Journal Pre-proof

Acetazolamide for Obstructive and Central Sleep Apnea: A Comprehensive Systematic Review and Meta-Analysis

Christopher N. Schmickl, MD, PhD, Shane A. Landry, PhD, Jeremy E. Orr, MD, Kazuo Chin, MD, PhD, Kimihiko Murase, MD, PhD, Johan Verbraecken, MD, Shahrokh Javaheri, MD, Bradley A. Edwards, PhD, Robert L. Owens, MD, Atul Malhotra, MD

PII: S0012-3692(20)31904-8

DOI: https://doi.org/10.1016/j.chest.2020.06.078

Reference: CHEST 3386

To appear in: *CHEST*

Received Date: 22 February 2020

Revised Date: 9 June 2020

Accepted Date: 26 June 2020

Please cite this article as: Schmickl CN, Landry SA, Orr JE, Chin K, Murase K, Verbraecken J, Javaheri S, Edwards BA, Owens RL, Malhotra A, Acetazolamide for Obstructive and Central Sleep Apnea: A Comprehensive Systematic Review and Meta-Analysis, *CHEST* (2020), doi: https://doi.org/10.1016/j.chest.2020.06.078.

TITLE PAGE
WORD COUNT: Abstract 300/max 300, Text Body 3589

TITLE: Acetazolamide for Obstructive and Central Sleep Apnea: A Comprehensive Systematic Review and Meta-Analysis

RUNNING HEAD: Acetazolamide for Sleep Apnea

AUTHORS' NAMES AND AFFILIATIONS:
Christopher N. Schmickl MD, PhD[1] cschmickl@health.ucsd.edu
Shane A. Landry PhD[2,3] shane.landry@monash.edu
Jeremy E. Orr MD[1] j1orr@health.ucsd.edu
Kazuo Chin MD, PhD[4] chink@kuhp.kyoto-u.ac.jp
Kimihiko Murase MD, PhD[4] kmurase@kuhp.kyoto-u.ac.jp
Johan Verbraecken MD[5] Johan.Verbraecken@uza.be
Shahrokh Javaheri MD[6,7,8] shahrokhjavaheri@icloud.com
Bradley A. Edwards PhD[2,3] bradley.edwards@monash.edu
Robert L. Owens MD[1] rowens@health.ucsd.edu
Atul Malhotra MD[1] amalhotra@health.ucsd.edu

[1] Division of Pulmonary, Critical Care and Sleep Medicine, University of California, San Diego (UCSD), CA 92037, USA
[2] Sleep and Circadian Medicine Laboratory, Department of Physiology, School of Biomedical Sciences and Biomedical Discovery Institute, Monash University, Melbourne, VIC, 3800, Australia
[3] Turner Institute for Brain and Mental Health, Monash University, Melbourne, VIC, 3800, Australia
[4] Department of Respiratory Care and Sleep Control Medicine, Kyoto University, Kyoto 606-8507, Japan
[5] Department of Pulmonology and Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, 2650 Edegem, Belgium
[6] Division of Pulmonary and Sleep Medicine, Bethesda North Hospital, Cincinnati, Ohio.
[7] Division of Pulmonary, Critical Care and Sleep Medicine, University of Cincinnati, Ohio
[8] Division of Cardiology, The Ohio State University, Columbus, Ohio

CORRESPONDING AUTHOR: Christopher Schmickl; Email: cschmickl@health.ucsd.edu; Phone (858) 246-2154; Fax (858) 534 3414; 9500 Gilman Dr, La Jolla, CA 92093.

FUNDING SUPPORT AND DECLARATION OF INTERESTS
This study did not have any specific funding. The following is a list of general funding sources: Dr. Schmickl received salary support from NHLBI (T32 grant HL134632 "Training the Next Generation in Respiratory Science") during the conduct of the study. **Dr. Landry and**

ABSTRACT

Background: Therapy options for obstructive (OSA) and central (CSA) sleep apnea are limited, thus many patients remain untreated. Clinically acetazolamide is sometimes used for central sleep apnea (CSA), but given overlapping pathophysiology 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 3/11/2019. Any study in which adults with OSA/CSA received oral acetazolamide vs no acetazolamide (control) reporting 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 SpO_2 nadir. Quality of evidence (QoE) was rated using GRADE-methodology.

Results: We included 28 studies (13 OSA/15 CSA; $N_{Subjects,Acetazolamide}$=542, $N_{Subjects,Control}$=553) enabling meta-analyses for 24 outcomes. Acetazolamide doses ranged from 36-1000mg/day and treatment duration from 1-90 days (median 6days). Overall, acetazolamide vs control lowered the AHI by -0.7 effect sizes (95%-CI -0.83 to -0.58; I^2=0%; moderate QoE) corresponding 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 500mg/day). Furthermore, acetazolamide improved SpO_2 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 including sleep quality measures and blood pressure (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 management of sleep apnea patients.

