Preface for the 3rd Clinical Update Sleep, 23rd February 2018, Royal College of Physicians, London, UK: year in review

Clinical Update Sleep 2017

Sleep medicine remains an exciting and fast-evolving field of medicine with insomnia, hypersomnia, parasomnia, sleep-disordered breathing and circadian rhythm disorders affecting significant proportions of the population. This update provides a selected overview about recent publications in the field.

Sleep-disordered breathing and comorbidities

The high prevalence of obstructive sleep apnoea (OSA) differs between genders, with male patients being more affected (1). In a US-nationwide study of 1,704,905 patients who had a diagnosis of OSA and 1,704,417 controls matched for age, sex and state of residence, the prevalence of co-morbidities [OR (95% CI)], such as type 2 diabetes [2.29 (2.28–2.31)], cardiac arrhythmia [3.26 (3.20–3.32)], ischaemic heart disease [2.54 (2.51–2.56)], stroke [3.51 (3.42–3.60)], hypertension [2.14 (2.13–2.15)], depression [4.99 (4.91–5.07)] and congestive heart failure [4.30 (4.21–4.39)] was increased (2). Non-communicable disease is important (3) and its link with comorbidities, predominantly its association with obesity (1), make OSA an important confounding factor that impacts on physical, social and mental health (4).

Diagnostic criteria for sleep apnoea

There have been ongoing discussions about the classification and diagnostic parameters of OSA. Study outcomes investigating OSA are dependent on accurate description, definition and comparisons of their patient groups. Heinzer *et al.* argue that the present International Classification of Sleep Disorders (ICSD-3) definition of sleep apnoea yields an unrealistically high prevalence of OSA (5), in part related to a low apnoea-hypopnoea index (AHI) threshold for normal subjects (5/h) and a high prevalence of coexisting symptoms and conditions such as fatigue, insomnia and hypertension which may not be related to the underlying OSA (6).

In a group of 2,121 patients who underwent full home polysomnography (PSG) ['HypnoLaus' cohort; 48% male, median age 57, (interquartile range, IQR 49–68) years, mean body mass index (BMI) 25.6 kg/m², standard deviation (SD) 4.1 kg/m²], they applied the 2013 American Academy of Sleep Medicine (AASM) criteria for OSA:

An apnoea was defined as $\geq 90\%$ reduction in airflow from baseline, lasting for ≥ 10 seconds; a hypopnea was defined as $\geq 30\%$ reduction in airflow from baseline, lasting for ≥ 10 seconds with either a $\geq 3\%$ drop in oxygen saturation or an arousal (7,8).

These criteria led to a diagnosis of moderate-to-severe OSA (sOSA) (AHI ≥ 15 /h) in 23.4% (95% CI: 20.9–26.0) of women and 49.7% (95% CI: 46.6–52.8) of men (9). However, analysing the same cohort in 2016, but using the ICSD-3 criteria which are defined by an AHI ≥ 15 /hour, or an AHI ≥ 5 /hour associated with one or more symptoms of OSA or cardiovascular and metabolic comorbidities, the prevalence of OSA increased to 74.7% of men, and 52.1% of women (5,6,10). The authors suggested that a better definition of OSA should be sought using prospective and large cohort follow-up studies.

Screening for OSA in a bariatric population

OSA and obesity commonly co-exist (11). However, OSA remains largely undiagnosed and untreated in the obese patient group (12,13). Bariatric surgery is an increasingly popular form of management in the severely obese population, where the co-existence of OSA is extremely likely (14). This can pose an increased risk of complication during general anaesthesia (15–20). Overnight PSG is the current gold standard diagnostic tool for OSA. The STOP-BANG questionnaire is a screening tool for diagnosing OSA and a score of >4 has a sensitivity of 88% (21). When combined with nocturnal pulse oximetry, the STOP-

BANG questionnaire has increased diagnostic accuracy (22,23).

Reed *et al.* studied the prevalence of undiagnosed OSA in pre-bariatric surgery patients using nocturnal pulse oximetry for patients with a STOP-BANG score >4 . Out of 141 pre-bariatric surgery patients [30% male, mean: age 49 ± 12 years, BMI 48.7 ± 7.3 kg/m², Epworth Sleepiness Scale (ESS) 7.3 ± 4.9 points], the authors identified 103 patients (73%) to have some form of sleep-disordered breathing. Of the 141 patients, 34 (24%) had mild OSA, 19 (13%) had moderate OSA and 13 (9%) had severe OSA. In these patients, 46% were advised or started on further respiratory management plans. On patient group analysis, the authors of this study concluded that bariatric patients with OSA were older ($P < 0.004$), had a higher BMI ($P < 0.008$), a higher ESS ($P < 0.05$) and more co-existing co-morbidities with hypertension ($P < 0.05$) and type 2 diabetes mellitus ($P < 0.05$) (24). These findings are consistent with earlier studies exploring OSA in bariatric surgery patients (25,26) and suggest diagnosis and treatment of OSA in this particular patient group is important to reduce peri-operative complications.

The physiology of sleep disordered breathing (SDB)

He *et al.* identified that hypoventilation in patients with COPD-OSA overlap syndrome is due to an increase in upper airway resistance, however in chronic obstructive pulmonary disorder (COPD) *alone* this is related to a reduction in neural respiratory drive (NRD) (27). NRD, as measured by electromyography (EMG) of the diaphragm or parasternal muscles, reflects the response to load on the respiratory system (28,29).

The authors utilised diaphragmatic EMG (EMG_{di}), in addition to full overnight polysomnography, to analyse the data of 35 patients [19 with COPD alone (FEV1, forced expiratory volume in 1 second, $38.5 \pm 16.3\%$), 16 with overlap syndrome (FEV1 $47.5 \pm 16.2\%$, AHI 20.5 ± 14.1 events/h)] with COPD, 12 healthy subjects and 14 patients with OSA. An oesophageal electrode was passed through the nose and into the stomach with careful positioning based on the EMG_{di} amplitude which was recorded from 5 pairs of electrodes as described previously (30,31). Maximal EMG_{di} was recorded using maximal inspiration to total lung capacity (TLC) and maximal inspiration against a closed airway at functional residual capacity for 3 seconds.

NRD decreased significantly in patients with COPD ($29.5 \pm 13.3\%$ *vs.* $23.0 \pm 8.9\%$ of maximal EMG_{di}, $P < 0.01$) and increased in patients with OSA ($14.2 \pm 7.9\%$ *vs.* $23.4 \pm 10.8\%$ of maximal EMG_{di}, $P = 0.001$) when they transitioned from wakefulness to non-REM sleep. In patients with the overlap syndrome, NRD did not significantly change ($29.3 \pm 15.8\%$ *vs.* $27.3 \pm 14.7\%$ of maximal EMG_{di}, $P > 0.05$). Tidal volume (V_T)/EMG_{di}, utilised as an assessment of upper airway resistance, was similar during the transition from wakefulness to NREM sleep in both healthy subjects (0.69 ± 0.18 *vs.* 0.69 ± 0.20 ; $P > 0.05$) compared to those with COPD alone (0.39 ± 0.23 *vs.* 0.37 ± 0.21 ; $P > 0.05$). However, in the COPD-OSA overlap syndrome there was a significant decrease (0.35 ± 0.21 *vs.* 0.28 ± 0.19 , $P < 0.05$), which was also true for the OSA group (0.56 ± 0.24 *vs.* 0.28 ± 0.13 , $P < 0.01$). The suggestion is that mild to moderate OSA can, in part, compensate for any reduction in NRD related to COPD acting as a protective factor against this mechanism. Although it might feel intuitive that OSA might decrease NRD further, these findings show the contrary, consistent with the author's previous findings (32).

Respiratory control at altitude is another interesting area of respiratory physiology. At high altitude, respiratory control is altered compared to sea-level whilst awake (33), but also when asleep (34). Differing levels of pO₂ and pCO₂ impact upon blood pH, and consequently respiratory control. Steier *et al.* studied mountaineers at sea level (London, UK) and at high-altitude at the Aconcagua (Andes, Argentina; peak ascent studied 5,560 m). NRD was measured using EMG_{di} overnight by a transoesophageal multi-electrode catheter on the healthy participants [3 men and 1 woman, 31 ± 3 years, body old; BMI 23.6 ± 0.9 kg/m², neck circumference 37.0 ± 2.7 cm, FEV1 $111.8 \pm 5.1\%$ predicted, and forced vital capacity (FVC) $115.5 \pm 6.3\%$ predicted]. Measurements were taken during 21 days at altitude. EMG of the neck muscles, parasternal intercostals and abdominal muscles were measured using surface electrodes from standardised positions (35).

