

REVIEW ARTICLES

The role of acetazolamide in sleep apnea at sea level: a systematic review and meta-analysis

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Study Objectives: The recognition of specific endotypes as drivers of sleep apnea suggests the need of therapies targeting individual mechanisms. Acetazolamide is known to stabilize respiration at high altitude but benefits at sea level are less well understood.

Methods: All controlled studies of acetazolamide in obstructive sleep apnea and/or central sleep apnea (CSA) were evaluated. The primary outcome was the apnea-hypopnea index.

Results: Fifteen trials with a total of 256 patients were pooled in our systematic review. Acetazolamide reduced the overall apnea-hypopnea index (mean difference [MD] -15.82 , 95% CI: -21.91 to -9.74 , $P < .00001$) in central sleep apnea (MD -22.60 , 95% CI: -29.11 to -16.09 , $P < .00001$), but not in obstructive sleep apnea (MD -10.29 , 95% CI: -33.34 to 12.77 , $P = .38$). Acetazolamide reduced the respiratory related arousal index (MD -0.82 , 95% CI: -1.56 to -0.08 , $P = .03$), improved partial arterial of oxygen (MD 11.62 , 95% CI: 9.13 – 14.11 , $P < .00001$), mean oxygen saturation (MD 1.78 , 95% CI: 0.53 – 3.04 , $P = .005$), total sleep time (MD 25.74 , 95% CI: 4.10 – 47.38 , $P = .02$), N2 sleep (MD 3.34 , 95% CI: 0.12 – 6.56 , $P = .04$) and sleep efficiency (MD 4.83 , 95% CI: 0.53 – 9.13 , $P = .03$).

Conclusions: Acetazolamide improves the apnea-hypopnea index and several sleep metrics in central sleep apnea. The drug may be of clinical benefit in patients with high loop gain apnea of various etiologies and patterns. The existence of high heterogeneity is an important limitation in applicability of our analysis.

Systematic Review Registration: Registry: PROSPERO; Name: The effect of acetazolamide in patients with sleep apnea at sea level: a systematic review and meta analysis; URL: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020163316; Identifier: CRD42020163316.

Keywords: acetazolamide, central sleep apnea, obstructive sleep apnea

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INTRODUCTION

Sleep apnea is a disease with intermittent cessation and/or decrease of airflow during sleep. Sleep apnea is associated with adverse cardiovascular and cerebrovascular outcomes and an increased risk of mortality.^{1–3} Positive airway pressure (PAP), whose main effect is keeping the upper airway open, is regarded as the first line therapy for obstructive sleep apnea (OSA) and is frequently used for treatment of central sleep apnea (CSA), but less effective in the latter one.^{4,5} Alternative therapies for OSA include oral appliances, surgical enhancement of the upper airway, weight loss, and hypoglossal nerve stimulation.⁶

Despite widespread use, PAP use is associated with insufficient adherence and variable degrees of residual apnea. In patients with OSA, only about 40–70% patients continue use of PAP for more than 3 months and up to 15–30% of patients may show a residual apnea-hypopnea index (AHI) > 5 events/h after PAP treatment.^{7–9} One reason for residual apnea is likely persistent high loop gain, leading to instability of respiratory rhythm in nonrapid eye movement sleep.¹⁰ Several mechanisms/endotypes that may drive/contribute to the AHI have been recognized, including high loop gain, low arousal threshold, poor muscle responsiveness, and sleep fragmentation.¹¹ Thus, there is a possible role for pharmacological adjuncts that may

target high loop gain to improve precision of treatment of sleep apnea syndromes, regardless of the phenotype established by conventional scoring.

Continuous PAP use in CSA is usually associated with substantial residual central apnea.¹² Adaptive servo-ventilation is an approved option for CSA, but efficacy is inconsistent,^{13,14} and sleep quality improvements are inferior to that achieved with CPAP in patients with OSA.¹⁵

Acetazolamide (ATZ) has been shown to improve CSA at high altitude.¹⁶ Physiological assessments in tightly controlled experimental conditions show that the drug attenuates elevated loop gain and the ventilatory response to arousal in patients with OSA at sea level.^{17,18} However, its clinical effect on patients with OSA and/or CSA at sea level remains unclear and is not part of any standard practice guideline. We performed this systematic review and meta-analysis to assess if the published literature may support such use.

