References

1. Hassoun PM. Pulmonary arterial hypertension. *N Engl J Med* 2021;385: 2361–2376.
2. Hemnes AR, Zhao M, West J, Newman JH, Rich S, Archer SL, *et al.* Critical genomic networks and vasoreactive variants in idiopathic pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2016;194: 464–475.
3. Rhodes CJ, Otero-Nunez P, Wharton J, Swietlik EM, Kariotis S, Harbaum L, *et al.* Whole-blood RNA profiles associated with pulmonary arterial hypertension and clinical outcome. *Am J Respir Crit Care Med* 2020; 202:586–594.
4. Hong J, Arneson D, Umar S, Ruffenach G, Cunningham CM, Ahn IS, *et al.* Single-cell study of two rat models of pulmonary arterial hypertension reveals connections to human pathobiology and drug repositioning. *Am J Respir Crit Care Med* 2021;203:1006–1022.
5. Newman JH, Rich S, Abman SH, Alexander JH, Barnard J, Beck GJ, *et al.* Enhancing insights into pulmonary vascular disease through a precision medicine approach. A joint NHLBI-Cardiovascular Medical Research and Education Fund workshop report. *Am J Respir Crit Care Med* 2017; 195:1661–1670.
6. Hemnes AR, Beck GJ, Newman JH, Abidov A, Aldred MA, Barnard J, *et al.* PVDOMICS: a multi-center study to improve understanding of pulmonary vascular disease through phenomics. *Circ Res* 2017;121: 1136–1139.
7. Harbaum L, Rhodes CJ, Wharton J, Lawrie A, Karnes JH, Desai AA, *et al.* Mining the plasma proteome for insights into the molecular pathology of pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2022;205: 1449–1460.
8. Harbaum L, Ghataorhe P, Wharton J, Jimenez B, Howard LSG, Gibbs JSR, *et al.* Reduced plasma levels of small HDL particles transporting fibrinolytic proteins in pulmonary arterial hypertension. *Thorax* 2019;74: 380–389.
9. Rhodes CJ, Batai K, Bleda M, Haimel M, Southgate L, Germain M, *et al.* Genetic determinants of risk in pulmonary arterial hypertension: international genome-wide association studies and meta-analysis. *Lancet Respir Med* 2019;7:227–238.
10. Rhodes CJ, Ghataorhe P, Wharton J, Rue-Albrecht KC, Hadinnapola C, Watson G, *et al.* Plasma metabolomics implicates modified transfer RNAs and altered bioenergetics in the outcomes of pulmonary arterial hypertension. *Circulation* 2017;135:460–475.
11. Forbes T, Pauza AG, Adams JC. In the balance: how do thrombospondins contribute to the cellular pathophysiology of cardiovascular disease? *Am J Physiol Cell Physiol* 2021;321:C826–C845.
12. Schroen B, Heymans S, Sharma U, Blankesteijn WM, Pokharel S, Cleutjens JP, *et al.* Thrombospondin-2 is essential for myocardial matrix integrity: increased expression identifies failure-prone cardiac hypertrophy. *Circ Res* 2004;95:515–522.

Drug Therapy for Obstructive Sleep Apnea: Are We There Yet?

Obstructive sleep apnea (OSA) is highly prevalent and can lead to major neurocognitive and cardiovascular impairments (1). Once believed to be a purely anatomical problem, it is now clear that nonanatomical factors (endotypes) are necessary for OSA to develop in up to 70% of patients (1–3). This paradigm shift has set the stage for increasingly promising research into endotype-targeted pharmacotherapies, which are urgently needed to help the many patients with OSA who are unable or unwilling to use current treatment options such as continuous positive airway pressure (CPAP) (4).

One strategy is to augment insufficient upper airway dilator muscle tone during sleep via drugs with combined adrenergic and antimuscarinic effects. In a landmark study by Taranto-Montemurro and colleagues, one dose of atomoxetine-oxybutynin at bedtime improved OSA severity as measured by the apnea–hypopnea index (AHI) by 63% (−16 events/h) (5). But it remains to be seen whether longer-term use of these or similar drugs maintains efficacy and, importantly, whether these reductions of the AHI (a surrogate outcome) translate into improved clinical outcomes. At least in theory, adrenergic medications may disrupt sleep quality and could have net adverse effects on cardiovascular health by increasing sympathetic tone despite improving OSA.

Another line of investigation aims to improve unstable ventilatory control (high loop gain), which is not only a driver of central sleep apnea but also a major contributor to OSA pathogenesis in 30–40% of patients (2). An individual with high loop gain tends to have periodic drops in respiratory drive that result in reduced activation of upper airway dilator muscles and thus can directly lead to repetitive respiratory events (i.e., OSA). One important regulator of ventilation is CA (carbonic anhydrase), which has 15 different isoforms that are ubiquitous in human tissues including kidneys, erythrocytes, endothelium, and central/peripheral chemoreceptors (6–8). By inducing a renal metabolic acidosis and other complex effects (7), CA inhibitors (CAIs) such as acetazolamide augment ventilation, which dampens fluctuations in CO_2 and thus respiratory drive (i.e., lower loop gain) (9). Consequently, acetazolamide has been found to reduce the AHI in patients with sleep apnea on average by ∼38% (−14 events/h) based on a meta-analysis of 26 small studies (10). Of note, effects were similar in obstructive and central sleep apnea, and a subsequent meta-analysis using a different methodology reported a nonsignificant but similar effect size for OSA (AHI −10 events/h), supporting the findings of the former analysis (10–12).

