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CONTEMPORARY CONCISE REVIEW

Contemporary Concise Review 2019: Sleep and ventilation

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INTRODUCTION

Considerable progress has been made in the area of sleep and breathing.[1] We write this review to summarize a number of important topics with recent advances put into the context of the existing literature. While we recognize major progress in many different areas of sleep and ventilation, ranging from anatomic and non-anatomic pathophysiological mechanisms of obstructive sleep apnoea (OSA), nocturnal symptoms and hypoxaemia in pulmonary disease and positive airway pressure (PAP), we have focused on those felt to be most important and likely to affect clinical practice.[2–8]

OBSTRUCTIVE SLEEP APNOEA

Key Points

- OSA is caused by multiple pathophysiological mechanisms (endotypes) which may predict clinical sequelae (phenotypes) and response to targeted therapies. In the future, endo/phenotypes may help personalize OSA care and improve trial design.
- HGNS may be particularly effective in older patients without marked obesity and has been shown to retain efficacy at 5-year follow-up.
- Two new drugs, solriamfetol and pitolisant, have shown promise in the treatment of residual sleepiness in OSA patients.
- Big data analyses suggest that bi-level PAP improves treatment effectiveness in patients suboptimally treated with CPAP; new technologies such as patient engagement tools may also improve PAP adherence.

A recent literature-based analysis estimated that nearly 1 billion adults are affected globally by OSA.[9] Wide geographical variation exists but prevalence exceeds 50% in some countries. The definitions and equipment used to diagnose OSA have varied over the years and many countries have no epidemiological data available. Nonetheless, the recent report highlights the need for a global strategy to address this major burden of disease. Advances in technology and care delivery are ongoing that may have an important impact on OSA management.[10] In addition, we are strong proponents that comprehensive OSA management addresses not only continuous PAP (CPAP) therapy, but also diet, exercise and other lifestyle modifications.[11] A recent systematic review and meta-analysis highlighted the beneficial effects of lifestyle interventions in improving OSA severity.[12]

We focus on four major areas of progress based on recent literature:

1. OSA is no longer considered a homogeneous disease but rather has a variety of underlying mechanisms (endotypes) and varying clinical manifestations (phenotypes).[13,14] The recent findings of Mazzotti *et al.* confirm prior reports that OSA has varying clinical manifestations.[15] While some patients are relatively asymptomatic, others complain of fragmented sleep or insomnia, whereas still others suffer from excessive daytime sleepiness.[16] In Mazotti *et al.*'s analyses of the Sleep Heart Health Study, increased risk for both prevalent and incident cardiovascular events was seen mainly in adults with moderate-to-severe OSA who were excessively sleepy.[15] That is, those patients with excessive sleepiness appear to be most susceptible to cardiovascular risk. These new insights may provide a basis for subsequent clinical trials as some have argued that stratifying risk of cardiovascular complications will be critical to demonstrate benefits for interventions in OSA. In other words, sleepy patients at high cardiovascular risk may be most likely to experience benefits from PAP therapy; these patients have not been systematically defined in prior clinical trials. In fact, sleepy patients are often excluded from such studies for ethical reasons due to the assumed benefits observed with therapy in afflicted individuals, as illustrated in the Sleep Apnea Cardiovascular Endpoints (SAVE) and Randomized Intervention with CPAP in Coronary Artery Disease and OSA (RICCADSA) trials.[17,18] These randomized clinical trials showing no beneficial effect of CPAP on overall cardiovascular events in moderate-to-severe OSA excluded severely sleepy patients. Thus, it remains unknown whether in the excessively sleepy OSA

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phenotype a beneficial effect on cardiovascular outcomes might have been observed.[17–20] Ongoing efforts to understand OSA mechanisms may also help to develop personalized therapy for OSA and to improve clinical trial design. Emerging evidence suggests that the mechanism underlying apnoea may influence apnoea consequences, that is, endotype could predict phenotype in OSA.[21]