Registration: PROSPERO (CRD42019147504)

KEY WORDS

Acetazolamide, Sleep apnea, Lung, Control of breathing

ABBREVIATIONS

AHI apnea-hypopnea index, BMI body mass index, CI confidence interval, CHF congestive heart failure, CPAP continuous positive airway pressure, CSA central sleep apnea, HA high altitude, IQR interquartile range, NNT number needed to treat, OSA obstructive sleep apnea, RCT randomized controlled trial, SD standard deviation, SMD, standardized mean difference, TST total sleep time

INTRODUCTION

Obstructive (OSA) and central (CSA) sleep apnea 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 arterial carbon dioxide [$paCO_2$]) 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, which induces bicarbonaturia thereby causing a hyperchloremic metabolic acidosis which increases ventilation quickly.[17] We recently completed a review of acetazolamide's side effect profile, which showed that serious events are rare, and that some common side effects such as paresthesias are dose-dependent raising 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 if 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 non-randomized studies were included *a priori* while considering 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[8-10,20-23] which focused on certain subtypes of sleep apnea (e.g. high altitude CSA), study designs (RCTs), few outcomes (usually <3) and/or English articles only (Table E1, online supplement). Consequently, prior reviews on this topic have included very few studies (0 to 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 previously reported in the form of an abstract.[24]

METHODS

This systematic review was registered at PROSPERO (CRD42019147504) and was performed according to a pre-specified protocol (Appendix E1, online supplement) following PRISMA and MOOSE guidelines (Table E2 & E3, online supplement).

Identification of Eligible Studies

We considered any study in which adults with obstructive or central sleep apnea received oral acetazolamide and were compared against a control condition (i.e. 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 [TST] with periodic breathing, SpO_2 mean, percent of TST with SpO_2 <90%, obstructive/central apnea-hypopnea indices, oxygen desaturation index), sleep parameters (TST, sleep efficiency, percent of TST in each sleep stage, arousal index), blood pressure, Epworth sleepiness score and any other patient-centered outcomes. We included

both randomized and non-randomized studies, but case reports were excluded. Further, we excluded studies in which subjects were non-human, <18y of age, intubated or on hemodialysis. Lastly, we excluded studies in which acetazolamide was administered parenterally, or co-administered with other interventions that precluded isolation of acetazolamide's effect on sleep apnea.

We (investigators) searched MEDLINE, EMBASE and ClinicalTrials.gov from inception until 3/11/2019, 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 retrieved records (CS, AM), assessed final eligibility based on full-text articles for every record which had not been unanimously excluded during the screening process (CS, SL), collected data from eligible studies using piloted Excel sheets (CS, SL), and assessed risk of bias for each included study as described below (CS, SL). All disagreements could be resolved by discussion and/or by seeking clarifications from authors.

Abstracted data included information about study participants (age, sex, body mass index [BMI], co-morbid congestive heart failure [CHF]), intervention (acetazolamide total daily dose, days of administration), pertinent labs (pH, pCO_2, pO_2, plasma bicarbonate, potassium, chloride, and creatinine concentration), and the outcomes listed above. For each outcome, we collected the mean, standard deviation and number of subjects in the acetazolamide vs control condition. If necessary, we estimated the mean from the reported median, and the standard deviation (SD) from reported standard errors, interquartile ranges or 95%-confidence intervals (CI) using standard techniques (Cochrane Handbook, Chapter 7.7.3).[25]

Risk of bias was assessed on the study-level using 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 (Appendix E1, online supplement). 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 using "weighted" mean differences. However, the AHI data were based on widely varying definitions and measurement techniques used across studies (e.g. some studies scored hypopneas based on arousals, others only based 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 using standardized

mean differences (SMD), but for better interpretability back-transformed[26] using the following equations:

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

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

Meta-Analyses & 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 using meta-regression (if $n_{studies}$ ≥8, considering the candidate effect modifiers listed below); 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, SpO_2 nadir), several sensitivity analyses were performed to assess the robustness of results. Quality of evidence was rated using GRADE.

Subgroup Analyses & Bias Assessment: According to our study objective, we assessed primary outcomes (AHI, SpO_2 nadir) for effect modification by sleep apnea type and dose using meta-regression (primary subgroup analyses). As pre-specified, for primary outcomes we further tested if duration of acetazolamide administration, population characteristics (e.g. mean age, but also study location as a proxy for race), laboratory values, or quality indicators (i.e. risk of bias,

study design, industry funding) modified the effect. The risk of publication bias was evaluated via funnel plots and Egger's test.

Post hoc Responder-Analyses: We were able to obtain individual patient-level data for the AHI from 8 cross-over studies through a combination of individual data reported in published tables and figures (using averaged values abstracted by two independent reviewers [CS, JEO]) and author communications. Thus, we explored variability of acetazolamide's effect across individuals and estimated the number needed to treat (NNT) for one sleep apnea patient to have an AHI reduction of at least 50% (+/- $AHI_{Acetazolamide}$<10/h), as well as the NNT for one sleep apnea patient to experience an increase in AHI by at least 50%.

Software: All meta-analyses were performed using Stata 12.1 (StataCorp, TX) with P<0.05 judged as significant.

RESULTS

We identified 28 eligible studies (subjects: $N_{Acetazolamide}$=542; $N_{Control}$=553)[14,29-55] including two Japanese-language articles[43,49] (Figure 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 see Table 4, online supplement): studies included mostly men, with a wide range of mean ages (31 to 69years) and mean BMIs (21.9 to 38.3kg/m^2); race was rarely reported, but about one third of studies were performed in Asia. Approximately half the studies focused on OSA, while the

others included subjects with CSA due to variety of causes. Studies administered between 36 to 1000mg/day (mean 528mg/day) of acetazolamide for 1 to 90days (median 6days). In one study acetazolamide was co-administered with CPAP (both in the acetazolamide and placebo arm, allowing isolation of the acetazolamide effect),[30] whereas in all other studies acetazolamide was given to sleep apnea patients off CPAP (i.e. untreated patients). Acetazolamide administration was randomized in about half the studies. Overall risk of bias was rated as low/unclear vs high in 46% vs 54%, respectively.

