Welcome to the fourth issue of Sleep Research Review.

One of the studies selected for this issue reports that treatment with positive airway pressure reduces 30-day readmission rates and emergency department visits in cardiac patients who are diagnosed with obstructive sleep apnoea. The study authors comment that reducing hospital admission rates for cardiac patients is essential for providing cost-effective care.

Another study reports improvement in patients suffering from restless legs syndrome occurring with iron deficiency anaemia after they received treatment with intravenous iron therapy. This effect was sustained for more than 6 months in several of the patients.

Best wishes for the festive season to all of our readers and I look forward to your comments and feedback throughout the coming year.

Kind Regards,
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Obstructive sleep apnea during REM sleep and hypertension. Results of the Wisconsin Sleep Cohort

Authors: Mokhlesi B et al.

Summary: These researchers examined the association between REM-related obstructive sleep apnoea (OSA) and hypertension, by analysing overnight in-laboratory polysomnography measurements (from 4,385 sleep studies involving 1,451 individuals) and blood pressure (BP) (including a subset with ambulatory BP data from 1,085 sleep studies involving 742 individuals) using data from the longitudinal community-based Wisconsin Sleep Cohort Study. Significant dose relationships were observed between REM apnoea-hypopnoea index (AHI) and prevalent hypertension. The higher relative odds of prevalent hypertension were most evident with REM AHI ≥15. Among individuals with non-REM AHI ≤5, a two-fold increase in REM AHI was associated with 24% higher odds of hypertension (odds ratio 1.24; 95% CI, 1.08 to 1.41). There was also a significant dose-response association between REM AHI categories and incident hypertension for the entire cohort (p for trend = 0.017). Non-REM AHI was not a significant predictor of hypertension in any of the models.

Comment: The significant association between REM AHI and incident and prevalent hypertension drawn from this community-based study applies after adjusting for non-REM AHI or in the latter’s absence, and contains a dose-response driver. Combined with data from other studies that describe the often asymptomatic nature of REM-predominant OSA (perhaps leading to delayed diagnosis and treatment) and the widespread pattern and duration of typical CPAP adherence in both REM- and non-REM predominant OSA (whereby average adherence to CPAP hours may not typically cover the second half of night REM periods) this study, despite admitted limitations, emphasises the importance of more sustained CPAP use across the whole night (to include REM periods) in the attempt to ameliorate cardiovascular (specifically systemic hypertension) risk in OSA patients using CPAP as the prime therapeutic intervention.

Reference: Am J Respir Crit Care Med. 2014;190(10):1158-67

Abstract
Enhanced upper-airway muscle responsiveness is a distinct feature of overweight/obese individuals without sleep apnea

Authors: Sands SA et al.

Summary: This study compared key physiological traits (upper airway anatomy, collapsibility, upper airway muscle responsiveness, ventilator stability, arousability from sleep) among overweight/obese individuals (body mass index >25 kg/m²) who either did have OSA (AHI ≥15 events/h; n=25) or did not (AHI <15 events/h; n=18) and among normal-weight patients without apnoea (controls; n=11). Overweight/obese subjects without apnoea exhibited a less collapsible airway than overweight/obese patients with apnoea (mean critical closing pressure −3.7 ± 0.6 cm H₂O; p=0.003), but a more collapsible airway relative to normal-weight controls (−8.8 cm H₂O; p<0.001). Notably, overweight/obese subjects without apnoea exhibited a three-fold greater upper-airway muscle responsiveness than both overweight/obese patients with apnoea (mean Δgenioglossus EMG/Δapnoea pressure −0.49 vs −0.15 %max/cm H₂O; p=0.008) and normal-weight controls (−0.16 %max/cm H₂O; p=0.02). Loop gain was elevated (more negative) in both overweight/obese groups and normal-weight controls (p=0.02).

Model-based analysis demonstrated that overweight/obese individuals without apnoea rely on both more favourable anatomy and collapsibility and enhanced upper-airway dilator muscle responses to avoid OSA.