However, acetazolamide is just one among dozens of CAIs, which vary somewhat in their affinity for the different CA isoforms and tissues, likely explaining a portion of the variability of clinical

C.N.S. is supported by the ATS Foundation (ASPIRE Fellowship). A.M. is supported by the National Institutes of Health.

Originally Published in Press as DOI: 10.1164/rccm.202202-0301ED on March 23, 2022

effects across CAIs (6, 8). For example, the CAIs zonisamide and topiramate are clinically used for epilepsy and weight loss management, which may be predicted by their effects on CA isoforms II/IIV (affecting pH and ionic composition of neurons) and VA/VB (involved in lipogenesis and gluconeogenesis), respectively. Yet despite similar affinities for these CA isoforms, acetazolamide has limited antiepileptic and antiobesity benefits (8). Given that obesity is a strong risk factor for OSA (1), and the complexity of how inhibition of different CA isoforms in different tissues can affect ventilatory control (7), one may wonder if CAIs differ with regard to their potential therapeutic value for sleep apnea. So far, two prior studies suggested relatively similar effects across CAIs. First, in a study of obese patients with OSA, 8 weeks of topiramate plus phentermine resulted in a placebo-adjusted AHI reduction by 37% (−16 events/h) (13). Second, a study by Eskandari and colleagues found that 4 weeks of zonisamide reduced the AHI in patients with OSA on average by 33% (−9 events/h) (14). However, these studies of CAIs showed high variability in interindividual response, ostensibly reflecting the variability to which loop gain contributes to sleep apnea pathogenesis in different individuals. These studies were further limited by short-term usage (⩽4 wk) and few data on clinical outcomes, although some data suggest that cardiovascular benefits may be more pronounced with CAIs than with CPAP for OSA (10, 14).

In the current issue of the *Journal*, Hedner and colleagues (pp. 1461–1469) present interesting findings from an industry-funded dose-finding phase II trial exploring safety (primary objective) and efficacy of a fourth CAI—sulthiame—for OSA (15). In brief, 68 adults with moderate/severe OSA who had abandoned CPAP therapy were randomized to 4 weeks of sulthiame or placebo. Following prespecified procedures, subjects in the sulthiame arm were randomized to either 200 mg ($n = 12$) or 400 mg ($n = 34$). Sulthiame's CA affinity profile greatly overlaps with that of acetazolamide, zonisamide, and topiramate (6, 8); thus, many of the findings were expected based on the prior studies. For example, side effects were more common with higher doses, were mostly mild and transient (causing study discontinuation in six patients without serious events), and included paresthesias, dyspnea, gastrointestinal upset, fatigue, and dysgeusia (13, 14, 16). Furthermore, similar to other CAIs, the relative AHI reduction was −32% and −41% with sulthiame 200 mg and 400 mg, respectively. However, the absolute AHI reduction by −21 and −22 events/h in the two sulthiame groups is remarkable compared with prior drug studies, including atomoxetine-oxybutynin. But most surprising and noteworthy is the consistency of the effect across individuals shown in Figure 2 of the article: unlike the marked heterogeneity seen with other CAIs, almost all subjects experienced pronounced AHI reductions of similar magnitude with sulthiame.

Using average AHIs from two PSGs at baseline and follow-up was a methodological strength, which likely reduced measurement errors and thus variance. Furthermore, the authors suggest that sulthiame may be a more efficient respiratory stimulant (and thus loop gain–lowering agent) than other CAIs, potentially explaining its more consistent and pronounced effects. Another potential explanation is that the eligibility criteria used (e.g., body mass index < 35 kg/m^2, CPAP abandonment) may have favored enrollment of patients with high loop gain who are expected to respond more vigorously to loop gain–lowering therapy. Furthermore, the similar effects in rapid eye movement (REM) and non-REM sleep suggest that sulthiame may also have beneficial effects on factors other than loop gain (which contributes less to OSA pathogenesis during REM sleep) (17, 18). Future endotyping at baseline and follow-up in this and other CAI trials could provide important insights into these underlying mechanisms.

