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GUEST EDITORIAL

Drug therapy for obstructive sleep apnea: From pump to pill?☆

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It is 38 y since the first description of CPAP treatment for Obstructive Sleep Apnoea (OSA) in 1981 [1]. What started as a research tool became a clinical treatment that transformed and saved lives, and uncovered the public health significance of OSA [2]. A recent estimate suggests that there are one billion suffers of OSA across the globe [3]. Despite the challenges associated with CPAP, particularly around patient acceptance and compliance, it has remained the treatment of choice because it is highly efficacious at resolving upper airway obstruction, regardless of the site and severity of collapse. In this sense it is an omnipotent therapy. However, a recent systematic review of 82 clinical trials indicated that the rate of CPAP adherence has remained persistently modest over the last 20 y [4]. This has spurred the search for alternative therapies to enhance patient and societal outcomes related to this major health problem.

The ultimate goals in the treatment of OSA are to prevent obstructive apnoeas and hypopneas and related physiological perturbations (intermittent hypoxia, arousals, exaggerated intrathoracic pressure swings), to improve symptoms and quality of life, and to attenuate the risk of chronic diseases (including hypertension, cardiometabolic diseases, and cognitive decline). Among the alternative management options are device-based therapies (oral appliances, position therapy, hypoglossal nerve stimulation), weight loss (medical or surgical), exercise (general and oral), and surgery to relieve or bypass upper airway obstruction [5]. A common theme with alternative therapies is that they tend to have unpredictable therapeutic effects, being only modestly efficacious on average, and with only a subgroup of patients showing an optimal response to therapy. This limitation may be turned into an advantage if we can define patient characteristics that predict a good response to a given therapy.

Pharmacotherapy for treating OSA is a highly attractive proposition, but it has been an elusive goal to date [6]. There is currently insufficient evidence to recommend any specific drug for OSA. Since the early descriptions of OSA there have been numerous attempts to study drugs for their utility in resolving or improving OSA. In retrospect such efforts have been somewhat haphazard, and they have not followed the traditional systematic path to drug discovery and testing. In large part this has stemmed from gaps in our understanding of the pathophysiology of OSA, although suboptimal metrics of the burden of OSA and lack of realistic animal models have contributed to the generally disappointing findings to date. This 50-y history has been well documented in this issue of Sleep Medicine Reviews in the paper by Gaisl et al. [7] who performed a systematic review and network meta-analysis of randomised controlled trials (RCTs) of drug therapies explored in OSA. They provide a comprehensive qualitative summary of the evidence in the field and identified 58 RCTs in which 44 different drugs or drug combinations were studied across 1710 patients. Unsurprisingly, their analysis demonstrates extreme heterogeneity of drugs across trials and small effect sizes, with poor reporting and underpowering being common themes. A common pitfall, particularly among earlier studies, was the use of unselected patient groups. Furthermore, the largest AHI reduction was seen in mild to moderate OSA, perhaps implying that the best we can hope for is an adjunctive role of drug therapy. Even if pharmacotherapy may not cure OSA per se, it may still enhance the effectiveness of, and adherence to, existing established treatments.

They were able to conduct a meta-analysis of 17 trials for seven drugs (acetazolamide, donepezil, mirtazapine, ondansetron, paroxetine, protriptyline, theophylline) and found a small effect for acetazolamide. The network meta-analysis of 51 RCTs (44 different drugs or combinations) found nine drugs (tramazoline, liraglutide, spironolactone/furosemide, acetazolamide, dronabinol, zonisamide, phentermine, spironolactone, and ondansetron/fluoxetine) that significantly lowered the AHI compared to placebo. An important consideration is that the vast majority of studies used AHI as the outcome measure. For too long the field has applied a 'one-size-fits-all' approach to OSA diagnosis and management. There is now growing awareness that OSA is a heterogeneous disorder and that the underlying mechanisms (i.e., endotype) and clinical manifestations (i.e., phenotype) may vary between patients, and they are not well captured by the AHI [8]. Gaisl et al. [7] found that only a few trials assessed additional clinically relevant outcomes e.g., sleepiness, quality of life, or blood pressure. There is a growing chorus against the utility of the AHI and the need to shift to more robust measures that better capture the burden of OSA and the effectiveness of therapy over the entire sleep period [6]. Such efforts by the field are critical in setting a more robust framework for evaluating the effectiveness of new therapies.

A novel and important aspect of the review by Gaisl et al. [7] was the attempt to classify drugs according to the underlying

☆ **Editorial on:** Efficacy of pharmacotherapy for OSA in adults: a systematic review and network meta-analysis. Thomas Gaisl, Sarah R. Haile, Sira Thiel, Martin Osswald, Malcolm Kohler. PII: S1087-0792(19)30050-4. DOI: https://doi.org/10.1016/j.smrv.2019.04.009.