Comment: As we approach the era of personalised medicine, a more sophisticated analysis of the relevant physiological traits that contribute to upper airway obstruction in OSA potentially provides opportunities of different treatment options beyond, although not necessarily relegating, CPAP. The authors of this study continue exploring the key physiological variables (upper airway collapsibility, neuromuscular compensatory responses to collapse, ventilatory stability, and sleep maintenance) employed in other recent work and apply that analytical approach to the clinical cohort of the “non-apnoic” (AHI <15/hr) overweight/obese. From this novel approach is described a 3-fold enhancement of neuromuscular compensatory drive by the non-apnoic overweight/obese, combined with an UA anatomy that is only moderately adverse of their apnoic overweight/obese cousins. This approach may offer, at least in principle, pathways to tailor specific non-CPAP treatments to particular OSA phenotypes.


Optogenetic stimulation of adrenergic C1 neurons causes sleep state-dependent cardiorespiratory stimulation and arousal with sighs in rats

Authors: Burke PG et al.

Summary: Outcomes are reported from the simultaneous optogenetic stimulation of sympathoexcitatory, hypoxia-responsive C1 neurons and central respiratory chemoreceptors (retrotrapezoid nucleus, RTN) located in the rostral ventrolateral medulla (RVLM) of tyrosine hydroxylase (TH)-Cre rats. The researchers injected a Cre-dependent vector expressing channelrhodopsin 2 (CH2R) fused with enhanced yellow fluorescent protein or mCherry into the RVLM of these animals and examined the response of CH2R-transduced neurons to light in anesthetised rats. The vast majority (95%) of CH2R-expressing neurons contained C1 neuron markers and innervated the spinal cord. RTN neurons were not transduced. During anaesthesia, C1 cells were activated by each light pulse up to 40 Hz. During quiet resting and non-REM sleep, C1 cell stimulation (20 s, 2–20 Hz) increased BP and respiratory frequency and produced sighs and arousal from non-REM sleep. Arousal was frequency-dependent (85% probability at 20 Hz). Stimulation during REM sleep increased BP, but did not affect EEG or breathing. C1 cell-mediated breathing stimulation was blocked by hypoxia (12% Fₐ)، but was unchanged by 6% Fₐᵢ.

Comment: Optogenetics is a relatively new and precise neuromodulation method that allows for in vivo exploration of the effects of stimulation of specific neurons or groups of neurons with similar characteristics. The authors of this study apply optogenetics methodology to the study of the brainstem of rodents, specifically the C1 neurons of the RVLM, which have previously been implicated, along with other associated non-C1 RVLM neurons, in arousal from sleep, along with breathing stimulation, a rise in BP, and sighs. The study confirmed that selective activation, specifically in non-REM sleep, of the C1 neurons increases breathing as well as BP and faithfully produces sighs and arousal from non-REM sleep, thereby reproducing most of the effects of hypoxia. While this exquisite approach helps to micro-dissect basic pathophysiological pathways in apnoea-related hypoxia, it remains unclear at this stage as to whether any potentially therapeutic inferences can be deduced.


Chronic sleep fragmentation induces endothelial dysfunction and structural vascular changes in mice

Authors: Carreras A et al.

Summary: In this study, adult male C57BL/6J mice were fed normal chow and exposed to daytime sleep fragmentation (SF) or control sleep (CTL) for 20 weeks. During the post-occlusive period, SF-exposed mice exhibited increased latencies to reach baseline perfusion levels and increased systemic BP values first seen at 8 weeks of SF persisted thereafter. Examination of excited aortas from SF-exposed mice failed to reveal any obvious atherosclerotic plaques, but there was evidence of marked elastic fibre disruption and fibre disorganisation, as well as increased numbers of foam cells and macrophages in the aorta wall. Senescence markers showed reduced TERT and cyclin A and increased p66Shc expression, with higher interleukin-6 plasma levels in SF-exposed mice.

Comment: Pathogenesis of the cardiovascular morbidities and attached mortality of OSA has been linked to repetitive hypoxic insults and their sequelae. It has been somewhat unclear, however, as to whether sleep fragmentation (SF) and associate arousals has an important separate contribution to that CV morbidity-mortality burden of OSA apart from hypoxia-driven consequences. This study provides basic support in an animal model to the notion that the fragmentation-arousals nexus of itself has important CV morbidity consequences in OSA at the endothelial level and on systemic BP, and may help to refocus efforts to consider interventions that address not just obstructions-hypoxia but also the other common feature of SF in sleep disorders, such as occurs in but is not limited to OSA. This work may also help to clarify our thinking more specifically about SF-arousal predominant OSA not characterised by significant hypoxaemia.


