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Acetazolamide for OSA and Central Sleep Apnea

A Comprehensive Systematic Review and Meta-Analysis

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BACKGROUND: Therapy options for OSA and central sleep apnea (CSA) are limited, thus many patients remain untreated. Clinically, acetazolamide is sometimes used for CSA; however, given overlapping pathophysiologic properties of OSA and CSA, we hypothesized that acetazolamide is equally effective for both types. Prior reviews focused on specific subtypes of sleep apnea, study designs, and languages, thus including few studies (typically ≤3) limiting insights.

RESEARCH QUESTION: How efficacious is acetazolamide for sleep apnea, and is its effect modified by sleep apnea type or acetazolamide dose?

STUDY DESIGN AND METHODS: We queried MEDLINE, EMBASE, and ClinicalTrials.gov from inception until March 11, 2019. Any study in which adults with OSA/CSA received oral acetazolamide vs no acetazolamide (control) that reported sleep apnea-related outcomes was eligible, independent of study design or language. Two reviewers independently assessed eligibility and abstracted data. Primary outcomes were apnea-hypopnea index (AHI) and oxygen saturation nadir. Quality of evidence (QoE) was rated with the use of Grades of Recommendation Assessment, Development and Evaluation methods.

RESULTS: We included 28 studies (13 OSA/15 CSA; $N_{Subjects,Acetazolamide} = 542$; $N_{Subjects,Control} = 553$) that enabled meta-analyses for 24 outcomes. Acetazolamide doses ranged from 36 to 1000 mg/d and treatment duration from 1 to 90 d (median, 6 d). Overall, acetazolamide vs control lowered the AHI by −0.7 effect sizes (95% CI, −0.83 to −0.58; $I^2 = 0\%$; moderate QoE) that corresponded to a reduction of 37.7% (95% CI, −44.7 to −31.3) or 13.8/h (95% CI, −16.3 to −11.4; $AHI_{Control} = 36.5$/h). The AHI reduction was similar in OSA vs CSA, but significantly greater with higher doses (at least up to 500 mg/d). Furthermore, acetazolamide improved oxygen saturation nadir by +4.4% (95% CI, 2.3 to 6.5; $I^2 = 63\%$; no evidence of effect modification; very low QoE) and several secondary outcomes that included sleep quality measures and BP (mostly low QoE).

INTERPRETATION: Short-term acetazolamide improved both OSA and CSA. Rigorous studies with long-term follow up are warranted to assess Acetazolamide's value for the chronic treatment of patients with sleep apnea.

CLINICAL TRIAL REGISTRATION: PROSPERO (CRD42019147504)

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KEY WORDS: acetazolamide; apnea-hypopnea index; sleep apnea

ABBREVIATIONS: AHI = apnea-hypopnea index; CSA = central sleep apnea; NNT = number needed to treat; RCT = randomized controlled trial; Spo_2 = oxygen saturation

AFFILIATIONS: From the Division of Pulmonary, Critical Care and Sleep Medicine (Drs Schmickl, Orr, Owens, and Malhotra), University of California, San Diego, CA; the Sleep and Circadian Medicine

OSA and central sleep apnea (CSA) are highly prevalent and have been associated with many important neurocognitive and cardiovascular sequelae.[1-4] Therapy for both conditions is currently imperfect; thus, pharmacotherapy has been a major goal, albeit largely elusive to date.[5-11] Ventilatory instability or "high loop gain" is the cause of most types of CSA (including CSA due to high altitude or heart failure, idiopathic CSA, and many cases of opioid-induced CSA),[3,11-13] but it is also increasingly recognized as an important contributory mechanism in OSA.[3,12-16] Loop gain has two major components: "controller" gain (chemoresponsiveness = the desired change in ventilation for a given change in $Paco_2$) and "plant" gain (change in $Paco_2$ for a given change in ventilation).[13,16] Importantly, plant gain, and thus overall loop gain, can be lowered with acetazolamide,[14] a carbonic anhydrase inhibitor that induces bicarbonaturia, thereby causing a hyperchloremic metabolic acidosis that increases ventilation quickly.[17] We recently completed a review of acetazolamide's side-effect profile that showed that serious events are rare and that some common side-effects, such as paresthesia, are dose-dependent, which raises questions about the optimal dose for sleep apnea.[18]

The objective of the present study was to test our hypothesis that acetazolamide improves sleep apnea-related outcomes and to test whether the effect on sleep apnea severity is modified by sleep apnea type or acetazolamide dose.

In the absence of large randomized controlled trials (RCTs), observational studies may be an important source of information for causal inferences[19]; thus, nonrandomized studies were included a priori while we considered study design as a potential source of heterogeneity. We further emphasized comprehensiveness by considering a broad range of outcomes and by including articles irrespective of language. This approach contrasts with prior reviews that focused on certain subtypes of sleep apnea (eg, high altitude CSA), study designs (RCTs), few outcomes (usually <3), and/or English articles only (e-Table 1).[8-10,20-23] Consequently, prior reviews on this topic have included very few studies (0-8 studies) and subjects, thus allowing only limited insights in the potential value of acetazolamide for sleep apnea. Some of the results of this study have been reported previously in the form of an abstract.[24]

Methods

This systematic review was registered at PROSPERO (CRD42019147504) and was performed according to a prespecified protocol (e-Appendix 1) according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-Analysis of Observational Studies in Epidemiology guidelines (e-Tables 2 and 3).

Identification of Eligible Studies

We considered any study in which adults with OSA or CSA received oral acetazolamide and were compared against a control condition (ie, no acetazolamide or placebo) with regards to sleep apnea-related outcomes. Primary outcomes were apnea-hypopnea index (AHI) and oxygen saturation (Spo_2) nadir. Secondary outcomes were other sleep apnea characteristics (percent of total sleep time with periodic breathing, Spo_2 mean, percent of total sleep time with Spo_2 <90%, OSA/central apnea-hypopnea indexes, oxygen desaturation index), sleep parameters (total sleep time, sleep efficiency, percent of total sleep time in each sleep stage, arousal index), BP, Epworth Sleepiness Score, and any other patient-centered outcomes. We included both randomized and nonrandomized studies, but case reports were excluded. Further, we excluded studies in which subjects were nonhuman, <18 y old, intubated, or on hemodialysis. Last, we excluded studies in which acetazolamide was administered parenterally or coadministered with other interventions that precluded isolation of acetazolamide's effect on sleep apnea.