METHODS

Search strategies

A comprehensive computer search of literature from 1946 to May 2020 was conducted by 2 independent investigators (Y.-N. N. and H.Y.) in PubMed, Medline, Embase, Information Sciences

Institute (ISI) Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) using the keywords of “acetazolamide” or “ATZ” or “Diamox” or “sleep apnea” or “sleep breathing” or “periodic breathing” or “Cheyne-Stokes breathing” without limitations in the publication type or language. The references listed in each identified article were reviewed, and the related articles were manually searched to identify all eligible studies to minimize potential publication bias.

Inclusion and exclusion criteria

Eligible clinical trials were identified based on the following criteria: 1) the participants enrolled in each study included patients with OSA and/or CSA (including those who received treatment but had persistent residual sleep apnea); 2) patients were compared before and after ATZ (pre-post) or divided into an experimental group, in which ATZ was applied, and a control group, in which patients were assigned to receive placebo or another drug; 3) outcomes included but were not limited to standard sleep breathing parameters. We excluded studies if they were performed in animals or in patients under 18 years of age, were conducted at high altitude (defined as a study in patients who ascended $\geq 2,500$ m or described as a high-altitude study in the title, abstract, or full manuscript), were designed to assess physiological responses, were published as reviews or case reports, or not undergone peer review.

Study selection

Y.-N. N. and H. Y. performed study selection in 2 phases. First, they screened titles. Second, noncontrolled studies were excluded by screening the abstracts. Third, according to the study inclusion and exclusion criteria listed above, eligible studies were extracted by reviewing full texts. Any discrepancies and doubts were resolved by consensus with a third investigator (R.J.T.).

Data extraction

Data extraction forms including authors, publication year, study design, population, demographic characteristics (age, sex, etc.), type of sleep apnea, comorbidities (heart failure, hypertension, etc.), details about the administration of ATZ (dose and duration), outcome measures, and study results were conducted by the 2 data collectors. A third investigator checked all the information and also resolved discrepancies if there was any disagreement.

Quality assessment

The risk of bias in estimating study outcomes was assessed as low, unclear, or high for each of the following items: sequence generation, allocation sequence concealment, blinding of participants and clinicians, blinding of outcome assessment, incomplete outcome data assessment, and other bias. The overall risk of bias for each included trial was categorized as low if the risk of bias was low in all domains, unclear if the risk of bias was unclear in 1 or more domains and with no judgment of high risk of bias, or high if the risk of bias was high in 1 or more domains. Any divergence was resolved by discussing with a third investigator.

Statistical analysis

Continuous outcomes were analyzed by the inverse variance weighting method and calculated as mean difference (MD) and

95% confidence interval (CI). A Z-value and P value $< .05$ indicated statistical significance. An initial test for clinical, methodological, and statistical heterogeneities was exploring by using χ^2 test. A value of $P < .1$ and $I^2 > 50\%$ indicates significance. In view of statistical heterogeneity, random-effects model was applied. We also performed a sensitivity analysis to substitute alternative decisions or ranges of values for decisions that are arbitrary or unclear. All meta-analyses were carried out by using Cochrane systematic review software Review Manager (RevMan; Version 5.3.5; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) and the results were displayed in Forest plots.

RESULTS

Initially, 6,541 records were identified, of which 6,539 were extracted from electronic databases and 2 were extracted from reference lists review (Figure 1). By screening the titles and abstracts, studies were discarded for duplication ($n = 6,385$), animal experiments ($n = 5$), non-adult patients ($n = 6$), non-sea level studies ($n = 22$), non-controlled studies ($n = 96$), and non-apnea patients ($n = 7$). We searched the full-text articles for the remaining 20 studies, and eventually 15 trials^{19–32} were enrolled in our final analysis. Two were not designed as expected, as multiple physiological challenges were utilized and could not truly reflect clinical effects,^{17,18} 2 were a subgroup analysis of another included study,^{33,34} 1 due to inability to obtain an English translation.³⁵