Diagnosis and treatment of sleep disordered breathing in hospitalized cardiac patients: a reduction in 30-day hospital readmission rates

Authors: Kauta SR et al.

Summary: This study involved 106 patients who reported symptoms consistent with sleep-disordered breathing (SDB) while being hospitalised for heart failure, arrhythmias, and myocardial infarction. Portable monitoring systems yielded conclusive diagnostic studies for 104 patients, 81 (78%) of whom had SDB (AHI ≥5 events/h). Sixty-five (60%) of the 81 patients had predominantly OSA, while 16 (20%) had predominantly central sleep apnoea. Positive airway pressure (PAP) treatment was initiated in the 81 patients diagnosed with sleep apnoea. Adequate adherence to treatment was defined as using PAP therapy ≥4 hours per night on ≥70% of nights. None of 19 patients with adequate PAP adherence, 6 of 20 (30%) with partial PAP use, and 5 of 17 (29%) of patients who did not use PAP were readmitted to the hospital or visited the emergency department for a cardiac issue within 30 days from discharge (p=0.025).

Comment: There is a very high prevalence of OSA in heart failure patients, and in cardiac patients more generally. Cardiovascular morbidity is an identified adverse outcome of untreated OSA, and OSA itself is highly prevalent. It is not surprising that OSA contributes to hospitalisation of heart failure patients, and to readmission rates. This study demonstrates a significant advantage in terms of reduced readmission rates to those cardiac patients who, during an acute admission, are diagnosed with OSA (using an unattended portable monitoring [type III in this instance device]) and initiated treatment with auto-CPAP. While there are limitations to this study, this result, if replicated in other health care systems, is advantageous not only potentially for individual patients but also for those concerned with the financing of acute hospital care.

**Continuous Positive Airway Pressure**

*Compared with placebo; measured by Maintenance of Wakefulness Test (MWT).*

Modavigil as an adjunct to CPAP* significantly increases wakefulness without reducing nightly CPAP use† in patients with obstructive sleep apnoea/hypopnoea syndrome.


**PBS Information:** Authority required for excessive daytime sleepiness associated with narcolepsy. This product is not on the PBS for obstructive sleep apnoea/hypopnoea syndrome. Refer to PBS Schedule for full information.


**MINIMUM PRODUCT INFORMATION:** Modavigil® modafinil. **Indications:** Improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy; treatment of excessive sleepiness associated with moderate to severe chronic shift work disorder where nonpharmacological interventions are unsuccessful or inappropriate; adjunct to continuous positive airways pressure (CPAP) in obstructive sleep apnoea/hypopnoea syndrome. **Contraindications:** Hypersensitivity to modafinil or any other product component, use in pregnancy. **Precautions:** Serious or life-threatening skin rash, multi-organ hypersensitivity reactions (see full PI); psychiatric symptoms and disorders (see full PI); operating automobile or other hazardous machinery; cardiovascular disorders (see full PI); increased risk of adverse events with higher doses, women using oral contraceptives, history of alcohol, drug or illicit substance abuse; children and adolescents < 18 years of age, not approved for use in paediatric patients, > 65 years of age, severe renal impairment, severe hepatic impairment, concomitant MAO inhibitors (see full PI); breastfeeding, pregnancy (Category B3). **Adverse Effects:** Very common (≥ 10%): headache, nausea; common (1% – 10%): nervousness, rhinitis, diarrhoea, back pain, anxiety, insomnia, dizziness, dyspepsia, flu syndrome, dry mouth, anorexia, pharyngitis, chest pain, hypertension, tachycardia, palpitation, vasodilation, constipation, abnormal liver function, depression, paraesthesia, somnolence, lung disorder, chest pain, vertigo, epistaxis, asthma, sweating, herpes simplex, delirium tremens, labile mood, taste perversion, eye pain, uric acid abnormalities, haematuria, pyuria. Post-marketing reports have included: psychiatric disorders (including suicidal ideation, suicide attempt, manic symptoms, aggression, depression and anxiety), serious skin reactions (including suspected cases of erythema multiforme and Stevens-Johnson syndrome), urticaria, angioedema, multi-organ hypersensitivity reactions, pruritus, abnormal ECG, oedema, ischaemic heart disease, cardiac arrhythmias, convulsions, tachycardia, dyskinesia (See full PI). **Interactions:** Co-administration with: CYP2C19 substrates (e.g. diazepam, phenytoin and propranolol); CYP3A4 substrates (e.g. steroidal contraceptives, cyclosporin and to a lesser degree, theophylline); potent CYP3A4 inducers (e.g. carbamazepine, phenobarbital, rifampicin) and potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole). No interaction studies have been performed with MAO inhibitors. **Dosage and Administration:** Always start at the lowest recommended dose. Tablets should be swallowed whole. **Narcolepsy and obstructive sleep apnoea:** 200 to 400 mg/day; given as a single dose in the morning or two divided doses (morning and at noon); chronic shift work disorder: 200 mg/day 1 hr prior to start of work shift; elderly: consider using lower doses; severe hepatic impairment: reduce dose by half; severe renal impairment: inadequate information to determine MODAVIGIL dosing in this population. **Presentation:** 100mg tablets; 10’s, 30’s, 60’s.