All subjects developed severe central sleep apnoea and periodic breathing, worsening with higher altitude [4,360 m; 4% ODI 61.4 (26.9; 18.5–104.2)/hour]. At sea-level, EMG activity decreased with sleep onset, however, at 3,380 m there was increased EMG activity of the diaphragm, parasternal intercostals, and the abdominal muscles throughout the night. The increased levels of NRD, as measured by the EMG_{di} overnight, are related to the development of sleep-disordered breathing. Additional diaphragmatic and extra-diaphragmatic muscle activity is recruited to support the respiratory system to maintain sufficient ventilation (35). This was the first study to record transoesophageal EMG_{di} at altitude to allow accurate

measurement of central motor neuron output (NRD) (32,36), but similar future studies are more and more relevant in understanding the physiological adaptation under pathophysiological conditions.

Treatment of OSA

Continuous positive airway pressure (CPAP) and mandibular advancement devices (MAD)

CPAP and MAD are the two most efficacious and commonly used treatments for OSA. MADs are often used as alternatives in patients who are unable to tolerate CPAP. They work by forcing the mandible and tongue into protrusion and so helping to maintain upper airway patency during sleep (37). A meta-analysis of 77 randomised controlled trials (RCT) confirmed that the AHI was reduced overall by $-9.3/\text{hour}$ (95% CI: -12.3 to -6.3 ; $P<0.001$) using a MAD, while CPAP reduced the AHI overall by $-25.4/\text{hour}$ (95% CI: -30.7 to -20.1 ; $P<0.001$). Although CPAP reduced the AHI by a higher margin, MAD might achieve a similar long-term impact on patients with mild disease; they found that MAD improved the ESS compared to controls by -2.0 (95% CI: -2.7 to -1.3 ; $P<0.001$), whereas CPAP improved this by -1.2 (95% CI: -2.2 to -0.3 ; $P=0.012$) in patients with a mild baseline AHI as defined by a AHI of between 5 to 14, or a desaturation index (DI) of between 5 to 9 (38).

Ifthikhar *et al.* [2016] conducted a further meta-analysis of 80 RCTs to demonstrate the importance of both CPAP and MAD. However, they also included studies with supervised aerobic exercise training either as an intervention compared with controls, or as comparator with one of the other interventions (39). Their literature search found four RCTs comparing supervised aerobic exercise training to controls (40-43) and one comparing exercise training to MADs and CPAP (44). Adjunctive exercise training had a beneficial effect on AHI and ODI [$-10.1/\text{hour}$ (-14.2 to $-5.9/\text{hour}$) and $-7.8/\text{hour}$ (-13.0 to $-2.6/\text{hour}$), respectively] compared to CPAP or MAD treatment alone at the end of each of the exercise regime. The exercise programmes varied from a total duration of 4 weeks to 3 months, and between 3 to 6 times weekly, from between 1 to 2.5 hours.

In a different study, Vecchierini *et al.* investigated custom made MAD to facilitate adherence, describing improvements in sleepiness, symptoms and quality of life not only in mild and moderate OSA, but also in severe OSA. About 60% of patients achieved an AHI of $<15/\text{h}$, and complete resolution was described in 38%. Mean subjective compliance was 6.7 ± 1.3 h/night during 6.7 ± 0.9 nights/week. Most participants (96.1%) used MAD for >4 h/night, >4 days/week, and 86% used the device every night (45). The excellent compliance indicated that this treatment modality could potentially be attractive for patients who are intolerant of CPAP therapy.

Bratton *et al.* published a meta-analysis on the impact of CPAP *vs.* MAD on blood pressure in patients with OSA. Fifty-one studies were included, comprising a total of 4,888 patients. Overall, in analysing 4 trials ($n=370$), they found that there was no statistically significant difference between CPAP and MADs in their relationship with systolic blood pressure (SBP) reduction (-0.5 mmHg, 95% CI: -2.0 to 1.0 mmHg; $P=0.55$) or diastolic blood pressure (DBP) reduction (-0.2 mmHg, 95% CI: -1.6 to 1.3 mmHg; $P=0.82$). However, the degree of significance regarding the association of CPAP on blood pressure appears stronger than that of MAD. Overall, CPAP compared to inactive control was associated with a SBP reduction of -2.5 mmHg (95% CI: -1.5 to -3.5 mmHg; $P<0.001$; 47 trials, $n=4,533$) and a DBP reduction of 2.0 mmHg (95% CI: 1.3 to 2.7 mmHg; $P<0.001$; 46 trials, $n=4,488$). With regards to the impact of MADs on blood pressure, when compared to inactive control in 6 trials ($n=473$), they were associated with a systolic reduction of -2.1 mmHg (95% CI: -0.8 to -3.4 mmHg; $P=0.002$), and a diastolic reduction of -1.9 mmHg (95% CI: -0.5 to -3.2 mmHg; $P=0.008$) (46). There had been no comprehensive meta-analyses comparing CPAP and MAD prior to this, with the most recent being in 2014 (47) only including 2 trials (48,49); the results of which were conflicting. A previous meta-analysis on oral appliances on blood pressure in OSA found no beneficial impact (50).

Transcutaneous electrical stimulation/hypoglossal nerve stimulation in OSA

Different approaches to use electrical stimulation to activate the upper airway dilator muscles have been reported to enhance airway patency in OSA (51-55). Pengo *et al.* investigated the impact and feasibility of overnight bilateral submental transcutaneous electrical stimulation in OSA in the first randomised sham-controlled double-blind trial in 36 patients [mean

age 50.8 (SD ± 11.2) years, 83.3% male, median BMI 29.6 (IQR 26.9–34.9) kg/m², ESS score 10.5 (4.6) points, ODI median 25.7 (IQR 16.0–49.1)/hour and AHI median 28.1 (IQR 19.0–57.0) (54). Electrical stimulation was well tolerated without significant adverse events and improved upper airway obstruction as defined by the primary outcome measure of the 4% ODI [sham stimulation: 26.9 (17.5–39.5)/hour *vs.* active treatment: 19.5 (11.6–40.0)/hour; $P=0.026$]. This RCT confirmed the observations from an earlier feasibility study (52). The strength of this study design was the measurement of sleep and sleep disruption during stimulation (56), although there are some limitations which include the length of stimulation being restricted to only one night before the primary outcome was assessed, a modest reduction of the 4% ODI in the whole group and a lack of impact of stimulation/intervention on the total group AHI during rapid-eye-movement sleep (57). The modest treatment effect could potentially be explained by the concept of different OSA patient phenotypes (58) with patients with an anterior pharyngeal collapse responding better to stimulation than patients who have multilevel or concentric obstructions; ongoing work suggests that only a portion of OSA patients have upper airway dilator muscle dysfunction (59,60). However, the responder group in the TESLA trial (47.2%) reduced by a more relevant margin with the AHI by 9.1 (95% CI: 2.0–16.2)/hour and the 4% ODI by 10.0 (95% CI: 3.9–16.0)/hour (54). Currently, the National Institute of Health and Care Excellence (NICE) has opened a public consultation on safety and efficacy of hypoglossal nerve stimulation in the UK. Guidelines will need to consider the recent evidence of hypoglossal nerve stimulation and TESLA, and future work needs to focus on the pathophysiology that predicts response to this method (55).

Trans-oral robotic surgery (TORS) for the treatment of OSA

With obesity fuelling OSA in a growing number of the population and CPAP compliance often below 50% (61–63), surgical treatment is gaining increasing popularity. Garas *et al.* conducted a best evidence topic review of 5 studies (2 prospective and 3 retrospective cohort studies) investigating the safety, efficacy and suitability of TORS as treatment for OSA in obese patients, following the failure of compliance to conventional treatments such as CPAP (64). TORS, a novel treatment option which has been around for over 5 years, is a surgical method that is able to overcome the obstacles linked to accessing the base of the tongue (BOT) and hypopharynx region and provides superior visualisation ideal for multilevel surgery, compared to traditional non-robotic trans-oral surgical approaches. However, patient suitability for successful TORS is determined by a number of patient characteristics, including BMI.

Based on the available evidence they concluded that BMI correlates with the efficacy of TORS and is a reliable marker for TORS success; however, they also commented on the lack of evidence from RCTs to validate this. Consistent findings throughout all five studies demonstrated: (I) TORS is effective in over 75% of non-obese OSA patients and over 50% of non-morbidly obese OSA patients (BMI 30–35 kg/m²); (II) an increasing BMI was associated with a decrease in surgical success with TORS; and (III) TORS is not beneficial in patients with a BMI greater than 40 kg/m² (with success rates lower than 20%) (64).