2. Advances in non-PAP therapy for OSA have recently occurred. Hypoglossal nerve stimulation (HGNS) was Food and Drug Administration (FDA)-approved in 2014 for the treatment of moderate-to-severe OSA in patients who are intolerant or have failed PAP and newer stimulation technologies are being developed to treat OSA in this context. Woodson *et al.* recently reported 5-year follow-up from the original Stimulation Therapy for Apnea Reduction (STAR) study showing persistent improvement in sleepiness, quality of life and apnoea–hypopnoea index (AHI) among the 97 patients who were available for follow-up.[22,23] Moreover, based on the data from a large multicentre registry, older age and lower body mass index (BMI) are predictive of HGNS response.[24] Furthermore, female sex had slightly better outcomes with HGNS as compared to men, but this finding did not reach statistical significance. The mechanisms underlying these predictors are unclear, but these data may help identify patients most suitable for HGNS. A recent small study demonstrated a reduction in loop gain with upper airway surgery in Chinese OSA patients, suggesting high loop gain may be acquired in OSA and a possible mechanistic target for therapeutics.[25] Traditionally, HGNS has been unilateral but Eastwood *et al.* recently reported on a novel bilateral HGNS without connective leads which reduced OSA severity (mean AHI decreased from 23.7 to 12.9/h) and improved daytime sleepiness as well as quality of life in a small cohort of afflicted patients at 6 months follow-up.[26] Of note, Walia *et al.* recently reported greater improvement in blood pressure with CPAP therapy as compared to HGNS.[27] In contrast, the subjective improvement in sleepiness was greater with HGNS compared to CPAP, again suggesting a role for an individualized approach to OSA therapy.
3. From the standpoint of pharmacology, several advances were reported in the past year. Two new drugs, solriamfetol and pitolisant, were approved in 2019 by the US FDA for the treatment of sleepiness in narcolepsy patients. In addition, solriamfetol was FDA-approved for the treatment of residual sleepiness in patients with OSA despite PAP therapy. Data suggest that up to 10–30% of patients with good adherence to PAP therapy may have residual sleepiness and be potentially amenable to pharmacological interventions.[28–30] Solriamfetol is a selective dopamine and norepinephrine reuptake inhibitor that has been shown in a randomized, placebo-controlled trial to improve sleepiness in OSA patients with excessive sleepiness in a dose-dependent response, with maintenance of efficacy now demonstrated at 1 year.[31–34] Pitolisant is a selective histamine H3-receptor inverse agonist, and it too was recently shown to improve subjective sleepiness in moderate-to-severe OSA patients over 12 weeks.[35] This study, however, excluded patients adherent with CPAP therapy. The mechanism underlying residual sleepiness in OSA is unclear but may include sleep disruption associated with PAP use, incomplete adherence to PAP, neurological injury related to prior untreated OSA or some combination of factors. Nonetheless, in clinical practice, the benefits of PAP therapy go beyond improving sleepiness and the use of wake-promoting pharmacotherapy to target selectively sleepiness alone without addressing the underlying cause raises concerns. Further data are clearly required to assess hard outcomes before widespread use of wake-promoting pharmacotherapy can be strongly advocated. In addition, there are no studies to date comparing the different wake-promoting agents in sleepy OSA patients.

   Regarding therapeutic pharmacotherapy for OSA, a recent study showed potential benefits of the combination of atomoxetine, a selective norepinephrine reuptake inhibitor, plus oxybutynin, an anti-muscarinic, for the treatment of OSA.[36] Based on the premise that norepinephrine drive is central to pharyngeal muscle tone and muscarinic activity to rapid eye movement (REM) sleep-related pharyngeal tone, the combination of atomoxetine and oxybutynin was hypothesized to cause an increase in genioglossus activity and reduce OSA severity. In this small study, the authors reported the results of overnight study showing improvements in the AHI and genioglossus muscle responsiveness, but longer term benefits on clinical outcomes are less clear. A multicentre study recently completed enrolment but the results are not yet available. Again, further data examining hard outcomes will be required before pharmacotherapy for OSA can be endorsed.
4. Technological advances have provided insights into the care of sleep apnoea patients. Cloud-based technologies allow the assessment of massive numbers of patients, although privacy issues prevent thorough characterization of the patients involved. A recent report in 2.62 million patients by Cistulli *et al.* showed 75% adherence with CPAP therapy based on US Medicare criteria at 3 months.[37] Several rescue strategies were also examined including the switch to adaptive servoventilation (ASV) therapy or the switch to bi-level PAP, both of which showed improvement in adherence and/or machine-detected events after versus prior to switch.[38,39] Similarly, Ishak *et al.* found bi-level PAP to be an effective alternative in improving adherence and symptoms in a cohort of OSA patients failing to adhere to CPAP with pressures >15 cm H_2O.[40] Patient engagement strategies have also been consistently shown to be associated with improved adherence to PAP therapy as compared to usual care, but confounding by healthy user bias cannot be excluded.[41,42]