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 including OSA and CSA studies, higher doses of acetazolamide were significantly associated with greater reductions in AHI (P=0.005; results were similar when stratified by sleep apnea type, Appendix E2, online supplement), but a *post hoc* analysis suggested that the dose-dependent effect of acetazolamide on the AHI plateaus at 500mg/day (Figure 2). Acetazolamide's effect on the AHI was similar in OSA vs CSA studies (Figure 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=0.22; Figure 3 and Appendix E2, online supplement). Overall, the reduction in AHI was significantly greater in high (4 CSA, 1 OSA) vs low altitude studies, in randomized vs non-randomized studies, in studies rated as low/unclear vs high risk of bias, and in studies performed outside of Asia (Figure 3). There was no effect modification by any other candidate

variable including acetazolamide duration (Appendix E2, online supplement). The results were similar across several sensitivity analyses, and there was no evidence of publication bias (P=0.11). A *post hoc* analysis of patient-level data from 8 studies[14,32,34,39,41,43,44,52] ($N_{Subjects}$=122) suggested that responses varied between individuals independent of OSA type or acetazolamide dose (Figure 4): in 48% of patients the AHI improved by 50% or more ($NNT_{>50\%\ AHI\text{-}Reduction}$=2.1 [95%-CI 1.7 to 2.5]), but in 9% of subjects the AHI worsened by 50% or more ($NNT_{>50\%\ AHI\text{-}Increase}$ = 11.1 [95%-CI 7.1 to 25.4]). 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 (Appendix E2, online supplement), 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=0.41).

Effects on Secondary Outcomes

Other Metrics of Sleep Apnea Severity: 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).

Sleep Parameters: 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 blood pressure. Based on *post hoc* analyses, the blood pressure reduction was most pronounced in two studies[31,38] which included a large fraction of untreated hypertensive subjects. Furthermore, one study[51,57] reported relative improvements in myocardial oxygen supply/demand ratio in high altitude CSA, and one study[32] measuring ventricular ejection fractions reported no difference after 6 days of acetazolamide vs placebo in 12 patients with CSA due to heart failure.

Neurocognitive & Other Outcomes: Overall based on a meta-analysis of three studies, there was no change in Epworth Sleepiness score (range 0-24), but in two of these studies[29,38] the control score was within the normal range (<10); in the third study[53] there was a statistically non-significant but clinically important[58,59] reduction by -2.7 points (N=10, P=0.08). Two studies further assessed psychomotor vigilance: in one[29] reaction time worsened (+17.3ms; P=0.004), but the other study[30] reported a non-significant improvement of similar magnitude (-15ms; P>0.05), thus results were not pooled (I^2=80%). In addition, six studies[32,34,41,42,44,45] provided data about subjective symptoms (e.g. sleepiness, insomnia, sleep quality, snoring; Table E6, online supplement): 5 studies[32,41,42,44,45] reported an improvement with acetazolamide vs 1 study[34] which reported no change in symptoms. These subjective data should be interpreted with caution as methods were variable and most studies lacked blinding. Based on meta-analyses of

laboratory tests (Table E7, online supplement), 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 which found a slight increase with acetazolamide 1000mg/day (+0.17mg/dl; P<0.05).[14]

DISCUSSION

Increasing evidence suggests that obstructive and central sleep apnea 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 3 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 including over 500 subjects we note several findings:

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[14] in which the AHI reduction among OSA patients was independent of patients' baseline loop gain. Third, acetazolamide's effect on the AHI is dose-dependent, but seems to plateau at approximately 500mg/day; this suggests that doses greater than 500mg/day may not be beneficial for sleep apnea patients while increasing the risk of side effects, which may adversely affect tolerance and adherence.[60] Of note, at 500mg/day the number needed to treat for common side effects are 2.1 for paresthesias, 22.3 for dysgeusia (abnormal taste), 17.0 for polyuria, and 11.1 for fatigue.[18] Importantly, these estimates include

many mild cases (especially paresthesias) which may not affect adherence/tolerance, and side effects typically cluster (i.e. patients tend to have either no side effects or several ones). Thus, many patients are expected to tolerate up to 500mg/day quite well.[18] Fourth, acetazolamide appears to be beneficial across several patient-centered outcomes including sleep quality measures and subjective symptoms. Importantly the observed reduction in blood pressure (SBP -8.2mmHg [-11.5 to -4.9], DBP -4.3mmHg [-6.8 to -1.8]) was substantially greater than what is commonly achieved with CPAP therapy (SBP -2 to -4mmHg, DBP -1 to -3mmHg)[61,62]. Interestingly, OSA has been associated with increased carbonic anhydrase activity,[63] and carbonic anhydrase inhibitors such as acetazolamide may lower vascular tone through several pathways.[64,65] Thus, the comparatively greater effectiveness may be due to mechanistic reasons, but the observed effect on blood pressure 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 (N~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, two of the determinants of overall loop gain[66]): Approximately one in 11 patients 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 4 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 pathophysiological 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 (Table E1, online supplement). Thus, in the official practice guidelines from the American Academy of Sleep Medicine (AASM) 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 2 studies[42,45]) and for CSA due to congestive heart failure (based on 1 study[32]), but concludes that there is insufficient evidence for acetazolamide's use in high altitude CSA (based on 1 study[33]). Neither the clinical guideline for the management of OSA[67], nor the practice parameters for the medical therapy of OSA[10,68] mention acetazolamide. We believe that the cumulative evidence of acetazolamide's efficacy for sleep apnea and its side effect profile (see [18]) warrants greater discussion in future revisions of these documents. But when "going from evidence to recommendations", patients' values, preferences and treatment costs will need to be taken into account.[69,70]