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mechanisms being targeted. Although this is challenging as certain drugs may impact on a variety of mechanisms, the analysis moves us in the direction of personalised medicine, whereby specific mechanisms are targeted by a drug or drug combination in an appropriately selected patient [5]. They included mechanistic targets such as muscle tone, airway diameter, mucosal surface, ventilatory drive ('loop gain'), and arousal threshold. It is noteworthy that systematic work has gone into mapping potential drug targets in the circuitry controlling upper airway motor output [9], and an animal study showed improved upper airway patency using a chemogenetic approach by deploying designer receptors exclusively activated by designer drug (DREADD) in the hypoglossal motorneurons [10]. It has really been the advent of new knowledge on non-anatomical endotypes, and particularly low arousal threshold, impaired upper airway muscle responsiveness, and ventilatory instability (high loop gain) that has opened up new druggable targets [11]. It is thought that in approximately one third of OSA patients these non-anatomical traits are important for OSA pathogenesis, and that these patients may particularly benefit from a non-CPAP approach to therapy [12]. Drug therapy may find a niche in this subgroup of patients. Pharmacotherapy to raise the arousal threshold (eg. eszopicone [13]), to enhance muscle responsiveness (eg. desipramine [14]), and to dampen loop gain (eg. acetazolamide [15]) are available, and proof-of-concept studies have been encouraging. However, these studies usually involve acute experimental designs, small samples, and are performed across a single night. It is encouraging to see that longer-term and larger scale studies are starting to be reported [16]. As the tools for measuring these endotypes and phenotypes in an efficient and cost-effective manner within the clinic context emerge, it will enhance the prospects of delivering clinically effective targeted drug therapies.

The review of Gaisl [7] et al. did not consider trials investigating pharmacological treatment of OSA-associated conditions (e.g., hypertension, cardiovascular consequences, excessive daytime sleepiness). Importantly, drug therapy can target other components of OSA, beyond pathophysiological factors, including symptoms (eg. sleepiness [17]), comorbidities (eg. hypertension [18–20]), and subclinical cardiometabolic dysfunction. The cardinal perturbations of OSA (intermittent hypoxia, arousals, and exaggerated intrathoracic pressure swings) drive a diversity of adverse physiologic and biochemical sequelae including systemic inflammation, oxidative stress, increased chemoreceptor reflex activity, sympathetic nervous system activation, and endothelial dysfunction, and these are all amenable to targeted drug therapy. Although many pharmacologic agents could fit this purpose, the case for statins, antioxidants, and angiotensin receptor antagonists has recently been put forward [21]. Moreover, a potential influence of genetic risk factors in the responsiveness to treatment, including drug therapy, warrants further research.

The field is now poised to capitalise on the opportunity to finally reach the holy grail of drug therapy for OSA. The tools, candidate targets and drugs are available, and the barriers are reasonably well understood. The task ahead is to develop a strategic approach to experimentation and clinical trials. To this end it is highly encouraging to see industry-sponsored trials now underway [22,23], and this activity augers well for rapid advances in the field. This represents a shift from the off-label use of existing drugs, to specifically designed substances for the sole purpose of treating OSA and its related components. Given the heterogeneity of OSA, it is very unlikely that an omnipotent drug for all OSA patients will ever be found. However, there is the very real prospect of targeted drug therapies (mono-drug or combination [24]) for specific patient phenotypes. For this to be realised we need to overcome the deficiencies of our past efforts by choosing selection criteria based on relevant phenotypes, by introducing more robust outcome measures, by considering an appropriate comparator, and by adequate powering of studies. There is also a pressing need for the field to develop a consensus for standardised reporting of diagnostic criteria and outcome measures. Whether the pump (CPAP) will ever be replaced by the pill remains to be seen!

Conflicts of interest

PAC holds an endowed academic chair at the University of Sydney that was established through funding from ResMed. He is also a consultant to ResMed. The relationship is managed by an independent oversight committee of the University of Sydney, and he receives no personal fees. He is an investigator in a Bayer-sponsored drug trial for OSA. He has received research support from ResMed, SomnoMed, and Zephyr Sleep Technologies, and has provided advisory services to Zephyr Sleep Technologies, Narval, and SomnoMed.

JH has received and administered grants to the European Sleep Apnea Data Base (ESADA) office from ResMed, Philips, and from the European Respiratory Society (CRC-grant). He has served on the speakers' bureaus for Philips Respironics, ResMed, Weinmann GmbH, and BresoTec. He has provided expert consultant services for AstraZeneca, Itamar, Jazz Pharmaceuticals, Merck Pharmaceuticals, Desitin and SomnoMed. He serves as a board member for Cereus Pharma.

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