Modavigil® is a registered trademark of Cephalon, Inc. Frazer, PA, USA. bioCSL™ is a registered trademark of CSL Limited.
Trauma associated sleep disorder: a proposed parasomnias encompassing disruptive nocturnal behaviours, nightmares, and REM without atonia in trauma survivors

Authors: Myslivec V et al.

Summary: Four young male, active duty US army soldiers who presented with disruptive nocturnal behaviours (DNB) and trauma-related nightmares underwent a clinical evaluation in a sleep medicine clinic and overnight sleep testing using the polysomnogram (PSG). DNB ranged from vocalisations and somnambulism to combative behaviours that injured bed partners. All patients had REM sleep without atonia (RSWA) during polysomnography; one patient had DNB and a nightmare captured during REM sleep. Treatment with prazosin improved DNB and nightmares in all patients.

Comment: Although this paper utilises the clinical and PSG findings of only 4 patients, it describes a syndromic presentation of parasomnia-like behaviours which are not readily classifiable under current sleep medicine nosologies. The authors propose the introduction of a new sleep disorder, trauma-associated sleep disorder, on the basis of these findings. Disruptive nocturnal behaviours, nightmares and RSWA were putative characteristic features, amongst others, following a traumatic experience. Use of SSRI and OSA were co-present in some subjects. Undoubtedly, this newly-proposed sleep disorder will not get a guernsey in the next ICSD unless other authors publish supportive case series. The current authors suggest that anecdotally this pattern of behaviours is widely recognised in health care systems catering for trauma survivors.


Simple snoring: Not quite so simple after all?

Authors: Derry V et al.

Summary: These UK-based researchers reviewed the literature surrounding the distinctions between simple snoring (SS), upper airway resistance syndrome (UARS) and OSA. They acknowledge the lack of consistency in the definition of snoring, methods of assessment, and the extent of concomitant complaints. They also highlight the controversy surrounding the question as to whether SS is independently associated with daytime sleepiness, or adverse health outcomes including cardiovascular disease and metabolic syndrome. This review discusses risk factors for SS, in as far as it can be distinguished from UARS and OSA, and describes common correlates of snoring, including cardiovascular disease, metabolic syndrome, and daytime sleepiness.

Comment: The Westmead Sleep Research Group and others have suggested that pathophysiological symptoms/mechanisms whereby snoring may impart cerebrovascular risk, but the findings of others have not been consistent with that work. In population studies, associations of snoring with adverse outcomes is bedevilled by inconsistent definitions and incomplete association data, and in the sleep laboratory methods of documenting snoring range across subjective listener report and varying audio technologies. In the lack of consensus as to an agreed objective snoring methodology it is likely that the many questions still posed regarding snoring's importance will remain unresolved. This review outlines the limited achievements and persisting troubles in close detail.