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 i.) loop gain is an

important pathophysiological component of all subtypes of sleep apnea included in this study providing an *a priori* rationale for this approach; ii.) for primary outcomes formal testing did not reveal significant differences across OSA/CSA-subtypes *a posteriori*; iii.) effect estimates are provided separately for significant subgroups (e.g. 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 3 studies limiting insights about acetazolamide's effects on purely obstructive events. Another key limitations is that most studies assess acetazolamide's effect on sleep apnea for a maximum of two weeks, thus results may not generalize to long-term therapy. Similarly, most study participants were male and lack of effect modification by sex only provides limited reassurance (low power; risk of ecological 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 biological variation considering that OSA in Chinese vs Caucasian patients is caused more by anatomical predisposition and less by ventilatory instability.[71] 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 lacked placebo-control. In RCTs high/unclear risk of bias was often due to a lack of details about the randomization methods used, which may reflect reporting issues rather than true methodological flaws. Importantly, the effect on the AHI was actually greater in low/unclear vs high risk of bias studies (and in placebo vs non-placebo controlled studies), suggesting that the net effects of potential biases was towards the null (i.e. 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 inter-individual variability noted. Potential imbalances in sleep position across study conditions are expected to be more pronounced in non-randomized studies, thus it is further reassuring that acetazolamide's effect on the AHI was actually greater in RCTs than in observational studies (i.e. unmeasured confounders such as sleep position or first-night effects likely did not drive the positive results).

INTERPRETATION

Short-term administration of acetazolamide appears beneficial for both central and obstructive sleep apnea. More research is needed to identify responders *a priori*, assess interaction effects with other therapies targeting pathophysiological 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 125-500mg/day (1-2doses/day; evening dose 2h 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[17,42,72] (for high altitude CSA initiation one day prior to ascend could be considered[51], same as what is recommend for the prevention of acute mountain sickness[73]). Common side effects (e.g. paresthesias) are dose-dependent.[18] Thus it may be prudent to start with 3.5mg/kg body weight[32] or 125-250mg/day and titrate up every 3-5days as needed and tolerated. Co-administration with thiazide diuretics or angiotensin-receptor blockers increases the risk of hypokalemia and thus requires close monitoring and/or should be avoided.[18]

ACKNOWLEDGMENTS

Author contributions: The study was designed by CS, RO, AM; data were collected by CS, SL, JO, KC, KM, JV, SJ, AM; data were analyzed by CS and results interpreted by all authors. The manuscript and figures were drafted by CS and critically revised by all authors. CS serves as the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to publication of the article.

We would like to thank the following authors who generously provided additional clarifications and/or information (in alphabetic order): Dr Parisa Adimi, Dr Evgeny Belyavskiy, Dr Konrad Bloch, Dr Susmita Chowdhuri, Dr Geoffrey Ginter, Dr Jan Hedner, Dr Aizat Myrzaakhmatova, Dr Silvia Ulrich, and Dr Ding Zou.

REFERENCES

1 Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019;7:687-698.
2 Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet*. 2014;383:736-747.
3 Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. *J Am Coll Cardiol*. 2017;69:841-858.
4 Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol*. 2013;177:1006-1014.
5 Zinchuk A, Edwards BA, Jeon S, et al. Prevalence, Associated Clinical Features, and Impact on Continuous Positive Airway Pressure Use of a Low Respiratory Arousal Threshold Among Male United States Veterans With Obstructive Sleep Apnea. *J Clin Sleep Med*. 2018
6 Campos-Rodriguez F, Martinez-Alonso M, Sanchez-de-la-Torre M, et al. Long-term adherence to continuous positive airway pressure therapy in non-sleepy sleep apnea patients. *Sleep Med*. 2016;17:1-6.
7 Cistulli PA, Armitstead J, Pepin JL, et al. Short-term CPAP adherence in obstructive sleep apnea: a big data analysis using real world data.
8 Mason M, Welsh EJ, Smith I. Drug therapy for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev*. 2013:Cd003002.
9 Gaisl T, Haile SR, Thiel S, et al. Efficacy of pharmacotherapy for OSA in adults: A systematic review and network meta-analysis. *Sleep Med Rev*. 2019;46:74-86.
10 Veasey SC, Guilleminault C, Strohl KP, et al. Medical therapy for obstructive sleep apnea: a review by the Medical Therapy for Obstructive Sleep Apnea Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. *Sleep*. 2006;29:1036-1044.
11 Eckert DJ, Jordan AS, Merchia P, et al. Central sleep apnea: Pathophysiology and treatment. *Chest*. 2007;131:595-607.
12 Malhotra A, Owens RL. What is central sleep apnea? *Respiratory Care*. 2010;55:1168-1178.
13 Orr JE, Malhotra A, Sands SA. Pathogenesis of central and complex sleep apnoea. *Respirology*. 2017;22:43-52.
14 Edwards BA, Sands SA, Eckert DJ, et al. Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. *J Physiol*. 2012;590:1199-1211.
15 Eckert DJ, White DP, Jordan AS, et al. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *Am J Respir Crit Care Med*. 2013;188:996-1004.
16 Schmickl CN, Owens R, Edwards BA, et al. OSA Endotypes: What Are They and What Are Their PotentialClinical Implications? Current Sleep Medicine Reports (2018) 4:231–242.
17 Swenson ER. Carbonic anhydrase inhibitors and ventilation: a complex interplay of stimulation and suppression. *Eur Respir J*. 1998;12:1242-1247.
18 Schmickl CN, Owens RL, Orr JE, et al. Side effects of acetazolamide: a systematic review and meta-analysis assessing overall risk and dose dependence. *BMJ Open Respir Res*. 2020;7
19 Shrier I, Boivin JF, Steele RJ, et al. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. *Am J Epidemiol*. 2007;166:1203-1209.

