cure sleep apnoea; numerous patients can come off CPAP treatment once weight has been lost. One dilemma is whether all weight loss surgery varieties are equal? This type of bypass surgery is the third major variety of weight loss surgery available. This study shows that reductions in sleep apnoea are achieved with LRYGB. Two questions are raised by this study. Firstly, is this technique any better than gastric sleeve or bariatric band? Is the technique more or less complicated, better tolerated, easier to perform? Secondly, some patients, despite weight loss, are still prone to developing OSA in the follow-up period. Therefore should sleep physicians be testing and appraising weight loss patients more regularly after weight loss surgery, rather than being comforted just because body mass index has decreased?

Reference: *Sleep Med* 2017;35:85-90
[Abstract](#)

Continuous positive air pressure improves orthonasal olfactory function of patients with obstructive sleep apnea

Authors: Walliczek-Dworschak U et al.

Summary: This prospective study evaluated the impact of CPAP treatment on orthonasal olfactory function in patients with OSA. 44 patients who were eligible for CPAP treatment had orthonasal olfactory and gustatory function measured before and after CPAP treatment. Olfaction was impaired at baseline in OSA patients, but improved significantly after CPAP therapy. In contrast, taste function before or after treatment did not appear to be affected.

Comment: Exactly why the sense of smell in individuals with sleep apnoea is altered is unclear. Sleep apnoea patients tend to draw breath through the mouth, and may have underlying nasal obstruction which predisposes them to mouth breathing. Altered flora may alter the sense of smell. Blocked noses or propensity towards rhinosinusitis often have reduced sense of smell. Anecdotally, patients do mention that sense of smell improves on CPAP treatment. Is this really true? This study shows small but definite improvements in sense of smell. The authors claim significant improvements, but the improvements appear modest on the rating scales used. In the face of modest improvements, this study supports patient reports, and at least CPAP does not adversely alter sense of smell!

Reference: *Sleep Med* 2017;34:24-29
[Abstract](#)

A randomized, controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea

Authors: Benoist L et al.

Summary: This study investigated the effectiveness of positional therapy with a sleep position trainer (SPT) compared with an oral appliance therapy (OAT) in patients with positional OSA. 91 patients with mild to moderate positional OSA (AHI 5–30 events/h) were randomised to use an SPT or OAT. Polysomnography was repeated after 3 months. Intention-to-treat analysis showed a reduction in median AHI in both groups: from 13.0 to 7.0 events/h in the SPT group ($p < 0.001$) and from 11.7 to 9.1 events/h in the OAT group ($p < 0.001$). Mean adherence (≥ 4 h/night, ≥ 5 days/week) was 89.3% in the SPT group and 81.3% in the OAT group.

Comment: Mild to moderate sleep apnoea when supine is a very common phenotype in individuals complaining of sleep disorder/snoring. Both treatment approaches used in this study (body position modification or a mandibular advancement splint) are quite reasonable to pursue. Is one better than the other? Positional treatments mean avoiding sleep on the back, i.e. encouraging side sleep, front lateral sleep, and/or positioning more upright. There are cheap and easy ways to do this (elasticised T-shirt with a pouch into which tennis ball/golf ball/squash ball/corks/nuts and bolts are placed), and various positional designs have come and gone. Another commercially available device is the SPT, designed to be worn around the chest, with variable feedback and learning modes. It should be noted that the senior author is on the medical advisory committee for the company which produces this device. This study finds that both mandibular advancement splints and body position modification using the SPT device are effective. A question for further study is whether this device is any better (comfort wise, cost wise, effectiveness) than the 'Night Shift' device currently available.