Study description

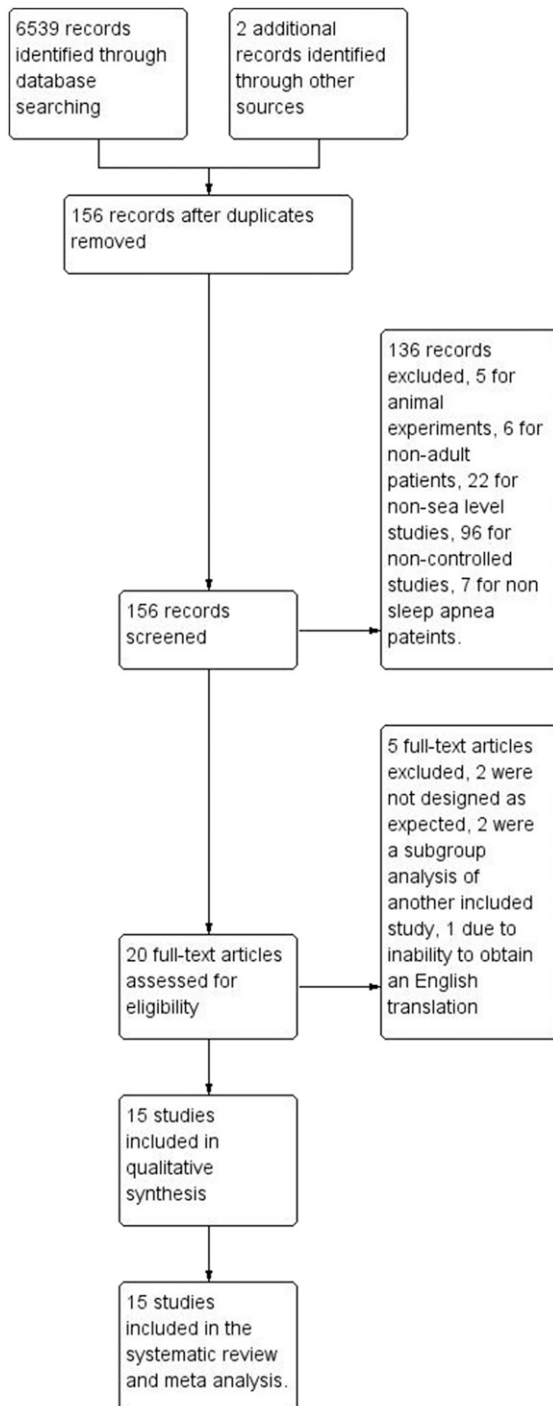
All studies explored the role of ATZ in sleep apnea patients. Nine studies were pre-post studies,^{19,20,22,23,26–28,30,31} 6 studies were randomized crossover studies,^{21,24,25,29,32,36} among which 1 study included patients using continuous positive airway pressure (CPAP) and was not included in the meta-analysis.²¹ Among the 14 studies included in the meta-analysis,^{19,20,22–32} the obstructive apnea index (OAI) was reported in 5 studies,^{20,24–26,30} and the central apnea index was reported in 6 studies,^{20,24–26,30,36} and the duration of respiratory events was reported in 4 studies.^{19,26,27,32} The lowest saturation of oxygen (SaO₂) was reported in 7 studies.^{19,22–24,27,28,32} 3 studies reported the mean SaO₂,^{19,29,36} arterial partial carbon dioxide pressure (PaCO₂) was reported in 8 studies,^{20,22,24,27–31} the respiratory related arousal index was reported in 4 studies,^{24,30,31,36} the slope of the hypercapnic ventilatory response was reported in 7 studies.^{19,20,22,24,28,30,36} Two studies focused only on patients with OSA,^{21,32} 8 studies only included patients with CSA,^{20,22,24,25,29–31,36} among which 1 was caused by opioid drugs,²⁵ and 1 was caused by chronic spinal cord injury.³⁶ Three studies included patients with both sleep breathing disorder and heart failure.^{19,22,24} Table 1 lists the details of each study.

A total of 256 patients was pooled from all the included trials in our final systematic review and meta-analysis. Details of baseline characteristics of patients in each enrolled study are shown in Table 2.

Quality assessment

Quality assessments of the 15 enrolled studies showed no bias in attribution, detection, or reporting in 6 studies, but high bias in

Figure 1—Study flow.



selection, performance, and detection was showed in another 9 studies (Figure S1 and Figure S2 in the supplemental material). No studies were excluded for low quality or dubious decisions in the sensitivity analysis. No publication bias was found (Figure S3).

Overall effects of ATZ

ATZ reduced the overall AHI (MD -15.82 , 95% CI: -21.91 to -9.74 , $Z = 5.10$, $P < .00001$) (Figure S4). When

divided by different sleep apnea types, ATZ reduced the AHI in patients with CSA (MD -22.60 , 95% CI: -29.11 to -16.09 , $Z = 6.80$, $P < .00001$) and unknown or mixed sleep apnea (MD -8.14 , 95% CI: -11.70 to -4.59 , $Z = 4.49$, $P < .00001$), but not in patients with OSA (MD -10.29 , 95% CI: -33.34 to 12.77 , $Z = 0.87$, $P = .38$) (Figure S5). The results remained unchanged when divided into those with and without heart failure (Figure S6).