20 Aurora RN, Chowdhuri S, Ramar K, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. *Sleep*. 2012;35:17-40.
21 Hudgel DW, Thanakitcharu S. Pharmacologic treatment of sleep-disordered breathing. *Am J Respir Crit Care Med*. 1998;158:691-699.
22 Liu HM, Chiang IJ, Kuo KN, et al. The effect of acetazolamide on sleep apnea at high altitude: a systematic review and meta-analysis. *Ther Adv Respir Dis*. 2017;11:20-29.
23 Wongboonsin J, Thongprayoon C, Bathini T, et al. Acetazolamide Therapy in Patients with Heart Failure: A Meta-Analysis. *J Clin Med*. 2019;8
24 Owens RL, Malhotra A. Acetazolamide for Sleep Disordered Breathing: A Systematic Review and Meta-Analysis of Effects and Side Effects. Presented as RAPID-Poster (A109) at ATS Conference; May 1, 2019.; A2596-A2596
25 Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.
26 Fu R, Vandermeer BW, Shamliyan TA, et al. Handling Continuous Outcomes in Quantitative Synthesis. 2013 Jul 25. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK154408/ (last accessed 12/20/2019).
27 Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *Bmj*. 2003;327:557-560.
28 Friedrich JO, Adhikari NK, Beyene J. The ratio of means method as an alternative to mean differences for analyzing continuous outcome variables in meta-analysis: a simulation study. *BMC Med Res Methodol*. 2008;8:32.
29 Ulrich S, Keusch S, Hildenbrand FF, et al. Effect of nocturnal oxygen and acetazolamide on exercise performance in patients with pre-capillary pulmonary hypertension and sleep-disturbed breathing: randomized, double-blind, cross-over trial. *Eur Heart J*. 2015;36:615-623.
30 Latshang TD, Nussbaumer-Ochsner Y, Henn RM, et al. Effect of acetazolamide and autoCPAP therapy on breathing disturbances among patients with obstructive sleep apnea syndrome who travel to altitude: a randomized controlled trial. *Jama*. 2012;308:2390-2398.
31 Nussbaumer-Ochsner Y, Latshang TD, Ulrich S, et al. Patients with obstructive sleep apnea syndrome benefit from acetazolamide during an altitude sojourn: a randomized, placebo-controlled, double-blind trial. *Chest*. 2012;141:131-138.
32 Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. *Am J Respir Crit Care Med*. 2006;173:234-237.
33 Fischer R, Lang SM, Leitl M, et al. Theophylline and acetazolamide reduce sleep-disordered breathing at high altitude. *Eur Respir J*. 2004;23:47-52.
34 Whyte KF, Gould GA, Airlie MA, et al. Role of protriptyline and acetazolamide in the sleep apnea/hypopnea syndrome. *Sleep*. 1988;11:463-472.
35 Hackett PH, Roach RC, Harrison GL, et al. Respiratory stimulants and sleep periodic breathing at high altitude. Almitrine versus acetazolamide. *Am Rev Respir Dis*. 1987;135:896-898.