One notable finding of this trial is that despite the substantial AHI reductions from sulthiame, few patients (fewer than five) achieved resolution of OSA (e.g., AHI $<$ 10–15 events/h). Although the effective AHI reduction from gold standard therapy with CPAP is also often incomplete once taking variable adherence into account (14), the high residual AHI in this trial suggests that sulthiame should perhaps be reserved for patients with milder OSA and/or combined with other interventions. Ultimately, improvements in hard outcomes will be required for new interventions such as sulthiame to be embraced clinically. The lack of improvements in clinical outcomes in the current study may be related to the relative short treatment period or the high residual OSA burden but could also reflect adverse effects from CAIs. For example, fatigue may adversely affect measures of quality of life (16), or inhibition of central nervous system CA can potentially impair neurocognitive function (8). Thus, as suggested by the authors, longer-term studies of sulthiame including rigorous assessments of clinical outcomes would be welcome. In conclusion, we are "not there yet," but this study by Hedner and colleagues is likely another milestone in our journey toward developing pharmacotherapy for OSA. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Christopher N. Schmickl, M.D., Ph.D.
Division of Pulmonary, Critical Care, and Sleep Medicine
University of California San Diego
San Diego, California

Bradley A. Edwards, Ph.D.
School of Biomedical Sciences and Biomedical Discovery Institute
and
Turner Institute for Brain and Mental Health
Monash University
Melbourne, Victoria, Australia

Atul Malhotra, M.D.
Division of Pulmonary, Critical Care, and Sleep Medicine
University of California San Diego
San Diego, California

ORCID ID: 0000-0001-5417-9980 (C.N.S.).

References

1. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet* 2014;383:736–747.
2. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *Am J Respir Crit Care Med* 2013;188: 996–1004.
3. Schmickl CN, Owens RL, Edwards BA, Malhotra A. OSA endotypes: what are they and what are their potential clinical implications? *Curr Sleep Med Rep* 2018;4:231–242.

4. Pépin JL, Bailly S, Rinder P, Adler D, Szeftel D, Malhotra A, *et al.*; On Behalf of the medXcloud Group. CPAP therapy termination rates by OSA phenotype: a French nationwide database analysis. *J Clin Med* 2021;10:936.
5. Taranto-Montemurro L, Messineo L, Sands SA, Azarbarzin A, Marques M, Edwards BA, *et al.* The combination of atomoxetine and oxybutynin greatly reduces obstructive sleep apnea severity: a randomized, placebo-controlled, double-blind crossover trial. *Am J Respir Crit Care Med* 2019;199:1267–1276.
6. Temperini C, Innocenti A, Mastrolorenzo A, Scozzafava A, Supuran CT. Carbonic anhydrase inhibitors. Interaction of the antiepileptic drug sulthiame with twelve mammalian isoforms: kinetic and X-ray crystallographic studies. *Bioorg Med Chem Lett* 2007;17:4866–4872.
7. Swenson ER. Carbonic anhydrase inhibitors and ventilation: a complex interplay of stimulation and suppression. *Eur Respir J* 1998;12:1242–1247.
8. Supuran CT. Carbonic anhydrases: novel therapeutic applications for inhibitors and activators. *Nat Rev Drug Discov* 2008;7:168–181.
9. Schmickl CN, Landry S, Orr JE, Nokes B, Edwards BA, Malhotra A, *et al.* Effects of acetazolamide on control of breathing in sleep apnea patients: mechanistic insights using meta-analyses and physiological model simulations. *Physiol Rep* 2021;9:e15071.
10. Schmickl CN, Landry SA, Orr JE, Chin K, Murase K, Verbraecken J, *et al.* Acetazolamide for OSA and central sleep apnea: a comprehensive systematic review and meta-analysis. *Chest* 2020;158:2632–2645.
11. Ni YN, Yang H, Thomas RJ. The role of acetazolamide in sleep apnea at sea level: a systematic review and meta-analysis. *J Clin Sleep Med* 2021;17:1295–1304.
12. Amrhein V, Greenland S, McShane B. Retire statistical significance. *Nature* 2019;567:306–307.
13. Winslow DH, Bowden CH, DiDonato KP, McCullough PA. A randomized, double-blind, placebo-controlled study of an oral, extended-release formulation of phentermine/topiramate for the treatment of obstructive sleep apnea in obese adults. *Sleep (Basel)* 2012;35:1529–1539.
14. Eskandari D, Zou D, Karimi M, Stenlöf K, Grote L, Hedner J. Zonisamide reduces obstructive sleep apnoea: a randomised placebo-controlled study. *Eur Respir J* 2014;44:140–149.
15. Hedner J, Stenlöf K, Zou D, Hoff E, Hansen C, Kuhn K, *et al.* A randomized controlled clinical trial exploring safety and tolerability of sulthiame in sleep apnea. *Am J Respir Crit Care Med* 2022;205:1461–1469.
16. Schmickl CN, Owens RL, Orr JE, Edwards BA, Malhotra A. Side effects of acetazolamide: a systematic review and meta-analysis assessing overall risk and dose dependence. *BMJ Open Respir Res* 2020;7: e000557.
17. Landry SA, Andara C, Terrill PI, Joosten SA, Leong P, Mann DL, *et al.* Ventilatory control sensitivity in patients with obstructive sleep apnea is sleep stage dependent. *Sleep (Basel)* 2018;41:zsy040.
18. Messineo L, Eckert DJ, Taranto-Montemurro L, Vena D, Azarbarzin A, Hess LB, *et al.* Ventilatory drive withdrawal rather than reduced genioglossus compensation as a mechanism of obstructive sleep apnea in REM sleep. *Am J Respir Crit Care Med* 2022;205: 219–232.