We (investigators) searched MEDLINE, EMBASE, and ClinicalTrials.gov from inception until March 11, 2019, hand-searched reference lists from eligible articles and prior systematic reviews, and contacted several authors for additional information. The final search strategies were:

- MEDLINE: ("Acetazolamide"[Mesh] OR "Acetazolamide"[tiab]) AND ("Sleep Apnea Syndromes"[Mesh] OR "Sleep Apnea"[tiab] OR "AHI"[tiab] OR "apnea hypopnea index"[tiab])
- EMBASE: ('acetazolamide':ti,ab,kw OR 'acetazolamide'/exp) AND ('sleep disordered breathing'/exp OR 'sleep apnea':ti,ab,kw OR 'apnea hypopnea index':ti,ab,kw) NOT 'review'/it

Study Selection, Data Collection, and Risk of Bias Assessment

Two authors independently screened the retrieved records (C. N. S., A. M.), assessed final eligibility based on full-text articles for every record

Laboratory, Department of Physiology (Drs Landry and Edwards), School of Biomedical Sciences and Biomedical Discovery Institute, and the Turner Institute for Brain and Mental Health (Drs Landry and Edwards), Monash University, Melbourne, VIC, Australia; the Department of Respiratory Care and Sleep Control Medicine (Drs Chin and Murase), Kyoto University, Kyoto, Japan; the Department of Pulmonology and Multidisciplinary Sleep Disorders Centre (Dr Verbraecken), Antwerp University Hospital and University of Antwerp, Edegem, Belgium; the Division of Pulmonary and Sleep Medicine (Dr Javaheri), Bethesda North Hospital, Cincinnati, OH; the Division of Pulmonary, Critical Care and Sleep Medicine (Dr Javaheri), University of Cincinnati, OH; and the Division of Cardiology (Dr Javaheri), The Ohio State University, Columbus, OH.

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that had not been excluded unanimously during the screening process (C. N. S., S. A. L.), collected data from eligible studies using piloted Excel spread sheets (C. N. S., S. A. L.) (Microsoft Corporation, Redmond, WA), and assessed risk of bias for each included study as described later (C. N. S., S. A. L.). All disagreements could be resolved by discussion and/or by seeking clarifications from authors.

Abstracted data included information about study participants (age, sex, BMI, comorbid congestive heart failure), intervention (acetazolamide total daily dose, days of administration), pertinent laboratory results (pH, P_{CO_2}, P_{O_2}, plasma bicarbonate, potassium, chloride, and creatinine concentration), and the outcomes listed above. For each outcome, we collected the mean, SD, and number of subjects in the acetazolamide vs control condition. If necessary, we estimated the mean from the reported median, and the SD from reported SEs, interquartile ranges, or 95% CIs using standard techniques.[25]

Risk of bias was assessed on the study-level with four domains of the Cochrane risk-of-bias tool for RCTs (selection, performance, detection, and attrition bias) and three domains of a modified Newcastle-Ottawa scale (selection, comparability, outcome assessment) for observational studies (e-Appendix 1). Each domain was rated as "high," "unclear," or "low" risk of bias; the overall risk of bias for a given study was defined as the highest risk in any of the domains.

Synthesis of Results

Summary Measures: For outcomes reported by at least two studies a pooled effect estimate was attempted with the use of "weighted" mean differences. However, the AHI data were based on widely varying definitions and measurement techniques used across studies (eg, some studies scored hypopneas based on arousals, others based only on oxygen desaturations of varying degrees, and some did not include hypopneas at all; some used nasal pressure transducers, others only oronasal thermistors). Thus, the overall effect on the AHI was estimated with standardized mean differences, but for better interpretability back-transformed[26] with the use of the following equations:

$$\text{Absolute AHI change} = \text{SMD} \times \text{SD}_{\text{pooled[acetazolamide,control]}}$$

$$\text{Percent AHI change} = \frac{\text{Absolute AHI change}}{\text{AHI}_{\text{pooled[control]}}} \times 100$$

Meta-Analyses and Heterogeneity: Based on the I^2 statistic, we arbitrarily categorized heterogeneity as low (<30%), moderate (30-50%), or high (>50%).[25,27] If I^2 was <30%, then results were pooled based on a fixed effects model. In case of I^2, ≥30% attempts were made to identify the source of heterogeneity based on qualitative assessments and/or the use of meta-regression (if $n_{studies} \geq 8$, considering the candidate effect modifiers listed later); in select cases, we also explored "baseline risk" as a potential source of heterogeneity by calculating "relative" rather than "absolute" effect estimates via the ratio-of-means method.[28] If heterogeneity could not be resolved, then we estimated the overall effect based on a random effects model, unless the direction of individual study effects was in opposing directions, in which case a pooled estimate would be misleading and thus was deferred. For primary outcomes (AHI, Sp_{O_2} nadir), several sensitivity analyses were performed to assess the robustness of results. Quality of evidence was rated with the use of the Grades of Recommendation Assessment, Development and Evaluation. All meta-analyses were performed with Stata software (version 12.1; StataCorp) with a probability value of <.05 judged as significant.

Subgroup Analyses and Bias Assessment: According to our study objective, we assessed primary outcomes (AHI, Sp_{O_2} nadir) for effect modification by sleep apnea type and dose with the use of meta-regression (primary subgroup analyses). As prespecified, for primary outcomes, we further tested whether duration of acetazolamide administration, population characteristics (eg, mean age, but also study location as a proxy for race), laboratory values, or quality indicators (ie, risk of bias, study design, industry funding) modified the effect. The risk of publication bias was evaluated via funnel plots and Egger test.

Post hoc Responder Analyses: We were able to obtain individual patient-level data for the AHI from eight cross-over studies through a combination of individual data reported in published tables and figures (with the averaged values abstracted by two independent reviewers [C. N. S., J. E. O.]) and author communications. Thus, we explored variability of acetazolamide's effect across individuals and estimated the number needed to treat (NNT) for one patient with sleep apnea to have an AHI reduction of at least 50% ($\pm AHI_{Acetazolamide} < 10/h$), as well as the NNT for one patient with sleep apnea to experience an increase in AHI by at least 50%.