36 Apostolo A, Agostoni P, Contini M, et al. Acetazolamide and inhaled carbon dioxide reduce periodic breathing during exercise in patients with chronic heart failure. *J Card Fail*. 2014;20:278-288.
37 Rodway GW, Edsell ME, Wong B, et al. Improving sleep at altitude: a comparison of therapies. *Wilderness Environ Med*. 2011;22:316-320.
38 Eskandari D, Zou D, Grote L, et al. Acetazolamide Reduces Blood Pressure and Sleep-Disordered Breathing in Patients With Hypertension and Obstructive Sleep Apnea: A Randomized Controlled Trial. *J Clin Sleep Med*. 2018;14:309-317.
39 Fontana M, Emdin M, Giannoni A, et al. Effect of acetazolamide on chemosensitivity, Cheyne-Stokes respiration, and response to effort in patients with heart failure. *Am J Cardiol*. 2011;107:1675-1680.
40 Inoue Y, Takata K, Sakamoto I, et al. Clinical efficacy and indication of acetazolamide treatment on sleep apnea syndrome. *Psychiatry Clin Neurosci*. 1999;53:321-322.
41 Sakamoto T, Nakazawa Y, Hashizume Y, et al. Effects of acetazolamide on the sleep apnea syndrome and its therapeutic mechanism. *Psychiatry Clin Neurosci*. 1995;49:59-64.
42 DeBacker WA, Verbraecken J, Willemen M, et al. Central apnea index decreases after prolonged treatment with acetazolamide. *Am J Respir Crit Care Med*. 1995;151:87-91.
43 Chin K, Ohi M, Fukui M, et al. [Therapy and clinical symptoms in patients with obstructive sleep apnea in Japan]. *Nihon Kyobu Shikkan Gakkai Zasshi*. 1992;30:270-277.
44 Tojima H, Kunitomo F, Kimura H, et al. Effects of acetazolamide in patients with the sleep apnoea syndrome. *Thorax*. 1988;43:113-119.
45 White DP, Zwillich CW, Pickett CK, et al. Central sleep apnea. Improvement with acetazolamide therapy. *Arch Intern Med*. 1982;142:1816-1819.
46 Ginter GM, Vaughan SE, Carroll SW, et al. Acetazolamide decreases susceptibility to hypocapnic central apnea in chronic sci. *American Journal of Respiratory and Critical Care Medicine*. 2018;197
47 Pranathiageswaran S, Badr MS, Chowdhuri S. Acetazolamide stabilizes breathing in healthy older adults during NREM sleep. *American Journal of Respiratory and Critical Care Medicine*. 2014;189
48 Belyavskiy E, Litvin A, Mareev V. Effects of acetazolamide in patients with obstructive sleep apnea syndrome and chronic heart failure. *European Heart Journal*. 2010;31:857.
49 Inoue H. Therapeutic effects of a carbonic anhydrase inhibitor (acetazolamide) on sleep apnea syndrome. Multicenter clinical investigation. *Japanese Journal of Neuropsychopharmacology*. 1987;9:493-513.
50 Sutton JR, Houston CS, Mansell AL, et al. Effect of acetazolamide on hypoxemia during sleep at high altitude. *N Engl J Med*. 1979;301:1329-1331.
51 Caravita S, Faini A, Lombardi C, et al. Sex and acetazolamide effects on chemoreflex and periodic breathing during sleep at altitude. *Chest*. 2015;147:120-131.
52 Verbraecken J, Willemen M, Boudewyns A, et al. Effect of a single dose of acetazolamide on central apnea index in patients with central sleep apnea. *Sleep-Wake Research in The Netherlands*. 2005;16:177-180.
53 Adimi Nagan P. NCT02371473: Effect of Acetazolamide on Central Sleep Apnea Related to Opium Consumption
54 Wellman A. NCT01377987: Predicting Successful Sleep Apnea Treatment With Acetazolamide in Heart Failure Patients
55 Strohl KP. NCT00746954: Buspirone as a Potential Treatment for Recurrent Central Apnea

56 Myrzaakhmatova AK. Development of the optimal therapy for obstructive sleep apnea syndrome associated with pulmonary hypertension patients living at high altitude. *Pulmonologiya*. 2016;26:379-384.
57 Salvi P, Revera M, Faini A, et al. Changes in subendocardial viability ratio with acute high-altitude exposure and protective role of acetazolamide. *Hypertension*. 2013;61:793-799.
58 Crook S, Sievi NA, Bloch KE, et al. Minimum important difference of the Epworth Sleepiness Scale in obstructive sleep apnoea: estimation from three randomised controlled trials. *Thorax*. 2019;74:390-396.
59 Patel S, Kon SSC, Nolan CM, et al. The Epworth Sleepiness Scale: Minimum Clinically Important Difference in Obstructive Sleep Apnea. *Am J Respir Crit Care Med*. 2018;197:961-963.
60 Schmickl CN, Owens RL, Orr J, et al. 0567 Side Effects of Acetazolamide - A Systematic Review and Meta-Analysis Assessing Overall Risk and Dose-Dependence. *Sleep*. 2019;42:A225-A226.
61 Montesi SB, Edwards BA, Malhotra A, et al. The effect of continuous positive airway pressure treatment on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *J Clin Sleep Med*. 2012;8:587-596.
62 Fava C, Dorigoni S, Dalle Vedove F, et al. Effect of CPAP on blood pressure in patients with OSA/hypopnea a systematic review and meta-analysis. *Chest*. 2014;145:762-771.
63 Wang T, Eskandari D, Zou D, et al. Increased Carbonic Anhydrase Activity is Associated with Sleep Apnea Severity and Related Hypoxemia. *Sleep*. 2015;38:1067-1073.
64 Pickkers P, Hughes AD, Russel FG, et al. In vivo evidence for K(Ca) channel opening properties of acetazolamide in the human vasculature. *Br J Pharmacol*. 2001;132:443-450.
65 Aamand R, Dalsgaard T, Jensen FB, et al. Generation of nitric oxide from nitrite by carbonic anhydrase: a possible link between metabolic activity and vasodilation. *Am J Physiol Heart Circ Physiol*. 2009;297:H2068-2074.
66 Javaheri S, Sands SA, Edwards BA. Acetazolamide attenuates Hunter-Cheyne-Stokes breathing but augments the hypercapnic ventilatory response in patients with heart failure. *Ann Am Thorac Soc*. 2014;11:80-86.
67 Epstein LJ, Kristo D, Strollo PJ, Jr., et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med*. 2009;5:263-276.
68 Morgenthaler TI, Kapen S, Lee-Chiong T, et al. Practice parameters for the medical therapy of obstructive sleep apnea. *Sleep*. 2006;29:1031-1035.
69 Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol*. 2011;64:1283-1293.
70 Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *Bmj*. 2008;336:1049-1051.
71 O'Driscoll DM, Landry SA, Pham J, et al. The physiological phenotype of obstructive sleep apnea differs between Caucasian and Chinese patients. *Sleep*. 2019;42
72 Alper AB, Jr., Tomlin H, Sadhwani U, et al. Effects of the selective cyclooxygenase-2 inhibitor analgesic celecoxib on renal carbonic anhydrase enzyme activity: a randomized, controlled trial. *Am J Ther*. 2006;13:229-235.
73 www.uptodate.com "Acetazolamide". (last accessed 1/10/2020).