Treatment in patients without excessive daytime sleepiness (EDS)

EDS is a typical presenting symptom of OSA, however, approximately 40–50% of OSA patients do not complain of EDS (65,66). Indeed many patients in the community have undiagnosed OSA with minimal symptoms (67,68), and the implications of CPAP on *non-sleepy* OSA patients are less well described (69). Zhang *et al.* published a meta-analysis in addition to previous studies (70–72), they reviewed 7 eligible trials comprising 1,541 minimally sleepy patients concluding that CPAP can reduce OSA severity in non-sleepy patients and reduce DBP (-0.92 , 95% CI: -1.39 to -0.46 mmHg, $P<0.001$) (70), similar to the results found in 2014 by Bratton *et al.* in patients using CPAP >4 h/night (-1.4 , 95% CI: -2.5 to -0.4 mmHg, $P=0.008$), but there was no link with the SBP (69). Zhang's review found no overall effect of CPAP therapy on SBP or cardiovascular risk. Another meta-analysis by Guo *et al.* (18 studies, 4,146 patients) further corroborated this point of view describing no decrease in cardiovascular events *vs* controls [odd ratio (OR) 0.84; 95% CI: 0.62–1.13; $P=0.25$], albeit a slightly lower 24 h systolic (-2.03 mmHg, 95% CI: -3.64 to -0.42 mmHg, $P=0.01$) and diastolic BP (-1.79 mmHg, 95% CI: -2.89 to -0.68 mmHg, $P=0.001$) (73).

CPAP adherence in OSA

Campos-Rodriguez *et al.* carried out a prospective multicenter 4-year follow-up (IQR 3.0–4.4 years) of 357 non-sleepy patients with moderate-to-severe OSA [(AHI ≥ 20 , ESS 7 IQR 5.0–8.0 points; age 53.5 (IQR 44.6–59.6) years, 87.7% male, BMI 30.8 (IQR 28.0–34.2) kg/m², SBP 130 (IQR 120–140) mmHg, DBP 80 (IQR 70–90) mmHg]. A total of 64.4% of patients had an adherence of ≥ 4 h/night [median 5 (IQR 2.18–6.25) h/night]. While it is clear that limited adherence to treatment leads to adverse outcomes in sleepy OSA patients, the authors point out that there are sparse data on non-sleepy OSA patients. This is a relevant problem, as subjective sleepiness is a factor that impacts on adherence (74). The authors found that baseline OSA severity, as measured by AHI severity ($P < 0.001$), and the percent of time spent with an SpO₂ $< 90\%$ ($P < 0.013$) were predictive of CPAP adherence in this non-sleepy cohort. Multivariate analysis revealed that the presence of hypertension combined with a high AHI (> 47 events/h) was also predictive of adherence ($P = 0.0107$) (75). Clinicians might be encouraged to reiterate these points in the non-sleepy hypertensive OSA cohort whenever adherence remains a problem.

Turnbull *et al.* investigated CPAP use in 195 minimally symptomatic OSA patients who were randomised to CPAP therapy from the MOSAIC trial cohort group [median age 59 (IQR 51–63) years, 78.5% male, 96.4% white, BMI median 31.1 (IQR 28.0–34.4) kg/m², ESS median 8 (IQR 4–11), ODI median 10.2 (IQR 4.7–17.5)]. The authors found no correlation between adherence with OSA severity (ODI) and symptom burden [ESS, sleep apnoea quality of life index (SAQLI), 36-item short form survey (SF-36)]. In their study, male gender was associated with better 6-month use in minimally symptomatic OSA patients (male CPAP usage 2:56 *vs.* female 1:57 h/night; $P = 0.02$). There was a moderate correlation between short-term use (2 and 4 weeks) with CPAP use at a 6-month (76). The authors concluded that patterns of CPAP use can be identified at an early stage which might be useful for clinicians with respect to predicting long-term CPAP adherence.

Xiao *et al.* recently investigated the hypothesis that regularly used nocturnal CPAP might be at pressures higher than required to maximally offload the respiratory system while awake due to “state-dependent contribution of the upper airway”, and that this in turn could result in breathlessness and adversely impact adherence. The team carried out an observational study on 15 obese participants (age 48 ± 10 years, 12 males, BMI 38.9 ± 5.8 kg/m²) with OSA (AHI 32.2 ± 21.1 /h, 95th percentile of CPAP 14.1 ± 3.8 cmH₂O) and measured NRD during a CPAP incremental titration (4–20 cmH₂O, increments of 2 cmH₂O/3 min) whilst they were lying supine. Both parasternal (EMG_{para}) and abdominal (EMG_{abdo}) surface EMG was utilised to quantify respiratory muscle recruitment. EMG_{para} demonstrated a significant reduction from baseline to $70.1\% \pm 17.2\%$ at CPAP levels of 10.7 ± 3.4 cmH₂O ($P = 0.026$). However, beyond this point, further increases led to an increase in EMG_{para} recruitment and associated breathlessness. The authors suggest this breathlessness, which is a consequence of an excess of CPAP pressures needed for sufficient NRD, would contribute to poor compliance during routine CPAP. The study also revealed that breathlessness as measured by mBorg scores had a negative correlation with the number of nights that CPAP was used ($r = -0.738$, $P = 0.006$) (77). Utilising measures of NRD to ensure the respiratory system in the obese individual is offloaded to the appropriate, but not excessive degree, may enhance compliance by reducing subjective breathlessness.

CPAP withdrawal

CPAP is the current gold standard treatment for OSA and may consequently decrease cardiovascular risk in OSA patients, who are commonly obese with many cardiovascular risk factors already present. Thus, CPAP withdrawal and the effect of this on blood pressure is a clinically relevant area of study in sleep medicine, both from an observational and a predictive point of view. Schwarz *et al.* combined data from three RCTs of CPAP-compliant OSA patients ($n = 149$) and compared blood pressure measurements from the therapeutic CPAP group [$n = 65$; 82% male; mean: age 62.8 ± 7.9 years; BMI 33.8 ± 5.9 kg/m²; hypertension ($> 140/90$ mmHg) 65%; SBP 132.7 ± 15.2 ; DBP 81.1 ± 11.2 mmHg] and the CPAP withdrawal group [$n = 84$; 87% male; mean: age 62.8 ± 9.0 years; BMI 33.3 ± 5.9 kg/m²; hypertension ($> 140/90$ mmHg) 77%; SBP 131.0 ± 14.4 ; DBP 81.8 ± 9.1 mmHg] over a 2-week period. The authors found increased office and home mean SBP (5.4 and 9.0 mmHg; $P < 0.003$ and $P < 0.001$ respectively) and DBP (5.0 and 7.8 mmHg; $P < 0.001$ and $P < 0.001$ respectively) following a 2-week CPAP withdrawal period compared to CPAP therapy group. OSA severity was also an independent marker for the increase in BP following CPAP withdrawal (78). Short-term CPAP withdrawal has clinically relevant blood pressure elevations. It is important to note a relatively short study period, which does not account for additional delayed effects of

CPAP withdrawal.

Although OSA is diagnosed using polysomnography, routine clinical studies provide little insight into the underlying phenotypes. In a recent RCT, Schwarz *et al.* investigated the use of electrospray-ionization-mass spectrometry (SESI-MS), as part of an exhaled breath analysis, in detecting and phenotyping OSA recurrence during CPAP withdrawal. Their study included 26 patients with moderate-to-severe OSA (ODI >20/h) who were treated with CPAP and withdrawing CPAP resulted in an expected recurrence of OSA (i.e., an ODI >15/h); patients demonstrated a distinct metabolic breathing profile. There were changes in 62 exhaled features, 16 identified metabolites, with significant discriminatory features in the breath analysis of OSA and untreated OSA (79). This approach opens the path for the identification of diseases, such as OSA, whilst potentially directing therapeutic interventions based on metabolic profiling. This novel approach may be cost and time effective, and this technique could also be used to assess CPAP effectiveness.

Identification of OSA by ear, nose and throat (ENT) specialists

Surgical treatment of OSA is becoming an increasing first-line option for a subgroup of OSA patients (80). Consequently, ENT specialists commonly encounter and treat OSA patients who opt for this treatment approach. Confidence in the polysomnographic diagnosis of OSA is, therefore, an important skill required of ENT specialists. ENT specialists should be able to competently identify if potential surgical candidates are truly affected by isolated OSA and not by other complex comorbidities, such as COPD and muscular neuropathies, which can present similarly with SDB but are better treated with a conservative therapy.