Results

We identified 28 eligible studies (subjects: $N_{Acetazolamide} = 542$; $N_{Control} = 553$)[14,29-55] including two Japanese-language articles[43,49] (Fig 1). We received clarifications and/or additional information from authors of nine studies.[29,30,32,38,42,46-48,53,56]

Table 1 provides an overview of the study characteristics (for details of individual studies, e-Table 4): studies included mostly men, with a wide range of mean ages (31-69 y) and mean BMIs (21.9-38.3 kg/m^2); race was rarely reported, but about one-third of studies were performed in Asia. Approximately one-half the studies focused on OSA, while the others included subjects with CSA due to a variety of causes. Studies administered 36 to 1000 mg/d (mean, 528 mg/d) of acetazolamide for 1 to 90 d (median, 6 d). In one study, acetazolamide was coadministered with CPAP (both in the acetazolamide and placebo arm, which allowed isolation of the acetazolamide effect),[30] whereas in all other studies acetazolamide was given to patients with sleep apnea off CPAP (ie, untreated patients). Acetazolamide administration was randomized in approximately one-half of the studies. Overall risk of bias was rated as low/unclear vs high in 46% vs 54%, respectively.

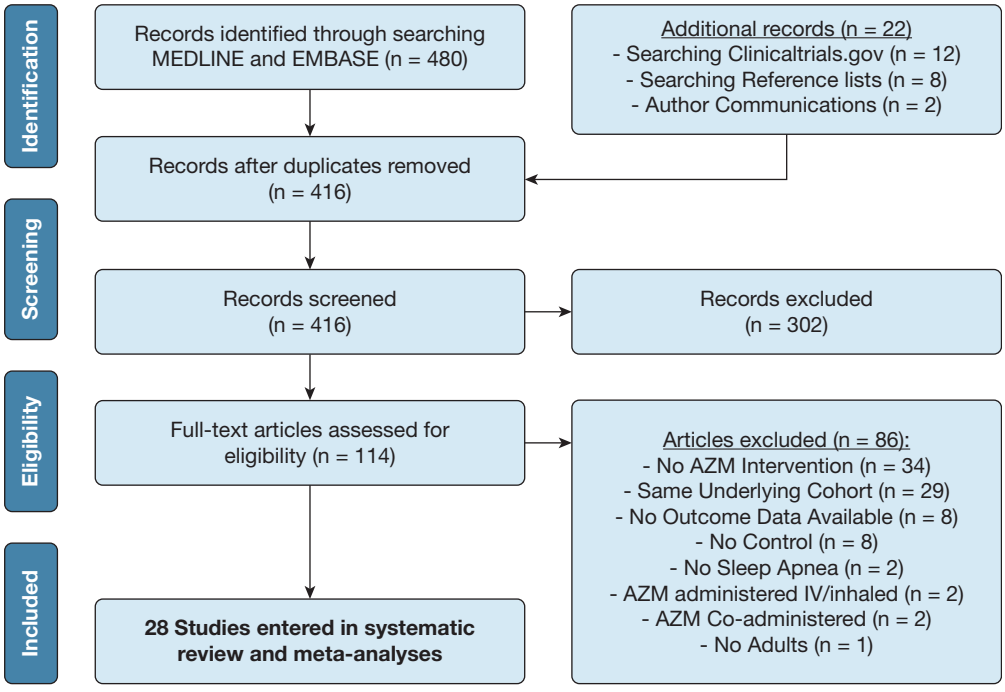

Figure 1 – *Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart. AZM = acetazolamide.*

Effects on Primary Outcomes

Based on moderate quality evidence from 26 studies,[14,29-34,36-49,51-55] acetazolamide reduced the AHI overall by −0.70 effect sizes (95% CI, −0.83 to −0.58; $I^2 = 0\%$) (Table 2), which corresponds to a reduction in AHI of 37.7% (95% CI, −44.7 to −31.3) or 13.8/h (95% CI, −16.3 to 11.4; $AHI_{Control} = 36.5$/h) for those with severe sleep apnea. In meta-regression that included OSA and CSA studies, higher doses of acetazolamide were associated significantly with greater reductions in AHI ($P = .005$; results were similar when stratified by sleep apnea type, e-Appendix 2), but a post hoc analysis suggested that the dose-dependent effect of acetazolamide on the AHI plateaus at 500 mg/d (Fig 2). Acetazolamide's effect on the AHI was similar in OSA vs CSA studies (Fig 3); the effect was numerically larger in studies of CSA due to high altitude or heart failure, but the differences across sleep apnea subtypes did not reach statistical significance ($P = .22$)(Fig 3; e-Appendix 2). Overall, the reduction in AHI was significantly greater in high (four CSA, one OSA) vs low altitude studies, in randomized vs nonrandomized studies, in studies rated as low/unclear vs high risk of bias, and in studies performed outside of Asia (Fig 3). There was no effect modification by any other candidate variable that included acetazolamide duration (e-Appendix 2). The results were similar across

TABLE 1] Characteristics of Included Studies (N = 28)

Characteristic	Mean (SD)	Median [Interquartile Range]	Percentage ($N_{Studies}$)	Range	$N_{Studies}$
Population					
Age, y	55.4 (9.4)	…	…	31-69[a]	25
Women, %	…	8 [0-18]	…	0-75	22
BMI, kg/m^2	29 (4)	…	…	21.9-38.3	17
Weight, kg	81 (10.8)	…	…	65.4-96.1	7
Sleep apnea type					28
Primarily OSA[b]	…	…	46 (13)	…	
Comorbid congestive heart failure	…	…	11 (3)	…	

(Continued)