Table 1. Characteristics of Included Studies (N=28).

	Mean (SD) or Median [IQR] or % ($N_{Studies}$)	Range	$N_{Studies}$
Population Characteristics			
Mean-Age, years	55.4 (9.4)	31 to 69[a]	25
Percent Female	8 [0 to 18]	0 to 75	22
Mean-BMI, kg/m^2	29 (4)	21.9 to 38.3	17
Mean-Weight, kg	81 (10.8)	65.4 to 96.1	7
Sleep Apnea Type			28
Primarily Obstructive Sleep Apnea[b]	46% (13)	na	
Comorbid Congestive Heart Failure	11% (3)	na	
Performed at High Altitude	4% (1)	na	
Primarily Central Sleep Apnea	54% (15)	na	
CSA-High Altitude	21% (6)	na	
CSA-Congestive Heart Failure	11% (3)	na	
CSA-Opioids	4% (1)	na	
CSA-Idiopathic	11% (3)	na	
CSA-Other[c]	7% (2)	na	
Study Location			28
North America	32% (9)	na	
Europe	39% (11)	na	
Asia	29% (8)	na	
Japan	18% (5)	na	
Intervention Characteristics			
Acetazolamide			
Total Daily Dose, mg/day[d]	528 (308)	36 to 1000	28
Total Daily Dose (categorical)			28
<500 mg/day	54% (15)	na	
≥500 mg/day	46% (13)	na	
Days of Administration (continuous)	6 [3 to 9]	1 to 90	28
Days of Administration (categorical)			28
<3 days	21% (6)	na	
3 to 7 days	50% (14)	na	
>7 days	29% (8)	na	
No. Subjects, Acetazolamide Arm	12 [9 to 21]	4 to 75	28
No. Subjects, Control Arm	12 [9 to 22]	4 to 75	28
Quality Indicators			
Overall Bias			28
Low	7% (2)	na	
Unclear	39% (11)	na	
High	54% (15)	na	
Study Design			28
RCT	57% (16)	na	
Parallel Group	46% (13)	na	
Cross-Over	14% (4)	na	
Observational	43% (12)	na	
Industry Funding			28
Yes/Unclear	39% (11)	na	
No	61% (17)	na	

[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, respectively.
[b] Five studies[31,36,47,49,54] included patients judged to have primarily OSA but potentially including also some patients with CSA (subgroup analyses were similar when classifying these studies as CSA instead, Appendix E2, online supplement)
[c] One study included subjects with CSA in the setting of pre-capillary pulmonary hypertension[29], the other study included subjects with CSA in the setting of spinal cord injury[46]
[d] One study[32] administered 3.5 to 4mg/kg/day - assuming an average weight of 75kg we estimated the mean daily dose as 75kg x 3.75mg/kg/day = 281mg/day. One study[48] administered 250mg/week, thus we estimated the daily dose as 250mg/7days = 36mg/day.

Table 2. Effect of Acetazolamide on Sleep Apnea Severity, Sleep Parameters, Cardiovascular and Other Outcomes. For details of meta-analyses including forest plots see Appendix E2, online supplement.