CSA

ATZ reduced CSA and the central apnea index was reduced (MD -12.23 , 95% CI: -19.43 to -5.02 , $Z = 3.33$, $P = .0009$). Significant heterogeneity was found in ($I^2 = 79\%$, $\chi^2 = 29.05$, $P < .0001$) (Figure 2). The results remained unchanged when divided into those with and without heart failure (Figure S7).

OSA

Overall, no significant effect of ATZ in reducing the OAI was found (MD -2.26 , 95% CI: -5.62 to 1.10 , $Z = 1.32$, $P = .19$). ATZ showed a trend of lower the OAI in patients without heart failure (MD -3.64 , 95% CI: -7.47 to 0.20 , $Z = 1.86$, $P = .06$), but statistic significant was not found (Figure S8). Statistical heterogeneity existed in this analysis ($I^2 = 68\%$, $\chi^2 = 12.39$, $P = .01$) (Figure 3). Percentages of change in AHI, OAI, and central apnea index are listed in the Table S1.

Respiratory event duration

No significant effect of ATZ in reducing the duration of respiratory events was found (MD 0.96 , 95% CI: -1.32 to 3.24 , $Z = 0.82$, $P = .41$). Significant heterogeneity existed in this analysis ($I^2 = 55\%$, $\chi^2 = 11.08$, $P = .05$) (Figure S9).

Respiratory related arousal index

ATZ reduced the respiratory related arousal index (MD -0.82 , 95% CI: -1.56 to -0.08 , $Z = 2.17$, $P = .03$). Significant heterogeneity was found ($I^2 = 57\%$, $\chi^2 = 6.94$, $P = .07$) (Figure S10).

PaO₂, lowest SaO₂, and mean SaO₂

Higher PaO₂ was found when patients were treated with ATZ (MD 11.62 , 95% CI: 9.13 – 14.11 , $Z = 9.15$, $P < .00001$) (Figure 4). High heterogeneity was found in the analysis ($I^2 = 58\%$, $\chi^2 = 11.91$, $P = .04$). ATZ did play a role in improving the lowest SaO₂ in the overall analysis (MD 2.95 , 95% CI: 0.61 – 5.29 , $Z = 2.47$, $P = .01$) (Figure S11 and Figure S12). However, no significant role was found in each sleep apnea type. High heterogeneity was found in the analysis ($I^2 = 52\%$, $\chi^2 = 16.57$, $P = .03$). ATZ increased the mean SaO₂ minimally (MD 1.78 , 95% CI 0.53 – 3.04 , $Z = 2.78$, $P = .005$) especially in the crossover study (MD 2.15 , 95% CI 0.40 – 3.90 , $Z = 2.40$, $P = .02$) and patients with CSA (Figure S13 and Figure S14)

Sleep architecture

ATZ increased total sleep time (MD 25.74 , 95% CI: 4.10 – 47.38 , $Z = 2.33$, $P = .02$) (Figure S15) and improved sleep efficiency (MD 4.83 , 95% CI: 0.53 – 9.13 , $Z = 2.20$, $P = .03$) (Figure S16). However, ATZ did not change the percentages of N1

Table 1—Characteristics of included studies.