TABLE 1] *(Continued)*

Characteristic	Mean (SD)	Median [Interquartile Range]	Percentage ($N_{Studies}$)	Range	$N_{Studies}$
High altitude	…	…	4 (1)	…	
Primarily central sleep apnea	…	…	54 (15)	…	
High altitude	…	…	21 (6)	…	
Congestive heart failure	…	…	11 (3)	…	
Opioids	…	…	4 (1)	…	
Idiopathic	…	…	11 (3)	…	
Other[c]	…	…	7 (2)	…	
Study location					28
North America	…	…	32 (9)	…	
Europe	…	…	39 (11)	…	
Asia	…	…	29 (8)	…	
Japan	…	…	18 (5)	…	
Intervention: acetazolamide					
Total daily dose, mg/d[d]	528 (308)	…	…	36-1,000	28
Total daily dose (categorical)					28
<500 mg/d	…	…	54 (15)	…	
≥500 mg/d	…	…	46 (13)	…	
Continuous administration, d	…	6 [3-9]	…	1-90	28
Categoric administration, d					28
<3	…	…	21 (6)	…	
3-7	…	…	50 (14)	…	
>7	…	…	29 (8)	…	
Subjects in the acetazolamide arm, No.	…	12 [9-21]	…	4-75	28
Subjects in the control arm, No.	…	12 [9-22]	…	4-75	28
Quality indicators					
Overall bias					28
Low	…	…	7 (2)	…	
Unclear	…	…	39 (11)	…	
High	…	…	54 (15)	…	
Study design					28
Randomized controlled trial	…	…	57 (16)	…	
Parallel group	…	…	46 (13)	…	
Cross-over	…	…	14 (4)	…	
Observational	…	…	43 (12)	…	
Industry funding					28
Yes/unclear	…	…	39 (11)	…	
No	…	…	61 (17)	…	

[a]Range of mean ages reported for the different studies; the youngest and oldest subject enrolled in the included studies were reported as 22 and 80 years, respectively.
[b]Five studies included patients judged to have primarily OSA but potentially including some patients with central sleep apnea (subgroup analyses were similar when these studies were classified as central sleep apnea instead (e-Appendix 2).[31,36,47,49,54]
[c]One study included subjects with central sleep apnea in the setting of precapillary pulmonary hypertension[29]; the other study included subjects with central sleep apnea in the setting of spinal cord injury.[46]
[d]One study administered 3.5 to 4 mg/kg/d; assuming an average weight of 75 kg, we estimated the mean daily dose as 75 kg × 3.75 mg/kg/d = 281 mg/d[32]; one study administered 250 mg/wk, thus we estimated the daily dose as 250 mg/7d = 36 mg/d.[48]

TABLE 2] Effect of Acetazolamide on Sleep Apnea Severity, Sleep Parameters, and Cardiovascular and Other Outcomes

Outcome	Δ (95% CI)	I^2	$N_{Studies}$	$P_{\Delta = 0}$	Δ Type	GRADE	Acetazolamide			Control		
							$Mean_{wt}$	(SD_{wt})	N_{Subj}	$Mean_{wt}$	(SD_{wt})	N_{Subj}
Primary outcomes												
AHI, effect sizes	−0.70 (−0.83 to −0.58)	0%	26	<.001[a]	S_F	⊕⊕⊕◯	22.9	(19.2)	529	36.5	(23.2)	540
AHI/h[b]	−13.8 (−16.3 to 11.4)											
AHI, % of control[b]	−37.7 (−44.7 to 31.3)											
Spo_2 nadir, %[c]	+4.4 (2.3 to 6.5)	63%	13	<.001[a]	W_R	⊕◯◯◯	81.1	(6.6)	245	76.8	(8.2)	247
Secondary outcomes												
Sleep apnea severity												
Mean Spo_2, %[d]	+3.5 (2.3 to 4.8)	82%	12	<.001[a]	W_R	⊕⊕◯◯	88.9	(2.5)	218	85.3	(3.4)	215
Time with Spo_2 <90%, %TST[e,f]	−15.1 (−31.9 to 1.6)	84%	5	.08	W_R	⊕◯◯◯	9.7	(18.2)	101	24.8	(27.8)	101
Oxygen desaturation index, h^{-1}[g]	−12.2 (−19.2 to 5.2)	65%	5	.02[a]	W_R	⊕⊕◯◯	9.0	(11.1)	107	21.3	(16.9)	107
Obstructive AHI, h^{-1}[h]	−7.5 (−16.9 to 1.8)	49%	3	.11	W_R	⊕◯◯◯	28.6	(21.9)	77	36.2	(21.0)	77
Central AHI, h^{-1}[e,i]	−9.5 (−14.0 to −4.9)	56%	8	<.001[a]	W_R	⊕◯◯◯	5.8	(10.5)	214	15.3	(19.2)	214
Hypopnea index, h^{-1}[j]	−2.3 (−6.6 to 1.9)	45%	6	.29	W_R	⊕◯◯◯	11.7	(10.9)	96	14.0	(12.0)	96
Periodic breathing, %TST[e,k]	−24.2 (−53.1 to 4.7)	88%	3	.10	W_R	⊕◯◯◯	17.6	(16.9)	36	41.8	(19.2)	36
Apnea-hypopnea duration, s[l]	+0.8 (−1.5 to 3.1)	53%	6	.50	W_R	⊕◯◯◯	24.3	(5.9)	106	23.5	(5.5)	107
Sleep parameters												
Total arousal index, h^{-1}[m]	−6.6 (−11.3 to −2.0)	32%	6	.005[a]	W_R	⊕⊕◯◯	23.9	(14.5)	140	30.5	(16.2)	140
TST, min [m]	+20.0 (7.1 to 32.9)	28%	10	.002[a]	W_F	⊕⊕◯◯	377.2	(72.4)	292	357.2	(86.3)	292
Sleep efficiency, %[m]	+5.5 (3.2 to 7.8)	0%	12	<.001[a]	W_F	⊕⊕◯◯	80.8	(12.9)	305	75.3	(15.8)	305
Stage N1, %TST[m]	−4.7 (−7.6 to −1.9)	14%	5	.001[a]	W_F	⊕⊕◯◯	18.0	(10.1)	118	22.7	(12.2)	118
Stage N2, %TST	+4.0 (0.9 to 7.1)	0%	5	.01[a]	W_F	⊕◯◯◯	51.4	(12.1)	118	47.4	(12.2)	118
Stage N3, %TST	+1.4 (0.1 to 2.6)	6%	7	.02[a]	W_F	⊕⊕◯◯	7.8	(6.8)	237	6.5	(6.4)	237
Stage rapid eye movement, %TST[m]	0.0 (−1.4 to 1.4)	38%	11	.99	W_R	⊕⊕⊕◯	12.0	(6.1)	300	12.0	(6.9)	300
Cardiovascular outcomes												
Systolic blood pressure, mm Hg[k]	−8.2 (−11.5 to −4.9)	0%	5	<.001[a]	W_F	⊕⊕◯◯	128.0	(12.1)	99	136.2	(12.2)	114
Diastolic blood pressure, mm Hg	−4.3 (−6.8 to −1.8)	0%	5	.001[a]	W_F	⊕⊕◯◯	79.0	(8.7)	99	83.3	(9.8)	114
Mean blood pressure, mm Hg	−5.2 (−7.5 to −2.8)	0%	4	<.001[a]	W_F	⊕⊕◯◯	98.0	(9.4)	128	103.1	(9.7)	129
Heart rate, min^{-1}	−1.7 (−4.2 to 0.7)	26%	7	.16	W_F	⊕⊕◯◯	66.7	(11.7)	164	68.5	(10.6)	165
Other outcomes												
Weight, kg	−1.6 (−5.9 to 2.8)	0%	3	.47	W_F	⊕◯◯◯	93.9	(17.2)	116	95.5	(16.2)	116