Reference: *Sleep Med* 2017;34:109-117
[Abstract](#)

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References: 1. BELSOMRA Product Information. 2. Herring WJ, Connor KM, Snyder E, *et al.* Suvorexant in Patients with Insomnia: Pooled Analyses of Three- Month Data from Phase-3 Randomized Controlled Clinical Trials. *J Clin Sleep Med.* 2016;12(9):1215–25 & Supplementary Tables. 3. Bennett T, Bray D, Neville MW. Suvorexant, a dual orexin receptor antagonist for the management of insomnia. *Pharm Ther.* 2014;39(4):264–266.



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Sleep in schizophrenia

Authors: Chan M-S et al.

Summary: This systematic review and meta-analysis of case-control studies investigated sleep abnormalities in schizophrenia. A search of various major databases identified 31 case-control studies (574 patients and 515 healthy controls) that were suitable for analysis. Patients with schizophrenia were found to have significantly shorter total sleep time, longer sleep onset latency, more wake time after sleep onset, lower sleep efficiency, and decreased stage 4 sleep, slow wave sleep, and rapid eye movement sleep compared with healthy controls. Patients with antipsychotic withdrawal for >8 weeks had fewer sleep architectural abnormalities than patients with a shorter duration of withdrawal, but the abnormalities in sleep continuity were similar. Slow wave sleep deficit was found in patients who had had schizophrenia for >3 years, while sleep onset latency was increased in medication-naïve, medication-withdrawn, and medicated patients.

Comment: Schizophrenia is a major mental health condition in our society, often hidden through institutionalisation, and treatment by a dedicated but small group of psychiatrists/psychotherapists, and outreach mental health care nurses. Sleep physicians often don't see the schizophrenic patient unless they have a special interest. Schizophrenia is often treated by major antipsychotic medications, which themselves may have effects on sleep (drowsiness, altered sleep stages, body movements). Better definition of the abnormalities found on testing in schizophrenics will have two implications. The first is understanding how the illness may impact on sleep and alter sleep health, and the second is to better determine whether therapies for schizophrenia are also having a beneficial effect on sleep and sleep parameters. This may lead to determination that some therapies are better than others in certain clinical situations by virtue of their effect on sleep.

Reference: *Sleep Med Rev* 2017;32:69-84

[Abstract](#)

Relationships between school start time, sleep duration, and adolescent behaviors

Authors: Wahlstrom K et al.

Summary: This analysis of survey data examined the impact of high school start times on adolescent sleep duration, and the association between sleep duration and mental health in teens. Data were collected from >9000 high school students in 8 high schools across the US in 2010–2013 using the 97-item Teen Sleep Habits Survey. Later school start times were associated with greater sleep duration, which was associated with fewer reports of various mental health- and substance use-related issues and behaviours (all $p < 0.01$). For each additional hour of sleep reported, there was a 28% reduction in the adjusted odds of a student feeling unhappy, sad or depressed. Later wake-up times were associated with a reduction in risk for some but not all factors.

Comment: The concept of accommodating the natural phenomenon of delayed sleep phase and lengthened circadian cycle in adolescence remains a hot potato. Do we try to shoehorn adolescents and their habits into the established timeframes, or do we make adjustments? If we make adjustments, is society making a rod for its own back, by potentially lengthening the school day even further? And what of the observations that American teenagers are getting progressively less sleep times, with stagnant achievement levels in science and mathematics, increasing obesity and reductions in physical activity? This study supports the contention that adolescents should be allowed to sleep later to achieve longer sleep times, which in turn may improve their sense of well-being, and hopefully lead to better learning outcomes. In other words the family unit may need to accommodate the late sleeping teenager, embrace it, and perhaps encourage it!

Reference: *Sleep Health* 2017;3(3):216-21

[Abstract](#)



Independent commentary by Dr Peter Solin, MBBS FRACP PhD

Dr Peter Solin is the medical director of the Sleep & Respiratory Group and a highly trained authority in sleep and respiratory medicine. Covering all facets of sleep medicine, he has a particular interest in the effects of cardiovascular and cerebrovascular diseases on sleep and performance, the impact of ill-health and infirmity on sleep, how medications interfere with sleep and rest, as well as unusual causes of fatigue and sleepiness, particularly in young adults. Dr Solin is also a dedicated teacher, educating medical students, GPs, as well as public and professional audiences. In recent years, he has delivered expert healthcare and sleep diagnostic services in more regional and remote centres, such as his program of home sleep testing through National Sleep Diagnostics.