Electroencephalographic slow waves prior to sleepwalking episodes

Authors: Perrault R et al.

Summary: In this study, 12 adult sleepwalkers underwent one night of diagnostic PSG. The study aimed to compare spectral power for delta (1–4Hz) and slow delta (0.5–1.5Hz) as well as slow oscillation density before the onset of somnambulistic episodes versus non-behavioural awakenings in these subjects. It also sought to describe the time course of observed changes in slow-wave activity and slow oscillations during the 3 min immediately preceding the occurrence of somnambulistic episodes. Slow-wave activity and slow oscillation density were significantly greater prior to somnambulistic episodes as compared with non-behavioural awakenings. There was no evidence for a gradual increase over the 3 min preceding the episodes.

Comment: Advances in the understanding of the pathophysiology of non-REM parasomnias such as sleepwalking (SW) have been hindered until recently by methodological barriers. Recent work largely emanating from the Montreal group headed byMontplaisir and Zadra has changed this perspective; laboratory-based sleep studies enhanced by controlled sleep deprivation and acoustic stimulation enables a more reliable demonstration of SW and other non-REM parasomnias behaviours in a laboratory setting, thereby enabling further close examination of the EEG phenomenology of SW. This study drills down into the EEG features just prior to SW episodes and non-behavioural awakenings in known sleepwalkers and describes slow-wave activity and slow oscillation density EEG changes, which were significantly greater prior to patients’ SW episodes as compared with non-behavioural awakenings. This work potentially leads toward a reliable in-laboratory diagnostic method for SW that has been lacking to date.


The effects of cannabinoid administration on sleep: a systematic review of human studies

Authors: Gates PJ et al.

Summary: These researchers conducted an extensive literature search of research investigating the effects of cannabinoid administration on sleep in humans.

Comment: You can hardly walk along an inner city street in the early 21st century in many countries without the sharp-sweet odour of smoked cannabis wafting into your breathing space – undoubtedly active inhalers of smoked cannabis will often intake near sleep time. There is also an increased use and proposed increase of medicinal cannabis in many countries in the context of adjunctive pain management strategies and other clinical indications. Although there have been earlier reviews of the sleep effects of cannabis use, this current review is a careful systematic appraisal of relevant data drawn from 39 source papers including, of course, the most recently published research. Similarly to earlier reviews, the authors caution that because of significant methodological limitations in most of these studies results are mixed and firm conclusions are not readily available. Slow-wave sleep may be reduced, a finding of some potential relevance for example in forensic sleep medicine. Medicinal use of cannabis may improve sleep via enhanced pain management and better studies are recommended.


Response to intravenous iron in patients with iron deficiency anemia (IDA) and restless leg syndrome (Willis-Ekbom disease)

Authors: Mehmood T et al.

Summary: Outcomes are reported for 42 patients with restless leg syndrome (RLS) caused by iron deficiency anaemia (IDA) who underwent baseline evaluations prior to an intravenous infusion of low-molecular-weight iron dextran (1000 mg) and were followed-up at 7-12 months after the infusion. Patients were classified as respondent versus nonrespondent for RLS improvement. At follow-up, RLS symptoms were reduced from baseline in 32 patients, 20 of whom experienced an extended response lasting >6 months. Response was unrelated to age or gender, but was apparently related to race, with fewer responses occurring among African-Americans than Whites (2/5 [40%] vs 30/37 [81%]; p=0.078). White respondents versus nonrespondents had higher haemoglobin levels after treatment (12.1 vs 11.3 g/dl; p=0.03).

Comment: Given the occurrence of contemporary successful class action lawsuits in Australia for plaintiffs affected by major side effects of dopamine agonists in the treatment of Parkinson's disease and RLS, sleep medicine practitioners may be helped to refocus on nonpharmacological and effective treatment options in the case of RLS particularly when related to iron deficiency states, which predict a high likelihood of RLS. In such states, IV infusion rapidly reverses the status of deficient iron storage and this study showed a beneficial and sustained effect on RLS, although about a quarter of treated patients did not respond. Being retrospective in nature, this study serves mainly to point out the need for careful controlled prospective evaluation of the intervention of IV iron infusion.