   Remote delivery of OSA care is being increasingly facilitated by technological advances. Data suggest that remote monitoring of patients can occur in under-resourced areas.[43] The availability of cloud-based PAP monitoring systems has placed OSA management in a unique position for telemedicine,

but studies on the effects of telemedicine on PAP adherence have been mixed in different patient populations.[44–48] How best to incorporate telemedicine in the management of OSA remains to be determined.[49] Moreover, wearable technologies are being developed to improve the care of patients with sleep complaints.[50] Ongoing efforts may change the current paradigm of healthcare delivery to address the large burden of OSA patients, given that the majority remain undiagnosed and untreated.

NON-INVASIVE VENTILATION

Key Points

- High-intensity NIV, with the aim of lowering the partial arterial carbon dioxide pressure ($PaCO_2$), improves outcomes in stable persistently hypercapnic COPD patients.
- For patients with stable CF, NIV plus oxygen may be superior to oxygen alone, but more data are needed before firm conclusions can be reached.
- Volume-assured pressure support may be beneficial in neuromuscular conditions with progressively changing ventilation needs; auto-titration of expiratory PAP appears equivalent to manual titration.
- In stable OHS with severe OSA, initiation of therapy with bi-level PAP has not been consistently shown to confer benefits over CPAP, but by better defining clinical phenotypes of OHS, PAP management may improve.

Non-invasive ventilation (NIV) has proven benefits both during acute illness and for chronic disease management.[51] The bulk of the supportive data in the chronic setting are for the treatment of hypoventilation including neuromuscular disease and chest wall disorders, hypercapnic chronic obstructive pulmonary disease (COPD) and obesity hypoventilation syndrome (OHS). In our experience, clinical management of these patients is quite variable and potential room for improvement exists in their care.[52] We have chosen few points to emphasize based on recent literature.

1. Recent evidence now supports use of NIV in stable, chronic hypercapnic severe COPD patients. The use of high-intensity NIV with a goal of improving hypercapnia has shown improved outcomes in randomized trials.[53,54] Kohnlein *et al.* showed improved mortality in chronic hypercapnic COPD by lowering $PaCO_2$ levels as compared to usual care.[55] More recently, Murphy *et al.* showed reduced risk of COPD readmission or death within 12 months with NIV and oxygen as compared to oxygen alone in patients with persistent hypercapnia following a COPD exacerbation.[56] The combination of OSA plus COPD (so-called overlap syndrome) has not been the subject of randomized trials, although the observational data suggest a poor prognosis for those afflicted.[57] Our clinical practice typically includes a sleep assessment in COPD patients, particularly in those with disproportionate hypercapnia.[58] Whether NIV offers additional benefits over CPAP in this group is currently unknown but we favour use of NIV in hypercapnic COPD both in the acute and longer term setting. How best to initiate and titrate NIV, including use and incorporation of technological advances in monitoring systems are areas in need of research.[59]
2. For patients with cystic fibrosis (CF), 2019 was a landmark year given major advances in pharmacotherapy for these patients.[60] The care of these patients is rapidly changing with 'dry CF' now being a diagnosis frequently provided to patients who previously had recurrent exacerbations and hospitalizations. A recent randomized trial by Milross *et al.* was reported comparing the outcomes of nocturnal NIV plus oxygen versus oxygen alone in stable CF with sleep desaturation.[61,62] The authors performed a pilot study in 29 patients to assess the impact of their interventions on event-free survival, with events defined as failure of therapy with hypercapnia >60 or 10 mm Hg increase from baseline, >10 mm Hg increase in transcutaneous CO_2, lung transplantation or death. The authors observed that the NIV plus oxygen had an improved event-free survival at 12 months compared to oxygen alone. NIV was also recently explored as an adjunct to usual airway clearance techniques (ACT) in a small study of hospitalized CF patients improving from a pulmonary exacerbation.[63] While no difference in 24-h expectorated sputum wet weight was seen between NIV-supported ACT and ACT alone, the study was underpowered. The impact of these studies is unclear particularly given the changing landscape of CF, but further efforts into defining subgroups likely to respond to NIV therapy would be encouraged.[64]
3. Regarding neuromuscular disease, newer technologies including iVAPS (intelligent volume-assured pressure support) and AVAPS (average volume-assured pressure support) have been developed that automatically adjust pressure support within a defined range to target a pre-set level of ventilation for patients with hypoventilation. To our knowledge, there are no long-term randomized trials convincingly showing benefit to the volume-targeted pressure support approaches as compared to standard bi-level therapy.[65] However, we do sometimes use these newer technologies based on theoretical benefits. Of note, the mechanics of the respiratory system frequently change in progressive neuromuscular disease, such that volume assurance can be helpful to avoid deterioration in gas exchange with disease progression. On the other hand, the reassurance provided by the technology should not be a substitute for close clinical follow-up. A recent study examined the role of NIV technology with an automatically adjusting expiratory PAP algorithm (auto-EPAP) on a single night in chronic respiratory failure patients with established coexisting OSA and found satisfactory results using this technology.[66] Clearly, additional longer term studies looking at hard outcomes are needed before adoption of new technologies can be strongly recommended.[67] Research on