In a validation study, Bosi *et al.* investigated the effect of a 2-hour theoretical and practical interactive training session on compact PSG (CP) interpretation on the diagnostic accuracy of seven ENT specialists with no formal training in this. The focus was on identifying the four main oximetric patterns on CP traces (normal, phasic, prolonged and overlap patterns). When presented with 50 CP traces (ranging from normal traces to SDB) prior to the training session, there was a significantly low level of diagnostic accuracy coupled with high inter-operator variability. Diagnostic accuracy from the CP interpretation of the same 50 traces following the 2-hour teaching session improved significantly (before: 0.12–0.8; median 0.52, to after: 0.82–0.96; median 0.92; $P=0.006$) as well as reductions in inter-operator variability (before: kappa 0.180006, $P<0.0001$; after: kappa 0.754109, $P<0.0001$) (81).

The authors of this study have used the same educational model used in sleep surgery courses by the Italian Society of Otorhinolaryngology. They concluded that this model represents a rapid learning curve, although acknowledging the CP alone is not a diagnostic tool, but instead allows for verification of the quality of polysomnographic OSA diagnoses. The difficulty in differentiating between apnoeic events, such as obstructive or central, is a key limitation of CP interpretation discussed by the authors, as unstable control of breathing which can present with central and mixed apneas poses a high risk of surgical failure in some OSA patients. Ultimately, this easy-to-implement model could be of significant importance for the future practice of ENT specialists who frequently manage OSA patients and are not trained in CP interpretation.

New diagnostic strategies for OSA

New initiatives target physicians in charge of high-risk patient groups, such as patients with diabetes mellitus, by encouraging them to consider the co-diagnosis of OSA and to refer them to sleep clinics as appropriate (82). The identification and treatment of OSA has significant clinical and economic benefits (83). Prudon *et al.* investigated the effect of a novel approach to tackle the issue of the lack of diagnosis of OSA in the diabetic population with diabetic macular oedema (DMO), a particularly high-risk group, using a UK-wide postal-based diagnostic service with a domiciliary sleep study device, the ApneaLink (AL). The authors posted an AL device, a simple four-channel cardiorespiratory recording device, to 718 patients and successfully collected sleep data from 606 of these patients (84% of the original patient group; 66% males, mean: age 64.2 ± 10.3 years, ESS 9 ± 5) to aid diagnosis of OSA. Results from the ALs revealed a diagnosis of SDB in 75% of the individuals screened in this process (84). Not only does this study confirm the high incidence of OSA in the DMO patient population, but also, based on the preliminary success of this new diagnostic strategy, the authors concluded that a postal-based approach for OSA diagnosis is feasible and achievable. Important barriers to future improvements highlighted by the

authors included the economic sustainability of the approach; also, a notable percentage of patients (12%) required a repeat recording and 16% were unable to achieve any successful reading.

In collaboration with the British Lung Foundation (BLF), Boyes *et al.* used modern media to assess EDS using an online ESS. The scale was placed on the BLF's webpage (www.blf.org.uk) additionally collating demographic data such as age and gender. Automatic IP address checks meant that information was not duplicated, and filters screened for identical records, with data exportable from the database to Microsoft Excel. The team collated an average of 1,160 subjects per month, over 34-month period, demonstrating success in utilising this technique (85). Fifty-five percent of respondents were male, and more than half of the responses (51.5%) scored >10 on the ESS. Interestingly, they found a significant correlation between age and sleepiness in males ($P<0.001$), but not for females ($P=0.312$). The authors suggest, hypothetically, that this might be related to hormonal influences, as subtle changes to sleep structure are related to varying levels of progesterone, and women with severe premenstrual syndrome report insomnia and fatigue more often. This type of data collection is confounded by selection bias, however, the use of such screening tools on widely used webpages has huge potential in screening for disorders and understanding disease burden in the general population.

Non-invasive ventilation in COPD

The HOT-HMV trial is a phase 3 multicenter RCT on the utilisation of home nocturnal non-invasive mechanical ventilation with home oxygen therapy (HOT-HMV) *vs.* home oxygen therapy (HOT) alone for chronic hypercapnia in COPD. Murphy *et al.* randomised a total of 116 patients [mean (SD) age of 67 (10) years, 53% female, mean BMI of 21.6 (IQR 18.2–26.1)] from 13 UK centers, for a 12-month follow-up. These patients were included if they demonstrated persistent hypercapnia ($\text{PaCO}_2 >53$ mmHg), hypoxaemia ($\text{PaO}_2 <55$ mmHg), and an arterial pH >7.30 on room air between 2 to 4 weeks after attaining clinical stability following an acutely decompensated hypercapnic COPD exacerbation (86).

Sixty-four patients (28 HOT, and 36 HOT-HMV patients) completed the study with the 12-month follow-up. The HOT-HMV group had a 63.4% re-admission or death rate *vs.* 80.4% in the HOT group, representing an absolute risk reduction of 17%. The median time for re-admission or death for the HOT-HMV group was 4.3 (IQR 1.3–13.8) *vs.* 1.4 (IQR 0.5–3.9) months for the HOT group, with an adjusted hazard ratio of 0.49 (95% CI: 0.31–0.77; $P=0.002$). The HOT-HMV group also demonstrated a reduction in acute COPD exacerbation frequency, with a median of 3.8 (IQR 1.7–6.0) *vs.* 5.1 (IQR 1.0–9.2) exacerbations per year [adjusted odds ratio: 0.66 (95% CI: 0.46–0.95), $P=0.03$]. Health related quality of life improved significantly in the HOT-HMV group *vs.* HOT group as measured by the Severe Respiratory Insufficiency Questionnaire at 6 weeks [HOT-HMV: 50.6 points, HOT: 49.2 points; adjusted between-group difference of 4.48 (95% CI: 0.02–8.94; $P=0.05$), and the St George's Respiratory Questionnaire at 3 months (HOT-HMV: 62.9 points, HOT: 66.0 points; adjusted between-group difference of -4.85 (95% CI: -8.83 to -0.88 ; $P=0.02$)]. This was the first study to show that the use of domiciliary nocturnal non-invasive ventilation in COPD reduced mortality and re-admission.

SDB and cardiovascular disease

CPAP and cardiovascular disease

An increased cardiovascular risk in uncontrolled sleep-disordered breathing remains an important factor in the context of long-term treatment of OSA. CPAP provides an airspring to the collapsible airway in those with OSA and prevents intermittent hypoxia, high negative intra-thoracic pressure swings during obstruction and arousal from sleep, and normalises autonomic sympathetic tone which, eventually, is beneficial in the control of hypertension. A recent meta-analysis of seven RCTs investigated the effect of CPAP therapy on sleepy patients with OSA (87) finding that CPAP was associated with significant reductions in 24-hour ambulatory SBP (-2.32 mmHg; 95% CI: -3.65 to -1.00) and DBP (-1.98 mmHg; 95% CI: -2.82 to -1.14). Patients with treatment-resistant hypertension, or those already receiving antihypertensive medication benefited the most from CPAP.

A different study by Pengo *et al.* investigated the impact of home CPAP on sympathetic activity as measured by the blood pressure variability (BPV, standard deviation of 3 sequential BP readings) and pulse rate. BPV has prognostic

significance for future cardiovascular events (88) independent of absolute blood pressure values (89). In the 78 participants with OSA (76.9% men, BMI 36.2 ± 6.9 kg/m², age 49.0 ± 12.9 years) the investigators observed a decrease in systolic BPV (5.3 ± 4.9 vs. 4.2 ± 3.4 mmHg, $P=0.047$) and pulse rate (78.0 ± 14.5 vs. 75.5 ± 15.8 beats per minute, $P=0.032$) after 2 weeks of auto-titrating home positive airway pressure, although absolute systolic and DBP values did not change (90). Heart rate predicts long-term blood pressure changes in patients with OSA and treated with CPAP (91).