(Continued)

TABLE 2] *(Continued)*

Outcome	Δ (95% CI)	I^2	$N_{Studies}$	$P_{\Delta = 0}$	Δ Type	GRADE	Acetazolamide			Control		
							$Mean_{wt}$	(SD_{wt})	N_{Subj}	$Mean_{wt}$	(SD_{wt})	N_{Subj}
Epworth Sleepiness Score[n]	−0.7 (−2.2 to 0.9)	51%	3	.38	W_R	⊕◯◯◯	9.1	(3.6)	46	9.8	(3.9)	46
6-Minute walking distance, m	+3.2 (−20.5 to 26.9)	1%	3	.79	W_F	⊕◯◯◯	503.4	(77.3)	83	500.2	(83.4)	98

Details of meta-analyses, including Forest plots, are found in e-Appendix 2. Δ Type denotes whether comparison is based on "weighted" (W) or "standardized" (S) mean differences" (the subscript $_{F/R}$ denote fixed/random effects models); $Mean_{wt}$ (SD_{wt}) = weighted mean and SDs; N_{Subj} = number of subjects. As detailed in Based on GRADE methods, quality of evidence was rated as: very low (⊕◯◯◯), low (⊕⊕◯◯), moderate (⊕⊕⊕◯), or high (⊕⊕⊕⊕) (e-Table 5). AHI = apnea-hypopnea index; GRADE = Grades of Recommendation Assessment, Development and Evaluation; S_F = standardized mean differences using a fixed effects model; Spo_2 = oxygen saturation; TST = total sleep time; W_F = weighted mean differences using a fixed effects model; W_R = weighted mean differences using a random effects model.

[a]$P < .05$.

[b]Calculated based on the effect size, pooled SD ($SD_{Control,Acetazolamide} = 19.7$), and the pooled $AHI_{Control}$ (36.5/h); for details see the Methods section.

[c]We could not identify a clear source of the heterogeneity, but the direction of virtually all individual study effects was in favor of acetazolamide.

[d]Heterogeneity likely related to ceiling effects and the sigmoid shape of the oxygen desaturation curve (e-Appendix 2).

[e]Post hoc analyses suggested that heterogeneity, in part, may be due to effect modification by baseline risk: heterogeneity was less (lower I^2) when we estimated the effect using a relative rather than an absolute scale (ie, when taking into account baseline values).

[f]Based on a post hoc ratio-of-means analysis, time with Spo_2 <90% decreased by 64% (95% CI, 45 to 76); $I^2 = 30\%$; $P < .001$ with acetazolamide vs control.

[g]Heterogeneity was primarily due to one study[33]; results were similar when we excluded this study (−9.8 [95% CI, −12.0 to −5.5]; $I^2 = 0\%$; $P < .001$)

[h]Heterogeneity was primarily due to one study[14]; results remained nonsignificant when we excluded this study (−2.5 [95% CI, −11.1 to 6.0]; $I^2 = 0$; $P = .56$)

[i]Based on a post hoc ratio-of-means analysis, central AHI decreased by 64% (95% CI, 53 to 72; $I^2 = 0\%$; $P < .001$) with acetazolamide vs control subject.

[j]Differences in underlying hypopnea definitions likely contributed to the heterogeneity (lower I^2 when analysis was performed we used standardized mean differences, but overall results were similar; thus, results from the weight mean difference analysis are reported here; effect may also be more pronounced in OSA vs central sleep apnea studies (e-Appendix 2).

[k]Based on a post hoc ratio-of-means analysis, periodic breathing decreased by 58% (95% CI, 36 to 72; $I^2 = 0\%$; $P < .001$ with acetazolamide vs control subject.

[l]Post hoc analyses suggested potential effect modification by acetazolamide dose ($P = .053$); in studies that administered ≥500 mg/d event, duration increased by 3.2 seconds (95% CI, 0.6 to 5.9), $I^2 = 0\%$; $P = .02$ with acetazolamide vs control subject, whereas in studies that administered <500 mg/d, event duration was unchanged (−1.1 seconds [95% CI, −3.1 to 0.8]; $P = .21$).

[m]Results were similar when we included only randomized trials, which suggested that the change in outcome was not due to confounding by first night effects (ie, baseline/control subject during the first night vs acetazolamide administered during a subsequent night).

[n]In part, heterogeneity is likely due to varying baseline severity (only one of the three studies had a baseline Epworth Sleepiness Score within the abnormal range [ie, >10]).

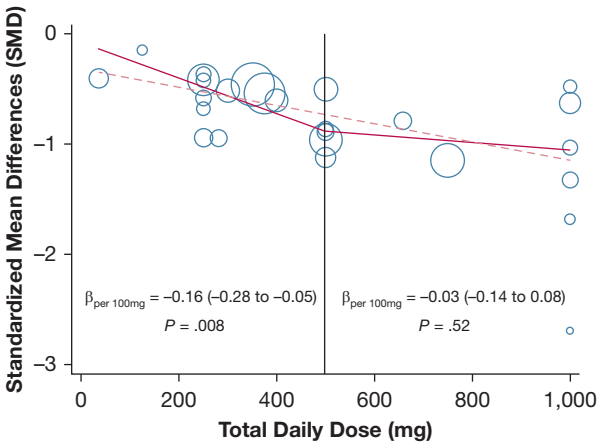

Figure 2 – *Meta-regression: dose-dependent effect of acetazolamide on apnea-hypopnea index. Based on primary analysis, higher doses of acetazolamide were associated with greater reductions in apnea-hypopnea index (dashed line). However, a post hoc analysis suggested that the dose-dependent effect of acetazolamide on the apnea-hypopnea index plateaus at 500 mg/d (solid line)(e-Appendix 2). SMD = standardized mean difference.*

