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Reply to Chen *et al.*

From the Authors:

We thank Dr. Chen and collaborators for their positive comments on our randomized controlled trial, which explored the carbonic anhydrase inhibitor sulthiame (STM) in obstructive sleep apnea (OSA) (1). Indeed, the study was the first to demonstrate a reduction of OSA severity after STM and, in addition, to demonstrate one of the strongest effects ever shown by a single drug administered for an extended period of 4 weeks. The study was designed to explore safety and tolerability, and the clinical effect encompassed several polysomnographic metrics, including improved overnight saturation, reduced arousal frequency, and improvement of sleep quality. In addition, a trend toward improved metabolic function was observed after STM. On the other hand, the data were inconclusive in terms of daytime symptomatic effects on, for example, sleepiness. Failure to demonstrate reduced sleepiness may, as pointed out by Chen and colleagues, have several explanations, including treatment duration and study size. A clinical development program including the ongoing FLOW study (a 12-week, multicenter, randomized, double-blind, placebo-controlled, dose-finding, four-arm, parallel-assignment study) has been sized to address the safety and efficacy of STM in OSA on respiratory function as well as OSA-associated symptoms and potential effects on cardiovascular and metabolic function (NCT 05236842). Studies in this field are advancing, and these areas of research and results so far are certainly promising (2).

In their letter, Chen and colleagues point to the solid theoretical basis for exploring long-term treatment effects on OSA within this drug class. Indeed, research has provided data showing a dampening effect of carbonic anhydrase inhibition (e.g., acetazolamide) on loop gain, a mechanism that contributes substantially to the pathogenesis of OSA (3). For STM, a direct central respiratory–stimulating effect and reanimation of upper airway muscle tone may also contribute to this striking improvement. A further step to evaluate the therapeutic effects of carbonic anhydrase inhibition might be to link blood- or tissue-borne carbonic anhydrase activity to the degree of hypoxic burden or to other metrics of apnea severity (4, 5).

Finally, Chen and colleagues also speculate on the position and clinical application of a drug such as STM in therapy for OSA. We agree that phenotyping of subjects with OSA may certainly enable early recognition of patients with OSA who may benefit most from STM treatment. We speculate that a future target group for STM treatment might include patients with metabolic derangement, residual apnea after treatment of positive airway pressure, mandibular advancement devices, or upper airway surgery and that STM may be combined with other therapies (6). ■

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Selecting the Right Patient: The Achilles Heel of COPD Clinical Trials

To the Editor:

We read with interest the article by Wise and colleagues which reported that, in 2020, patients with moderate chronic obstructive pulmonary disease (COPD) and emphysema, the angiotensin II receptor blocker losartan administered over 48 weeks did not prevent emphysema progression (1). Several previous studies suggested a potential benefit from angiotensin receptor blockers, as well as angiotensin-II receptor blocker losartan inhibitors, in delaying the progression of COPD-related pulmonary and systemic pathologies

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