SAVE trial

Although observational studies have suggested that treatment of OSA with CPAP might lower the risk of cardiovascular events (92), the Sleep Apnoea Cardiovascular Endpoints (SAVE) trial was the first large-scale multicentre RCT on cardiovascular endpoints in OSA. Patients between 45–75 years were recruited from 89 centres in 7 countries. The SAVE trial analysed 2,687 participants (61 years, 81% males, BMI 29 ± 5 kg/m²) with moderate to severe OSA (ODI $\geq 4\%$ from baseline; ODI = 28 ± 14 /h, ESS = 7.4 ± 3.6) with comorbid cardiovascular disease for a mean of 3.7 years. Treatment with CPAP plus usual care vs. usual care without CPAP was associated with significant improvements in daytime sleepiness (ESS -2.5 ; 95% CI: -2.8 to -2.2 ; $P<0.001$), quality of life, mood and work productivity, but the authors reported no superiority in the CPAP group in terms of the primary composite cardiovascular endpoints (cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, heart failure or transient ischaemic attack; hazard ratio 1.10; 95% CI: 0.91–1.32; $P=0.34$) (93). Limitations of the SAVE trial include the lack of established clinical diagnostic criteria and treatment for sleep apnoea in several of the countries at the time when the study began, and a limited CPAP adherence of 3.3 ± 2.3 h/night. Although this compliance is similar to the mean adherence in other reports of CPAP use in non- or minimally-symptomatic OSA patients (94,95), it may not be sufficient to provide the desired level of respiratory control to have cardiovascular effects. Additionally, the study was not powered to provide definitive answers regarding the impact of CPAP on secondary cardiovascular endpoints, despite the strong indication of a lack of any significant benefit. An earlier RCT in minimally symptomatic OSA patients (94) did not find any increased risk in untreated OSA either. In this cohort of patients however, although they had proven OSA on diagnostic sleep study (>7.5 /h oxygen desaturations of $>4\%$), they had insufficient daytime symptoms to warrant CPAP.

OSA and percutaneous coronary intervention (PCI)

In a large prospective multicenter study of 1,311 participants who underwent PCI, 45.3% were found to have OSA as defined by an AHI ≥ 15 events/h (OSA: AHI 28.9, IQR 21.1; non-OSA: AHI 5.9, IQR 7.1). Lee *et al.* observed that OSA patients had a higher 3-year MACCE score which is a composite of cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke and unplanned revascularisation compared to patients without OSA (18.9% vs. 14.0%, $P=0.001$; median follow-up 1.9 years, IQR 0.8 years), independent of age, sex, ethnicity, BMI, diabetes mellitus and hypertension (adjusted hazard ratio 1.57, 95% CI: 1.10–2.24; $P=0.013$) (96). It is worth noting that the OSA group ($n=594$) compared to the non-OSA group ($n=717$) were significantly older (59.0 ± 10.2 vs. 57.5 ± 10.3 , $P=0.008$) and had a greater percentage of males (88.1% vs. 82.9%, $P=0.008$). These findings are important in that there is an increased prevalence of OSA in patients undergoing PCI (97–100) and needs to be considered in the context of evidence that there is an increased cardiovascular risk in OSA (92,101–106) despite the sparse impact of CPAP on these outcomes.

In 2016, a single-centre, prospective, RCT (RICCADSA trial) followed 244 patients who were newly re-vascularised due to coronary artery disease (CAD) and who had OSA but were non-sleepy (AHI ≥ 15 , ESS <10) for about 5 years [median 56.9 (range, 6.5 to 90.2) months] after revascularisation (107). Following adjustment for comorbidities and treatment compliance there was a significant reduction in the primary end point (revascularisation, myocardial infarction, stroke, cardiovascular mortality) in CPAP users with ≥ 4 h/night vs. patients who used CPAP <4 h/night or did not receive treatment (hazard ratio 0.29, 95% CI: 0.10–0.86, $P=0.026$). This observation is consistent with observations from previous studies in sleepy participants (108).

The conclusions drawn from an ongoing multicenter, randomised Impact of Continuous Positive Airway Pressure on Patients with Acute Coronary Syndrome and Non-Sleepy OSA (ISAAC) study (Clinical Trial No. NCT01335087, Esquinas *et al.*, 2013) will be an interesting insight into the effectiveness of CPAP treatment in non-sleepy OSA patients with acute

coronary syndrome (109).

CPAP and atrial fibrillation (AF)

In 2016, Schlatzer *et al.* demonstrated that increased intrathoracic pressure swings in OSA promote premature atrial beats in patients with paroxysmal AF. This was an interventional cross-over study in 44 patients (mean age 60.1 ± 11.2 years, 86% male, BMI 26.6 ± 4.6 kg/m², SBP 134.8 ± 17.3 mmHg, DBP 80.5 ± 8.7 mmHg, heart rate 63.4 ± 13.9 bpm) with a prior ECG diagnosis of AF. The authors made use of the Mueller maneuver (MM) which simulated inspiratory effort observed during obstructive apneas. Atrial premature beats (APBs) occurred more frequently in patients during the MM (55% of patients) *vs.* normal breathing (9% of patients; $P < 0.001$). The authors found that the severity of OSA was independently associated with left atrial end-systolic diameter, as assessed by echocardiography. The MM also led to significant increases in ventricular polarisation [measured by QT_c and T_{peak-to-T_{end}} (TpTe_c) intervals ($+17.3$ ms, $P < 0.001$ and $+4.3$ ms, $P = 0.005$, respectively)]. This observation consolidates a causative pathophysiological link between OSA and AF, in addition to the increased propensity of sudden cardiac death due to arrhythmias. The authors recommend that patients with known paroxysmal AF should be screened for OSA to prevent progression of paroxysmal AF to chronic AF (110).

CPAP and sympathetic activity

Despite a known relationship between OSA and sympathetic activity, the exact pathophysiological interaction is less well understood. Henderson *et al.* studied 15 patients with OSA (13 male) with a mean age of 54 ± 2.6 years, and mean systolic blood pressure of 137.7 ± 4.9 mmHg and a diastolic BP of 80.6 ± 2.1 mmHg and compared them to 15 healthy controls (12 males, age 50.0 ± 2.9 years, SBP 121.4 ± 4.0 mmHg; $P = 0.04$, DBP 67.9 ± 3.6 mmHg; $P = 0.004$). Six-months of CPAP treatment lead to a significant decrease in resting muscle sympathetic nerve activity (MSNA) which was maintained after 12 months of treatment ($P < 0.0001$), as measured by microneurography. Utilising magnetic resonance imaging (MRI), the investigators were able to demonstrate that this reduction in MSNA was secondary to a restoration of brainstem and structural changes in the medullary raphe, rostral, ventrolateral medulla, dorsolateral pons, and ventral midbrain. They concluded that CPAP treatment can lead to these modulations and that investigation should focus on pathophysiological mechanisms to develop novel modulatory treatment interventions (111).

Markers of cardiovascular disease

In addition to increased sympathetic tone, arterial stiffening is also a marker of cardiovascular risk (112), and both are linked to OSA (113–115). Bisogni *et al.*, in a proof of principle study, wanted to find out whether EDS in patients with mild-to-moderate OSA was related to detectable signs of increased sympathetic activity and arterial stiffness. Investigating 31 “sleepy” normotensive men with mild-moderate OSA and an ESS > 10 (mean: age 44.1 ± 10.6 years, BMI 29.3 ± 6 , AHI 15.1 ± 6.7 events/h, ESS 15.6 ± 3.0) and 25 “non-sleepy” matched controls with mild-moderate OSA and an ESS < 10 (mean: 45.8 ± 9.5 , BMI 29.3 ± 4.8 , AHI 14.5 ± 7.4 , ESS 6.6 ± 2.7), they found that EDS was not associated with increased sympathetic activation [very low frequency power $18,947 \pm 11,207$ *vs.* $15,893 \pm 8,272$ ms², $P = 0.28$; low frequency (LH) power $17,753 \pm 8,441$ *vs.* $15,414 \pm 5,666$ ms², $P = 0.26$; high frequency (HF) power $7,527 \pm 1,979$ *vs.* $8,257 \pm 3,416$ ms², $P = 0.36$; LF/HF ratio 3.04 ± 1.37 *vs.* 2.55 ± 1.01 , $P = 0.15$] or mean arterial stiffness index (6.97 ± 0.83 *vs.* 7.26 ± 0.66 , $P = 0.18$) (116). Although the patients were well matched, the relatively small sample size, a consequence of careful patient selection, and also the cross-sectional nature impacts on the wider application of the results. There was a lack of BP measurements in the supine and upright posture, in addition to duration of OSA both of which may impact on sympathetic drive. However, the proof of principle provides evidence against generalising EDS as a determinant of potential sympathetic activation in this patient group.