National Sleep Foundation's sleep time duration recommendations

Authors: Hirshkowitz M et al.

Summary: The National Sleep Foundation convened an 18-member multi-disciplinary expert panel to update the National Sleep Foundation's sleep duration recommendations. Expert recommendations for sufficient sleep durations across the lifespan were assessed using the RAND/UCLA Appropriateness Method. The panel agreed that, for healthy individuals with normal sleep, the appropriate sleep duration is 14–17 hours for newborns, 12–15 hours for infants, 11–14 hours for toddlers, 10–13 hours for preschoolers, and 9–11 hours for school-aged children. This gradually decreases to 8–10 hours for teenagers, 7–9 hours for young adults and adults, and 7–8 hours for older adults. Individuals who habitually sleep outside the normal range may have serious health problems or, if done volitionally, may be compromising their health.

Comment: The disparity remains between what is regarded as a healthy sleep duration, and what individuals actually achieve with sleep durations, in this 24-hour society. So much activity can be crammed into the 24-hour day, that many of us remain partially sleep deprived, yet functional, and unaware or unlikely to want to do much about it. National expert panel guidelines for appropriate sleep times remain important. Expert committees bring their applicable knowledge to their patient and societal groups, and hopefully make rational and applicable guideline recommendations. In this light, it is reassuring to see that adequate duration of sleep remains an important factor in community health and well-being. The update confirms that infants and children need longer sleep times, and that adolescents deserve, and should be encouraged to have, a whole lot more sleep than they are probably getting! For any parent, the grumpy sleep-deprived teenager finally turning off lights and electronics at midnight is not going to be a happy and cooperative individual at 7 o'clock when woken for breakfast! Eight to ten hours of sleep should be the goal. Do the guidelines come with fail proof methods to get adolescents sleeping the healthy amount?

Reference: *Sleep Health* 2015;1(1):40-43

[Abstract](#)

Evaluation of effectiveness and safety of a herbal compound in primary insomnia symptoms and sleep disturbances not related to medical or psychiatric causes

Authors: Palmieri G et al.

Summary: This study evaluated the safety and effectiveness of a herbal compound composed of valerian, hop, and jujube (Vagonotte[®]) on primary insomnia symptoms and sleep disturbances. 120 patients with sleep disturbance symptoms were randomised to receive the herbal compound or placebo daily, 30 minutes before their scheduled bedtime. Sleep quality and daytime activity were assessed at baseline, after 10 days, and after 20 days of treatment. Patients taking the herbal compound had a shorter sleep onset, longer total sleep time and fewer night-time awakenings than patients taking placebo ($p < 0.001$). They also showed significant reductions in tension and irritability, difficulty in concentration, and fatigue intensity compared with placebo recipients ($p < 0.001$). No adverse events were reported.

Comment: Very few sleep physicians actively prescribe herbal compounds for insomnia. After all, which herbal remedy has the herbs you think you are prescribing, in adequate doses. Are off-the-shelf processed capsules any better or any worse than actual herbs measured out by weight, and made into a hot drink like a tea? Do herbs provide a superb placebo effect? They rarely have side effects. In this study, an active versus placebo 3-herb mixture was used, although the investigators may not have been blinded. The active group had measurable benefits, and none were affected by potential side effects. Therefore herbal compounds have a definite place at the table in the treatment of insomnia. The obvious questions are what are the effective herbs, and are capsule/tablet extracts as effective as raw herbs.

Reference: *Nat Sci Sleep* 2017;9:163-69

[Abstract](#)

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