							Acetazolamide			Control		
	Δ (95%-CI)	I^2	$N_{Studies}$	$P_{\Delta=0}$	Δ Type	GRADE	$Mean_{wt}$	(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*	S_F	⊕⊕⊕◯	22.9	(19.2)	529	36.5	(23.2)	540
- AHI, per hour[m]	-13.8 (-16.3 to -11.4)											
- AHI, % of control[m]	-37.7 (-44.7 to 31.3)											
SpO_2 Nadir (%)[a]	+4.4 (2.3 to 6.5)	63%	13	<.001*	W_R	⊕◯◯◯	81.1	(6.6)	245	76.8	(8.2)	247
Secondary Outcomes												
Sleep Apnea Severity												
SpO_2 Mean (%)[b]	+3.5 (2.3 to 4.8)	82%	12	<.001*	W_R	⊕⊕◯◯	88.9	(2.5)	218	85.3	(3.4)	215
Time with SpO_2 <90% (%TST)[c,d]	-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})[e]	-12.2 (-19.2 to 5.2)	65%	5	.02*	W_R	⊕⊕◯◯	9.0	(11.1)	107	21.3	(16.9)	107
Obstructive AHI (h^{-1})[f]	-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})[c,g]	-9.5 (-14.0 to -4.9)	56%	8	<.001*	W_R	⊕◯◯◯	5.8	(10.5)	214	15.3	(19.2)	214
Hypopnea Index (h^{-1})[n]	-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)[c,h]	-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 (sec)[i]	+0.8 (-1.5 to 3.1)	53%	6	.50	W_R	⊕◯◯◯	24.3	(5.9)	106	23.5	(5.5)	107
Sleep Parameters												
Arousal Index, total (h^{-1})[j]	-6.6 (-11.3 to -2.0)	32%	6	.005*	W_R	⊕⊕◯◯	23.9	(14.5)	140	30.5	(16.2)	140
Total Sleep Time, TST (min)[j]	+20.0 (7.1 to 32.9)	28%	10	.002*	W_F	⊕⊕◯◯	377.2	(72.4)	292	357.2	(86.3)	292
Sleep Efficiency (%)[j]	+5.5 (3.2 to 7.8)	0%	12	<.001*	W_F	⊕⊕◯◯	80.8	(12.9)	305	75.3	(15.8)	305
Stage N1 (%TST)[j]	-4.7 (-7.6 to -1.9)	14%	5	.001*	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*	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*	W_F	⊕⊕◯◯	7.8	(6.8)	237	6.5	(6.4)	237
Stage REM (%TST)[j]	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 (mmHg)[h]	-8.2 (-11.5 to -4.9)	0%	5	<.001*	W_F	⊕⊕◯◯	128.0	(12.1)	99	136.2	(12.2)	114
Diastolic Blood Pressure (mmHg)	-4.3 (-6.8 to -1.8)	0%	5	.001*	W_F	⊕⊕◯◯	79.0	(8.7)	99	83.3	(9.8)	114
Mean Blood Pressure (mmHg)	-5.2 (-7.5 to -2.8)	0%	4	<.001*	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
Epworth Sleepiness Score, ESS[k]	-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

Abbreviations & Explanations: 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}) denote weighted mean and standard deviations; N_{Subj} number of subjects. As detailed in Table E5 in the online supplement, based on GRADE methodology quality of evidence was rated as: very low (⊕○○○), low (⊕⊕○○), moderate (⊕⊕⊕○) or high (⊕⊕⊕⊕).

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

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

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

d 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<0.001 with acetazolamide vs control.

e Heterogeneity was primarily due to one study[33]; results were similar when excluding this study (-9.8 [95%-CI: -12.0 to -5.5], I^2=0%; P<.001)

f Heterogeneity was primarily due to one study[14], results remained non-significant when excluding this study (-2.5 [95%-CI: -11.1 to 6.0], I^2=0, P=.56)

g 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.

h 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.

i *Post hoc* analyses suggested potential effect modification by acetazolamide dose (P=.053); in studies administering ≥500mg/day event duration increased by 3.2 seconds (95%-CI: 0.6 to 5.9), I^2=0%, P=0.02 with acetazolamide vs control, whereas in studies administering <500mg/day event duration was unchanged (-1.1 seconds [95%-CI: -3.1 to 0.8]; P=0.21).

j Results were similar when including only randomized trials suggesting that the change in outcome was not due to confounding by first night effects (i.e. baseline/control during the first night vs acetazolamide administered during a subsequent night).

k In part heterogeneity is likely due to varying baseline severity (only one of the three studies had a baseline ESS within the abnormal range, i.e. >10)

m Calculated based on the effect size, pooled standard deviation ($SD_{Control,Acetazolamide}$ = 19.7), and the pooled $AHI_{Control}$ (36.5/h); for details see methods.

n Differences in underlying hypopnea definitions likely contributed to the heterogeneity (lower I^2 when analysis was performed using SMDs, but overall results were similar thus results from the WMD analysis are reported here; effect may also be more pronounced in OSA vs CSA studies; for details see Appendix E2, online supplement).

FIGURE-LEGENDS

Figure 1. PRISMA Flowchart.

Figure 2. Meta-Regression: Dose-Dependent Effect of Acetazolamide on AHI. Based on primary analysis higher doses of acetazolamide were associated with greater reductions in AHI ($\beta_{per100mg}$ = -0.08 [95%-CI -0.14 to -0.03], P=0.005; dashed line). However, a *post hoc* analysis suggested that the dose-dependent effect of acetazolamide on the AHI plateaus at 500mg/day ($\beta_{per100mg}$ = -0.16, P=0.008 up to 500mg, but $\beta_{per100mg}$ = -0.03, P=0.52 from 500-1000mg; solid line; for details see Appendix E2, online supplement).

Figure 3. Subgroup Analyses for the Apnea-Hypopnea Index. For complete results of subgroup analyses see Appendix E2 (online supplement). Abbreviations: OSA/CSA obstructive/central sleep apnea, HA high altitude, CHF congestive heart failure, P_{EM} p-value for effect modification, SMD standardized mean difference.

Figure 4. Individual Responses based on patient-level data from 8 cross-over studies[14,32,34,39,41,43,44,52]. Median percent-change was -49.8% (IQR -67.8 to -17.6%). Across responder strata there was no significant difference between OSA vs CSA, 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 AHI improved by -25 to 0% (P=0.047).