OSA, CPAP, neuroimaging and cognition

In a study of whole brain magnetisation transfer (MT) imaging data from 19 newly diagnosed and untreated patients with

OSA (50.4±8.6 years, 68.4% male, BMI 32.0±7.7 kg/m², AHI 39.7±24.3/hour) a negative correlation was found between the MT ratio (MTR) and the AHI in the insula, basal ganglia, basal forebrain, frontal areas, internal and external capsules, hypothalamus, amygdala, hippocampus, and temporal sites suggesting reduced white matter in these areas and significant effects of AHI on tissue integrity ($P<0.005$) (117).

A different study of 55 patients (mean 47.6±11.1 years) with newly diagnosed moderate-to-severe OSA [ODI 36.6 (25.2) events/h; ESS 12.8 (4.9) points] and 35 matched healthy volunteers found that one month of treatment with CPAP and best supportive care (BSC) resulted in right thalamus hypertrophy *vs.* the BSC only group (mean difference 4.04%, 95% CI: 1.47–6.61 *vs.* –2.29%, 95% CI: –4.34 to –0.24). Following treatment, significant benefit in ESS was also noted in CPAP plus BSC (mean difference –27.97%, 95% CI: –36.75 to –19.19 *vs.* 2.46%, 95% CI: –5.23 to 10.15; $P=0.012$), the change correlated with neuroplastic changes in the brainstem ($r=-0.37$; $P=0.05$) and improved delayed logical memory scores (57.20 marks, 95% CI: 42.94–71.46 *vs.* 23.41 marks, 95% CI: 17.17–29.65; $P=0.037$) on cognitive testing (118).

Results from a recent meta-analysis by Emamian *et al.* of five cross-sectional studies found the aggregate odds ratio for the occurrence of OSA in Alzheimer's disease (AD) compared to healthy controls to be 5.05 (90 patients, 146 controls; 95% CI: 2.41–10.56, $P<0.001$) (119). Another meta-analysis of 15 peer-reviewed cross-sectional studies that recruited a total of 290 OSA patients and 290 healthy controls found a significant convergence of structural atrophy and functional disturbances in the neuroimaging of OSA patients compared to healthy controls at two specific sites: the right amygdala/hippocampus and the right central insula ($P<0.05$). These findings also suggest a role of these structures in the abnormal emotional and sensory processing in OSA (120).

A study by Vorlová *et al.* demonstrated a decreased perception of HF sounds in severe OSA. The study involved 43 males (mean age 48.2 years, range 34–74 years) with confirmed SDB [11 mild OSA, AHI 5–15; 17 severe OSA, AHI ≥ 30 ; simple snoring in 15 (AHI <5)] without any co-morbidities/medication that could affect sleep or hearing. Pure tone audiometry revealed higher auditory thresholds at frequencies of 4,000 and 8,000 Hz in patients with severe OSA (AHI ≥ 30) compared to patients with an AHI <15 . Transient evoked otoacoustic emissions and brainstem auditory evoked potentials revealed no correlations and the authors concluded that the selective hearing pathway impairment was at the base of the organ of Corti by sOSA (121).

Sleep and Parkinson's disease (PD)

Sleep disturbance is a common complaint in PD, which usually presents as REM sleep behavior disorder (RBD) (122,123). Poor sleep quality is thought to be linked to poor motor outcomes in patients with PD, with a particular effect on gait impairment (124–126).

A recent prospective cohort study by O'Dowd *et al.* was the first study to investigate the relationship between sleep dysfunction and poor motor outcomes in PD. Twelve newly diagnosed idiopathic PD patients [recruited from the Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation-PD (ICICLE-PD) study; 66.7% males; mean: age 69.0±6.0 years, ESS 3.8±3.0, disease duration 6.1±3.5 months] and 12 healthy controls, matched for age (75% males, mean: age 64.6±11.3 years, ESS 7.7±4.7) were followed up over a period of 36 months. There was no significant relationship between sleep quality and gait impairment at baseline. However, the authors of this study found a significant correlation between poor sleep quality and an accelerated decline in gait and locomotor ability at 36 months in the PD group compared to controls ($P<0.005$). Moreover, a relationship between poor sleep quality and increased step width variability in the PD population compared to controls at follow up was also reported ($P=0.001$) (127). Despite the limiting cohort size, the rising PD population and the potential for intervention to improve poor sleep quality, means sleep dysfunction on motor outcomes in PD is certainly an area that warrants further investigation through large prospective studies.

Circadian rhythm disorders

Genome studies

The sleep chronotype, i.e., the preference of time to sleep, is known to be a manifestation of the internal biological 'body clock'. It is largely driven by circadian rhythm and light-sensing pathways. Chronotypes have been associated with various

sleep disorders (128), and mutations in the genes encoding the core circadian clock (*PER2*, *PER3*, *CSNK1D*) are present in the advanced and delayed sleep phase syndromes (ASPS and DSPS) (129). Hu *et al.* conducted the first genome-wide associated study (GWAS) in 89,283 individuals with self-reported morning chronotype from the customer database of '23andMe' Inc. Fifteen genetic variants were found to be significantly associated with self-reported 'morningness', of which 7 are well-established circadian genes (rs12736689 near *RGS16*, $P < 0.0001$; rs9479402 near *VIP*, $P < 0.0001$; rs55694368 near *PER2*, $P < 0.0001$; rs35833281 near *HCRTR2*, $P < 0.0001$; rs11545787 near *RASD1*, $P < 0.0001$; rs11121022 near *PER3*, $P < 0.0001$; rs9565309 near *FBXL3*, $P < 0.0001$). A significant genetic correlation between morning chronotype with a lower prevalence of insomnia [12.9% *vs.* 18.3%, OR = 0.66 (95% CI: 0.63–0.69); $P < 0.0001$] and depression [OR = 0.64 (95% CI: 0.61–0.66); $P < 0.0001$] was found compared to the evening chronotype. However, evidence for a causal relationship between 'morningness' and depression in Mendelian randomisation analysis could not be found (130).

Shortly after this study, Lane *et al.* conducted a large genome-wide association study of 100,420 White European individual chronotypes from the UK BioBank. They discovered 12 novel loci with implications on the core circadian rhythm and light-sensing pathway modulatory functions, including variants near four genes with well-defined circadian functions: *PER2*, *APH1A*, *FBXL13* and *RGS16* (131). Eight of the 15 loci identified by Hu *et al.* were replicated by Lane *et al.* Genetic correlations suggest an evening chronotype is related to increased educational attainment [greater years of education; r_g (s.e.) 0.161 (0.041), $P < 0.0001$] and increased schizophrenia risk [r_g (s.e.) 0.112 (0.034), $P = 0.0011$]. The relationship between chronotype and schizophrenia is consistent with previous findings (132–134). Furthermore, a morning chronotype has been suggested to be genetically correlated with increased BMI [r_g (s.e.) –0.0851 (0.0281), $P = 0.0025$]. Mendelian randomisation analysis demonstrated a causal link between chronotype genetic risk score and educational attainment ($P = 0.0167$), however, not for schizophrenia ($P = 0.101$) or BMI ($P = 0.285$).

A third GWAS of self-reported chronotype by Jones *et al.* of 128,266 White British individuals from the UK BioBank study reported 16 variants associated with self-reported chronotype ($P < 0.0001$), including two established circadian genes *RGS16* [1.21 odds of 'morningness' (95% CI: 1.15–1.27), $P < 0.0001$] and *PER2* [1.09 odds of 'morningness' (95% CI: 1.06–1.12), $P < 0.0001$] both listed by Hu *et al.* and Lane *et al.* Moreover, investigating loci related to sleep duration, Jones *et al.* replicated a known signal in *PAX8* 2.6 (95% CI: 1.9–3.2) minutes per allele ($P < 0.0001$) and identified and replicated two new associations at *VRK2* [2.0 (95% CI: 1.3–2.7) minutes per allele, $P < 0.0001$; and 1.6 (95% CI: 1.1–2.2) minutes per allele; $P < 0.0001$]. Genetic correlations were identified between chronotype and BMI ($r_G = 0.056$, $P = 0.048$); under-sleeping and BMI ($r_G = 0.147$, $P < 0.0001$) and oversleeping and BMI ($r_G = 0.097$, $P = 0.039$), but no causal relationships were found upon Mendelian randomisation analysis (135).