several sensitivity analyses, and there was no evidence of publication bias ($P = .11$). A post hoc analysis of patient-level data from eight studies ($N_{Subjects} = 122$) suggested that responses varied between individuals independently of OSA type or acetazolamide dose (Fig 4). In 48% of patients, the AHI improved by ≥50% ($NNT_{>50\%\ AHI\text{-}Reduction} = 2.1$ [95% CI, 1.7 to 2.5]); however, in 9% of subjects, the AHI worsened by ≥50% ($NNT_{>50\%\ AHI\text{-}Increase} = 11.1$ [95% CI, 7.1 to 25.4]).[14,32,34,39,41,43,44,52] Of note, 24% of the 122 subjects were "responders" according to standard definitions (AHI-reduction >50% and $AHI_{Acetazolamide}<10$/h; $NNT_{Responder} = 4.1$ [95% CI, 3.1 to 5.9]).

Spo_2 nadir improved overall by 4.4% (95% CI, 2.3 to 6.5; N = 13[14,31,32,34,36,38-40,43,44,50-52]), but heterogeneity was high ($I^2 = 63\%$) with no clear source of heterogeneity or effect modifier identified (e-Appendix 2), thus the level of evidence was rated as very low. The results were similar in sensitivity analyses, and there was no evidence of publication bias ($P = .41$).

Effects on Secondary Outcomes

Acetazolamide improved Spo_2 mean, oxygen desaturation index, and central AHI, but heterogeneity was high and quality of evidence for these outcomes was judged as low to very low (Table 2). Based on low to very low level of evidence, acetazolamide improved several markers of sleep quality: Sleep duration increased; the arousal index decreased, and there was a shift towards deeper sleep stages.

Cardiovascular Outcomes: Based on low level of evidence from five studies,[31,32,38,48,51] there was a statistically significant and clinically large reduction in BP. Based on post hoc analyses, the BP reduction was most pronounced in two studies that included a large fraction of untreated hypertensive subjects.[31,38] Furthermore, one study reported relative improvements in myocardial oxygen supply/demand ratio in high altitude CSA,[51,57] and one study[32] that measured ventricular ejection fractions reported no difference after 6 days of acetazolamide vs placebo in twelve patients with CSA due to heart failure.

Neurocognitive and Other Outcomes: Overall, based on a meta-analysis of three studies, there was no change in Epworth Sleepiness score (range, 0-24); however, in two of these studies, the control score was within the normal range (<10)[29,38]; in the third study, there was a statistically nonsignificant,[53] but clinically important,[58,59] reduction by −2.7 points (N = 10; $P = .08$). Two studies further assessed psychomotor vigilance. In one study, reaction time worsened (+17.3 msec; $P = .004$),[29] but the other study reported a nonsignificant improvement of similar magnitude (−15 msec; $P > .05$),[30] therefore, results were not pooled ($I^2 = 80\%$). In addition, six studies provided data about subjective symptoms (eg, sleepiness, insomnia, sleep quality, snoring)(e-Table 6)[32,34,41,42,44,45]: five studies reported an improvement with acetazolamide[32,41,42,44,45] vs one study that reported no change in symptoms.[34] These subjective data should be interpreted with caution because methods were variable and most studies lacked blinding. Based on meta-analyses of laboratory tests (e-Table 7), acetazolamide lowered pH, Pco_2, bicarbonate, and potassium concentrations ($P < .04$; high heterogeneity) and increased Po_2 ($P < .001$; $I^2 = 0$). Serum creatinine was reported by only one study that found a slight increase with acetazolamide 1000 mg/d (+0.17 mg/dL; $P < .05$).[14]

Discussion

Increasing evidence suggests that OSA and CSA share an overlapping pathogenesis, with CSA being characterized by elevated ventilatory instability or high loop gain.[12-16] By including studies independent of sleep apnea type, study design, and article language, we identified more than three times the number of studies, subjects, and outcomes compared with prior reviews on this topic.[8-10,20-23] This led to several important and novel insights. Specifically, from this large meta-analysis that included >500 subjects, we note several findings.