such technologies is, however, always challenged by both the wide range of devices and settings available. An assessment for need of respiratory adjuncts to NIV to assist with cough, impaired secretion clearance, speech and aspiration is also required in the comprehensive and individualized management of neuromuscular patients.[68,69]

4. Obesity continues to rise but despite the clear association between obesity and OHS, OHS frequently goes undiagnosed.[70] 10–20% of obese OSA patients undergoing evaluation have OHS as an underlying diagnosis.[71] In fact, among patients with BMI >40 kg/m^2, roughly 30% of patients have OHS. Despite this knowledge, the diagnosis of OHS is relatively uncommon. The use of serum bicarbonate as a screening test can be helpful to prioritize on which patients to consider daytime arterial blood gas sampling.[72] The argument has been ongoing about whether the diagnosis of OHS versus OSA actually changes clinical management. OHS has been associated with somewhat worse outcomes than OSA alone; however, the interventional data comparing CPAP versus bi-level PAP therapy are more mixed. A prior study in *Chest* suggested 43% of CPAP titrations have residual respiratory compromise using CPAP alone.[73] However, a recent randomized trial reported in *The Lancet* showed no significant difference in outcomes including gas exchange and adherence using bi-level therapy (volume-assured pressure support approach), compared to CPAP in patients with stable OHS and severe OSA.[74,75]

However, a number of points deserve emphasis. First, several studies have shown that a major proportion of OHS patients present decompensated in the intensive care unit, making the recent *Lancet* findings not applicable to such patients.[76,77] A recent American Thoracic Society (ATS) clinical practice guideline on the evaluation and management of OHS recommended acute NIV therapy for these patients with hospital to home transition until they can undergo outpatient diagnostic testing.[72] Second, some suggestive data have shown potential improvements in pulmonary haemodynamics with bi-level as compared to standard CPAP, suggesting that an OHS diagnosis may change management in some cases.[78] Third, the majority of randomized trials comparing bi-level to CPAP have studied OHS patients with coexistent severe OSA. These findings cannot be extrapolated to the approximate 10% of OHS patients without OSA and similar to OSA, further clinical phenotyping of obese patients with hypercapnic respiratory failure is suggested in future therapeutic trials.[56,79] Finally, our clinical practice has been to manage obesity aggressively in OHS, with many patients undergoing evaluation for bariatric surgery. The recent ATS clinical practice guidelines similarly recommended weight loss interventions that produce a sustained weight loss of 25–30% of actual weight in those afflicted.[80,81]

SUMMARY

Major progress is occurring in the area of sleep and breathing. Efforts in basic science, applied physiology and clinical trials are making an important impact on patient care. Further advances are likely to occur with coordinated multidisciplinary approaches by embracing new technology and by addressing individual patient-reported outcomes.

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Abbreviations: ACT, airway clearance technique; AHI, apnoea–hypopnoea index; ATS, American Thoracic Society; CF, cystic fibrosis; CPAP, continuous PAP; FDA, Food and Drug Administration; HGNS, hypoglossal nerve stimulation; NIV, non-invasive ventilation; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnoea; PAP, positive airway pressure.

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