A further GWAS by Lane *et al.* of 112,586 on White European individuals from the UK BioBank discovered loci associated with insomnia symptoms and EDS (AR/OPHN1; $P < 0.0001$) and replicated *PAX8* 8 loci linked to sleep duration [β (s.e.) = 2.34 (0.30) min/allele, $P < 0.0001$, effect allele frequency (EAF) = 0.213]. For insomnia symptoms a significant association was identified near *MEIS1* [OR (95% CI) = 1.26 (1.20–1.33), $P < 0.0001$, EAF = 0.057], *TMEM132E* [OR (95% CI) = 1.23 (1.13–1.35), $P < 0.0001$, EAF = 0.983], *CYCL1* [OR (95% CI) = 1.12 (1.07–1.16), $P < 0.0001$, EAF = 0.849], *TGFBI* [female-specific allele; OR (95% CI) = 1.10 (1.07–1.14), $P < 0.0001$] and *WDR27* [male-specific allele; OR (95% CI) = 1.14 (1.09–1.20), $P < 0.0001$]. In addition, genetic correlations were reported between increased sleep duration and schizophrenia risk ($r_g = 0.29$, $P < 0.0001$) and between raised levels of EDS and elevated measures for adiposity traits (BMI: $r_g = 0.20$, $P < 0.0001$; waist circumference: $r_g = 0.20$, $P < 0.0001$) (136).

Sleep and circadian rhythm

Lam *et al.* found over an 8-week period in 122 adult patients, that early morning bright light monotherapy ($P = 0.006$) in combination with fluoxetine hydrochloride ($P < 0.001$) were superior to the placebo in the treatment of non-seasonal major depressive disorder (MDD) (137). Male and female patients aged 19–60 years who had a diagnosis of MDD of at least moderate severity were included. The patients were free of any psychotropic medication for at least 2 weeks prior to baseline visit.

Another Study of Women's Health Across the Nation (SWAN) (138) assessed the homeostasis model assessment (HOMA)

to determine insulin resistance, i.e., HOMA-IR, and its impact with bedtime variability. HOMA-IR, a computation of fasting glucose and fasting insulin (139), is a more convenient method of assessing insulin resistance compared to the gold standard euglycaemic cap method (140). The authors followed 338 non-shift working women (mean age 52.12 ± 2.10 years, range 48–58 years, 47.6% Caucasian, 35.8% African American, 16.6% Chinese, BMI $=29.6 \pm 7.6$ kg/m², mean HOMA-IR 1.73 ± 1.29 units) over 5.4 ± 0.7 years. The authors demonstrated increased bedtime variability and bedtime delay to be associated with increased HOMA-IR and insulin resistance ($\beta = 0.128$; $P = 0.007$ and $\beta = 0.110$; $P = 0.013$, respectively) compared to those without increased variability in these indices. A greater bedtime advance (going to sleep earlier than usual) was associated with an increased BMI ($\beta = 0.095$; $P = 0.047$). The small sample size of each racial group in this study limited the generalisability to detect the effect of race and ethnicity.

In a study on 198 patients (65% male, 25.4 ± 9.6 years), Lane *et al.* demonstrated an association between the MTNR1B diabetes risk variant and delayed melatonin offset ($\beta = 1.36$ h, 95% CI: 0.28–2.44, $n = 95$, $P = 0.015$, $r^2 = 19\%$) and an increased duration of elevated melatonin ($\beta = 41$ min, 95% CI: 4.2–78, $n = 94$, $P = 0.032$, $r^2 = 2.5\%$) (141). Although these are preliminary findings, a delayed melatonin offset in the risk alleles may result in an increased food intake in the morning leading to decreased glucose tolerance and elevated risk of diabetes. The authors conclude that further studies are necessary to test the causality and impact of this current risk variant on melatonin offset on magnitude of basal and postprandial insulin secretion and glucose control.

Insomnia

In a recent meta-analysis of 153 studies by Itani *et al.* short sleep (<6 hours) was linearly associated with increased mortality [relative risk (RR) 1.12; 95% CI: 1.08–1.16, $P < 0.005$]. Short sleep impact was found in diabetes, hypertension, cardiovascular disease, coronary heart disease, and obesity, with a RR of 1.37 (1.22–1.53, $P < 0.005$), 1.17 (1.09–1.26, $P < 0.005$), 1.16 (1.10–1.23, $P < 0.005$), 1.26 (1.15–1.37, $P < 0.005$), and 1.38 (1.25–1.53, $P < 0.005$), respectively (142). A meta-analysis of 36 studies published in 2016 described an increased risk of diabetes associated with sleep disturbances. Cohort studies investigating the relationship between sleep disturbance and incident diabetes were eligible. The pooled RR of sleeping ≤ 5 hours a night (RR 1.48, 95% CI: 1.25–1.76), 6 hours a night (RR 1.18, 95% CI: 1.10–1.26), and ≥ 9 hours a night (RR 1.36, 95% CI: 1.12–1.65) were recorded. Poor sleep quality, OSA and shift work were related to diabetes with a pooled RR of 1.40 (95% CI: 1.21–1.63). This is similar to that of widely acknowledged risk factors such as physical inactivity (RR 1.20, 95% CI: 1.11–1.32) (143) and raises the question as to whether sleep should be assessed during the general work-up of diabetic patients (144), given its risk towards diabetes is comparable to better acknowledged risk factors. In addition whether public health policy should take proportional measures towards sleep and the metabolic syndrome in general (4).

Insomnia is a common sleeping disorder that can significantly impact on quality of life and medical health (145–147). Vgontzas *et al.* previously proposed two types of insomnia; firstly, insomnia with polysomnographically determined short sleep duration [total sleep time (TST) <6 hours] which holds a genetic predisposition and is characterised by physiological hyperarousal; and, secondly, insomnia with polysomnographically determined normal sleep duration (TST ≥ 6 hours) which lacks physiological hyperarousal (148). Following this, the Penn cohort studies, a cross-sectional analysis with 1,741 participants (of whom 199 suffered from insomnia), identified a link between insomnia with short sleep duration and hypertension (149), type 2 diabetes mellitus (150) and the total duration of insomnia, i.e., persistent insomnia (151).

The work of Johann *et al.* in 2017, in the Freiburg Insomnia Cohort, aimed to reproduce these findings using polysomnographic sleep studies over two consecutive nights, morning blood pressure measurements and routine fasting blood samples. Investigating 328 patients with primary insomnia (38.1% male; mean age 44.3 ± 12.2 years; mean BMI 23.8 ± 3.6 kg/m²), no significant association between short sleep duration insomnia and the presence of hypertension or type 2 diabetes mellitus were found. However, as in the Penn cohort study, they did find short sleep duration insomnia to be linked with increased total length of insomnia diagnosis. There was an increase in liver enzymes in short duration insomnia patients, which the authors suggest needs further evaluation (ALT: $\beta = 0.10$, $F = 6.31$, $P = 0.013$; γ GT: $\beta = 0.11$, $F = 6.68$, $P = 0.010$; sub-group classification based on the second night, ALT: $\beta = 0.16$, $F = 4.62$, $P = 0.033$; γ GT: $\beta = 0.13$, $F = 3.50$, $P = 0.063$). Causal links in this study could not be identified due to its cross-sectional design (152).

Melatonin

The synthesis and release of endogenous melatonin occurs during the night, as visual light inhibits its production. The primary physiological effect of melatonin reduces alertness and promotes a sleep state (153). Previous studies have demonstrated a beneficial effect of exogenous melatonin treatment on sleep parameters, such as sleep quality and sleep latency, in patients with primary and secondary sleep disorders (154–157).

Auld *et al.* conducted a meta-analysis of 12 randomised controlled studies to explore the effect of exogenous melatonin treatment in primary sleep disorders. The results from this meta-analysis demonstrated that, compared to placebo, melatonin decreases delayed sleep onset in primary insomnia (total mean difference = −5.05 min, 95% CI: −8.51 to −1.59; $P=0.002$) and reduces delayed sleep phase syndrome (total mean difference = −22.05 min, 95% CI: −32.02 to −12.09; $P<0.0001$) (158). These findings confirm that of an earlier meta-analysis (159). A publication bias might need to be considered and the small sample sizes of some of the RCTs included in the analysis may not provide definite answers. At present, very few trials have investigated the long-term effects and efficacy of exogenous melatonin treatment and this presents an avenue that requires further attention.

Hypersomnia, narcolepsy and cataplexy

Sodium oxybate, a central nervous system depressant, is thought to mediate its effects through GABA-B receptors. It is currently authorised by the European Medicines Agency and US Food and Drug Administration in the treatment of cataplexy and EDS in narcolepsy (160,161), and so while existing studies have explored its efficacy within strictly regulated prospective drug trials (162–165), few have done so outside this setting, and within more routine European clinical practice, where patients are likely have more severe disease and to be on a concoction of other treatments.