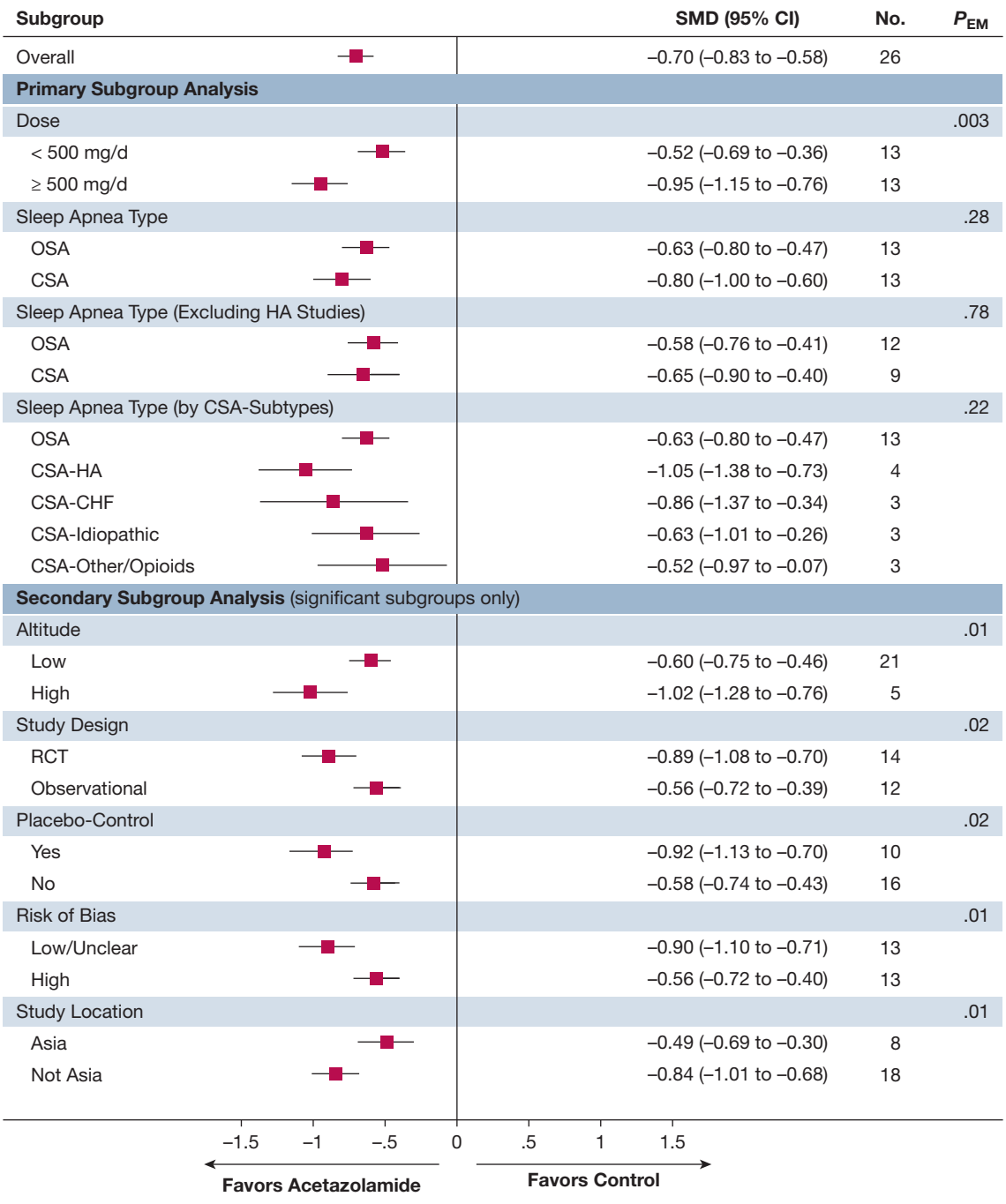

Figure 3 – *Subgroup analyses for the apnea-hypopnea index e-Appendix 2 contains complete results of the subgroup analyses. CHF = congestive heart failure; CSA = central sleep apnea; HA = high altitude; P_{EM} = probability value for effect modification; RCT = randomized controlled trial. See Figure 2 legend for expansion of other abbreviation.*

First, based on moderate quality evidence, acetazolamide reduced the AHI on average by more than one third. Second, the reduction in AHI was overall similar in OSA and CSA studies, which is consistent with data from a mechanistic study in which the AHI reduction among patients with OSA was independent of patients' baseline loop gain.[14] Third, acetazolamide's effect on the AHI is dose-dependent but seems to plateau at approximately 500 mg/d, which suggests that doses of >500 mg/d may not be beneficial for patients with sleep apnea while increasing the risk of side-effects, which may adversely affect tolerance and adherence.[18] Of note, at 500 mg/d, the NNT for common side-effects is 2.1 for paresthesia, 22.3 for dysgeusia (abnormal taste), 17.0 for polyuria,

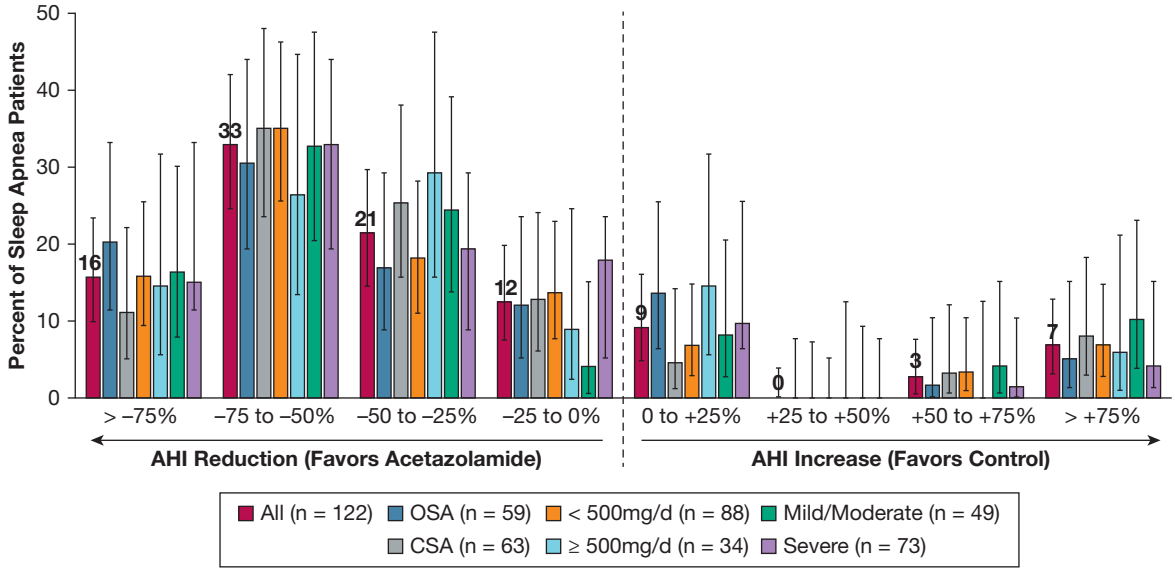

Figure 4 – *Individual responses based on patient-level data from eight cross-over studies*[14,32,34,39,41,43,44,52] *Median percent-change was −49.8% (interquartile range, −67.8 to −17.6%). Across responder strata, there was no significant difference between OSA vs central sleep apnea, or low vs high-dose acetazolamide. Responses were also similar in patients with mild-moderate vs severe sleep apnea, except there was a significantly greater percentage of patients with severe vs mild-moderate sleep apnea whose apnea-hypopnea index improved by −25% to 0% (P = .047). AHI =apnea-hypopnea index. See Figure 3 legend for expansion of other abbrevation.*