Drakatos *et al.* investigated the effect of sodium oxybate use in routine clinical practice in a retrospective single centre study of 90 patients (42.2% males; mean: age 42.5 ± 14.9 years, BMI 30.1 ± 7.8 kg/m²; ESS baseline 18.9 ± 3.4 ; cataplexy events/week baseline 26.2 ± 22.7) suffering from narcolepsy with cataplexy (as diagnosed by the ICSD-2 criteria) at a tertiary sleep centre in the UK. The participants had a total of 3,116 patient-months of sodium oxybate exposure and a median of 35.5 months (IQR 11.0–54.0) months of follow-up. ESS and cataplexy events significantly decreased (Δ ESS = -4.3 ± 4.4 to a final ESS of 14.5 ± 5.1 ; $P<0.0001$; Δ cataplexy = -21.8 ± 18.5 events/week to a final number of events/week of 4.4 ± 10.8 ; $P<0.0001$) (166).

The authors concluded that sodium oxybutate provided good clinical efficacy and safety for the routine treatment in patients with narcolepsy and cataplexy in line with previous studies (162–165,167), however, the tight regulation of its prescription in the UK means that the studied cohort likely represents patients with greater severity of narcolepsy and cataplexy.

Parasomnia

There have been many different approaches to study muscle activity during REM sleep with various different methods, undefined EMG features, and few patients (168–171) making it difficult to compare the results between studies; most used visual scoring. These methods are confounded by a lack of standardisation on what cut-off of muscle activity is considered pathological. Though automatic methods had been developed more recently (172–174), few have been validated (174,175).

Mayer *et al.* systematically analysed the impact of sodium oxybate on muscle tone in narcolepsy patients using a semi-automatic validated process (176) to assess muscle tone (177). The authors undertook a re-analysis of the polysomnographies of a previous international multicenter study (SXB-15) (178). This was a randomised, double-blinded phase 3 study of 116 patients with narcolepsy-cataplexy (placebo: $n=27$, 33.3% male, mean age 41.67 ± 17.49 years; dose 4.5 g: $n=34$, 38.2% male, mean age 41.35 ± 17.03 years; dose 6.0 g: $n=33$, 33.3% male, mean age 39.39 ± 17.11 years; dose 9.0 g: $n=22$, 45.5% male, mean age 38.27 ± 11.85 years) (177).

The authors reported a significant dose-dependent effect of sodium oxybate treatment on muscle activity throughout all sleep stages. REM duration decreased dose-dependently ($P<0.0005$) and over time ($P<0.0005$), with slow wave sleep increasing with higher doses ($P<0.001$). Short muscle activity indices and long muscle activity indices (LMI) decreased

significantly during light sleep, and LMI decreased significantly during REM sleep. A noted limitation of this study was the lack of healthy controls used for comparison in the analysis stages.

Polysomnographic features of catathrenia

Catathrenia, a rare rapid eye movement sleep parasomnia characterised by expiratory groaning and end-inspiratory apnoea, is a relatively new and poorly understood sleep phenomenon that can cause severe disturbance to patients and their partners (179,180). An understanding of the full clinical presentation, characteristics and implications of catathrenia remains largely unknown and thus there is little direction guiding successful therapeutic interventions. Drakatos *et al.* investigated the clinical and polysomnographic features of catathrenia in a polysomnographic study of the largest catathrenia patient group described in the literature to date ($n=38$, 60.5% males, mean age at diagnosis 33.1 ± 7.7 years, BMI 25.9 ± 5.3 kg/m², ESS 10.1 ± 5.3 points). The authors reported characteristic breathing patterns (deep inspiration followed by prolonged expiration and groaning) are present in this patient group. A key finding noted by the authors revealed that clusters of catathrenia events, known as catathrenia periods (CPs), which occurred predominantly during REM sleep, were mirrored by arousal on EEG. These CPs lasted longer than those not associated with EEG arousal (57.3 ± 56.8 compared to 32.2 ± 29.4 seconds; $P<0.001$). However, the authors were unable to identify the clinical significance and implications of these arousals. Key limitations of this study included the retrospective nature resulting in a lack of valuable information regarding symptom profiles and treatment outcomes for analysis. Moreover, with an overlap of sleep apnoea in some of the study population, the use of CPAP in these patients may have affected the study results and was not accounted for (181).

Restless leg syndrome (RLS) and limb movement

RLS, otherwise known as Willis-Ekbom disease, is a neurological sensorimotor condition that presents with uncontrollable movements of the lower limbs. These are typically at night, during rest, and associated with nocturnal dysaesthesia. The pathophysiology of RLS is not entirely understood (182,183). Diseases that impact on iron status may potentially contribute to RLS (184). However, the causal pathways and the best means to assess iron status in RLS remain unclear (185-188), as different studies tend to vary in study design, doses provided and the type of iron used for treatment.

Trenkwalder *et al.* compared the efficacy and tolerability of a single 1,000 mg infusion of intravenous iron, as ferric carboxymaltose (FCM), versus placebo (Pl), as a treatment for patients with RLS who also had low iron levels, but who were not anaemic. FCM was administered on day 1 over 15 ± 2 minutes. This was a prospective phase 4, double blind, placebo-controlled multicenter study with 12-weeks follow up. The primary efficacy end-point was the difference in change in the International Restless Leg Syndrome Severity Scale (IRLS) score at 4-weeks between FCM and placebo. There were 110 patients in total (mean $\pm$ SD age, 54.1 ± 15.8 years; 82% female), with 59 in the FCM group, and 51 in the placebo group. The groups had a similar age and gender characteristics (FCM: age 53.0 ± 15.7 years, 81% female; Pl: age 55.5 ± 15.9 years, 82% female) as well as baseline iron status (serum ferritin, FCM: 41.93 ± 34.55 μ g/L, Pl: 48.85 ± 45.95 μ g/L; transferrin saturation, FCM: $18.49\%\pm7.88\%$, Pl: $21.14\%\pm9.19\%$), and baseline IRLS scores (FCM: 25.9 ± 5.65 points, Pl: 26.0 ± 5.78 points) (189).

The FCM administration group had non-significant improvements in their IRLS score over placebo at 4 weeks [difference (95% CI), -2.5 (-5.93 to 1.02), $P=0.163$] and this difference reached significance at 12 weeks [-4.66 (-8.59 to -0.73), $P=0.021$]. Serum ferritin and TSAT level significantly increased in the FCM group compared to control ($P<0.001$). Baseline TSAT and IRLS improved with FCM treatment at week 4 ($r=0.37$; $P=0.006$) and at the end of study, i.e., week 12, or if terminated earlier ($r=0.28$; $P=0.031$). Serious adverse effects were reported in two patients, one from each group who were withdrawn from the study, but there were no hypersensitivity or anaphylactoid reactions (189).

The treatment regime for patients with RLS still remains an important area of further evaluation. Opioids can be effective in selected patient groups (190), and a number of non-opioid therapies, e.g., dopamine agonists and $\alpha 2\delta$ calcium channel ligands, tend to show initial beneficial treatment effect in RLS, but these might become less effective and even worsen symptoms with longer use (191-193). Although a causal link remains elusive, the current study supports a role of iron therapy replacement in RLS treatment and especially in improving symptoms by 12 weeks. Given the variation in the times at which individuals responded, and also the degree of response to treatment, the authors suggest that there are early *vs.* late

responders, and lack of response to iron replacement could represent specific patient phenotypes.

Given the lack of official consensus on treatment, in 2016, the International RLS Study Group (IRLSSG), the European RLS Study Group (EURLSSG) and the RLS Foundation have established a task force to review the current literature and develop guidelines for the prevention and treatment of RLS augmentation. The authors concluded that (I) $\alpha 2\delta$ ligands, which have minimal risk of augmentation, should be considered for initial treatment of RLS; (II) dopaminergic drugs, if selected for treatment, should be started at the lowest possible dose and not exceed the recommended dose for RLS; (III) patients with suboptimal iron levels, an exacerbating factor of augmentation, should be given iron supplementation; (IV) daily dopaminergic treatment should only be considered when symptoms severely impact quality of life (194).

Summary

Despite these exciting developments in sleep-related research in recent years, there remain many unknowns. The 3rd Clinical Update Sleep at the Royal College of Physicians will offer more insights and opportunities to discuss hot topics with experts, to network and get involved to educate the next generation of sleep research. We look forward to meeting you in London!

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