and 11.1 for fatigue.[18] Importantly, these estimates include many mild cases (especially paresthesia) that may not affect adherence/tolerance; side-effects typically cluster (ie, patients tend to have either no side-effects or several). Thus, many patients are expected to tolerate up to 500 mg/d quite well.[18] Fourth, acetazolamide appears to be beneficial across several patient-centered outcomes that include sleep quality measures and subjective symptoms. Importantly, the observed reduction in BP (systolic BP: 8.2 mm Hg [95% CI, −11.5 to −4.9]; diastolic BP: −4.3 mm Hg [95% CI, −6.8 to −1.8]) was substantially greater than what commonly is achieved with CPAP therapy (systolic BP: −2 to −4 mm Hg; diastolic BP, −1 to −3 mm Hg).[60,61] Interestingly, OSA has been associated with increased carbonic anhydrase activity,[62] and carbonic anhydrase inhibitors such as acetazolamide may lower vascular tone through several pathways.[63-66] Thus, the comparatively greater effectiveness may be due to mechanistic reasons, but the observed effect on BP may (in part) be independent of acetazolamide's effects on sleep apnea. Further, we note that the number of subjects in our meta-analysis for this outcome was relatively small (approximately 100), and the level of evidence was low, precluding firm conclusions. Fifth, based on a post hoc analysis, individual responses to acetazolamide appear to be quite variable (potentially due to varying effects on chemosensitivity vs plant gain, which are two of the determinants of overall loop gain[67]): Approximately one in 11 patients who were treated with acetazolamide experienced substantial worsening of the AHI, thus monitoring of sleep apnea severity during initiation or at close follow up is clearly warranted. On the other hand, about one in four patients experienced full resolution of sleep apnea based on standard criteria (independent of sleep apnea severity at baseline). Furthermore, combination of acetazolamide with therapies targeting pathophysiologic traits, other than loop gain, may result in additive effects and thus augment partial responses.[40] More research is needed to confirm that acetazolamide's effect is maintained long-term and to help identify responders a priori, but for many patients who do not tolerate standard therapies, such as CPAP, acetazolamide alone or in combination with other modalities may be an efficacious treatment option.

Previous reviews of acetazolamide for sleep apnea reported AHI reductions of similar magnitude as in our study, but for various reasons the number of included studies was generally ≤3 (e-Table 1). Thus, in the official practice guidelines from the American Academy of Sleep Medicine concerning treatment of sleep apnea, acetazolamide plays almost no role at all. The practice parameters for CSA[20] list acetazolamide as an "option"

for idiopathic CSA (based on two studies[42,45]) and for CSA due to congestive heart failure (based on one study[32]) but concludes that there is insufficient evidence for acetazolamide's use in high altitude CSA (based on one study[33]). Neither the clinical guideline for the management of OSA[68] nor the practice parameters for the medical therapy of OSA[10,69] mention acetazolamide. We believe that the cumulative evidence of acetazolamide's efficacy for sleep apnea and its side-effect profile warrants greater discussion in future revisions of these documents.[18] But when "going from evidence to recommendations," patients' values, preferences and treatment costs will need to be taken into account.[70,71]

A major strength of the current review is its comprehensiveness with regards to studies and outcomes. Moreover, robustness of results in sensitivity analyses, the dose-dependent effect on the AHI, and beneficial effects across a variety of outcomes (without any clear harmful effects on any outcome) increase our confidence in the validity of findings. To achieve this comprehensiveness and enable complex analyses, we deliberately combined data from somewhat different study populations. We believe this approach to be valid because (1) loop gain is an important pathophysiologic component of all subtypes of sleep apnea that were included in this study providing an a priori rationale for this approach; (2) for primary outcomes, formal testing did not reveal significant differences across OSA/CSA-subtypes a posteriori; and (3) effect estimates are provided separately for significant subgroups (eg, high vs low altitude). But we acknowledge that we had limited power to detect differences across sleep apnea subtypes, thus one may question the generalizability of our overall results for the different sleep apnea subtypes and view our findings as hypothesis-generating rather than definitive insights. Similarly, meta-analyses of obstructive AHI were based on only three studies, which limited insights about acetazolamide's effects on purely OSA events. Another key limitation is that most studies assess acetazolamide's effect on sleep apnea for a maximum of 2 weeks, thus results may not generalize to long-term therapy. Similarly, most study participants were male, and a lack of effect modification by sex only provides limited reassurance (low power; risk of ecologic bias when testing for patient characteristics). Further, we found insufficient data to test for effect modification by race, but the lower efficacy of acetazolamide in Asian studies may reflect true biologic variation considering that OSA in Chinese vs white patients is caused more by anatomic predisposition and less by ventilatory instability.[72] Another limitation is that the level of evidence for most outcomes was judged as low, most studies were rated as high or unclear risk of bias, and many of the studies lacked placebo-control. In RCTs, high/unclear risk of bias was often due to a lack of details about the randomization methods that were used, which may reflect reporting issues rather than true methodologic flaws. Importantly, the effect on the AHI was actually greater in low/unclear vs high risk of bias studies (and in placebo vs nonplacebo controlled studies), which suggests that the net effects of potential biases was towards the null (ie, not driving the positive results). Another issue is that sleep position can affect OSA severity but was not controlled in most studies, which may explain some of the interindividual variability that was noted. Potential imbalances in sleep position across study conditions are expected to be more pronounced in nonrandomized studies; therefore, it is further reassuring that acetazolamide's effect on the AHI was actually greater in RCTs than in observational studies (ie, unmeasured confounders such as sleep position or first-night effects likely did not drive the positive results).

Short-term administration of acetazolamide appears beneficial for both CSA and OSA. More research is needed to identify responders a priori, to assess interaction effects with other therapies that target pathophysiologic mechanisms other than loop gain, and to evaluate rigorously long-term efficacy with regards to patient-centered outcomes in mixed-sex cohorts of well-defined sleep apnea subgroups. A reasonable regimen for future studies would be 125 to 500 mg/d (1 to 2 doses/d; evening dose 2 h before bedtime) with close follow up to rule out worsening of sleep apnea. The maximal effect for a given dose is likely achieved within a few days[17,42,73] (for high altitude CSA initiation 1 day prior to ascend could be considered,[51] same as what is recommend for the prevention of acute mountain sickness[74]). Common side-effects (eg, paresthesia) are dose-dependent.[18] Thus, it may be prudent to start with 3.5 mg/kg body weight[32] or 125 to 250 mg/d and titrate up every 3 to 5 d as needed and tolerated. Coadministration with thiazide diuretics (and possibly angiotensin-receptor blockers) increases the risk of hypokalemia and requires close monitoring and/or should be avoided.[18]

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Additional information: The e-Appendixes and e-Tables can be found in the Supplemental Materials section of the online article.

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