Study	Study Design	Population	Inclusion Criteria	Dose of Acetazolamide	Comparison
Central					
DeBacker et al, 1995 ²⁰	Pre-post study	14	CSA	250 mg orally at night for 1 month	N/A
Fontana et al, 2011 ²²	Pre-post study	12	Hunter-Cheyne-Stokes breathing with AHI > 15 events/h and heart failure (LVEF < 50%). Patients with NYHA IV, acute coronary syndromes within the previous 6 months, glomerular filtration rate < 30 ml/min or pulmonary disease were excluded	250 mg twice a day orally for 4 days	N/A
Ginter and Sankari, 2020 ³⁶	Randomized crossover study	16	CSA with either chronic spinal cord injury (> 6 months) at or above the T6 level or able-bodied control	500 mg 2 times a day orally for 3 days	N/A
Javaheri, 2006 ²⁴	Randomized crossover study	12	CSA with AHI ≥ 15 events/h, Hunter-Cheyne-Stokes breathing, systolic heart failure with LVEF < 35%, and NYHA II or III	3.5 mg/kg orally at night for 6 days	Placebo (potassium chloride 30 mEq)
Naghan et al, 2019 ²⁵	Randomized crossover study	10	CSA caused by opioid drug	250 mg orally at night for 6 days	Placebo
Ulrich et al, 2015 ²⁹	Randomized crossover study	23	SBD and precapillary pulmonary hypertension or CTEPH, PaO ₂ ≥ 7.3 kPa during daytime. Patients with predominantly OSA, more than mild lung disease, or concomitant left ventricular disease were excluded	250 mg twice a day orally for 1 week	Placebo
Verbraecken et al, 1998 ³⁰	Pre-post study	8	CSA	250 mg orally at night for 1 month	N/A
White et al, 1982 ³¹	Pre-post study	6	5 patients with CSA, 1 with OSA	250 mg 4 times a day for at least 7 days	N/A
Obstructive					
Eskandari et al, 2018 ²¹	Randomized crossover study	13	OSA with AHI > 15 events/h, treated systemic hypertension, BMI ≤ 35 kg/m ² and ESS score > 6	250 mg orally twice a day for initial 3 days and 3 times a day for the following 2 weeks	AZT + CPAP and CPAP
Whyte et al, 1988 ³²	Randomized crossover study	10	OSA with AHI ≥ 15 events/h, with at least 2 of the following symptoms: daytime somnolence, loud snoring, unsatisfying nocturnal sleep, or recurrent nocturnal awakening	250 mg orally twice a day for 1st week and 250 mg 4 times a day for 2nd week	Placebo
Unknown or Mixed Type					
Apostolo et al, 2014 ¹⁹	Pre-post study	18	Heart failure with LVEF < 40%, NYHA II or III, PB during exercise	500 mg intravenous 3 times a day	N/A
Inoue et al, 1999 ²³	Pre-post study	75	Sleep apnea	Mean of 351.2 mg/day orally for mean 39.5 days	No
Sakamoto et al, 1995 ²⁶	Pre-post study	20	Sleep apnea	250 mg orally for 10 patients, 500 mg orally for 8 patients, and 750 mg orally for 2 patients for 17–115 days	N/A
Sharp et al, 1985 ²⁷	Pre-post study	10	4 patients with OSA, 2 with CSA, 4 with MSA	500–1,000 mg daily for 4–7 days	N/A
Tojima et al, 1988 ²⁸	Pre-post study	9	8 patients with OSA, 1 with CSA and Hunter-Cheyne-Stokes breathing	250 mg daily orally for 7–8 days	N/A

AHI = apnea-hypopnea index, BMI = body mass index, CPAP = continuous positive airway pressure, CSA = central sleep apnea, CTEPH = chronic thromboembolic pulmonary hypertension, ESS = Epworth Sleepiness Scale, LVEF = left ventricular ejection fraction, MSA = mixed sleep apnea, N/A = not available, NYHA = New York Heart Association, OAI = obstructive apnea index, OSA = obstructive sleep apnea, PaO₂ = arterial pressure of oxygen, PB = periodic breathing.

Table 2—Characteristics of patients in included studies.

Study	Mean Age (years)	Male (%)	BMI	AHI (events/h)	OAI (events/h)	CAHI (events/h)	Side Effect of Acetazolamide
Central							
DeBacker et al, 1995 ²⁰	47.9 ± 2.8	92.9	31.5 ± 1.7	37.2 ± 6.2	3.5 ± 1.5 (OAI)	25.5 ± 6.8 (CAI)	Some paresthesia
Fontana et al, 2011 ²²	62 ± 9	91.7	29 ± 4	36 ± 16	NR	NR	NR
Ginter and Sankari, 2020 ³⁶	Able-bodied: 59.5 ± 11.8; Spinal cord injury: 50.3 ± 12.8	81.25	Able-bodied: 29.2 ± 1.9; Spinal cord injury: 25.8 ± 2.8	Able-bodied: 21.3 ± 13.8; Spinal cord injury: 27.2 ± 32.0	Able-bodied: 1.7 ± 2.0 (OAI); Spinal cord injury: 2.8 ± 3.7 (OAI)	Able-bodied: 2.8 ± 4.5 (CAI); Spinal cord injury: 7.3 ± 14.6 (CAI)	NR
Javaheri 2006 ²⁴	66 ± 6	100	26.4 ± 4.2	55 ± 24	1 ± 2	44 ± 23	8% nocturia
Naghan et al, 2019 ²⁵	50.2 ± 13.6	90	29.6 ± 6	78.2 ± 39.9	1.7 (0.7–19.8)(OAI)	17.8 (13.3–24.8)(CAI)	NR
Ulrich et al, 2015 ²⁹	66 (56–71)	34.8	26.6 (25.2–29.3)	18 (6–40)	NR	NR	NR
Verbraecken et al, 1998 ³⁰	46 ± 5	87.5	30 ± 1	39 ± 10	3 ± 2	25 ± 10	Some paresthesia
White et al, 1982 ³¹	57.67 ± 13.63	100	NR	54 ± 12 (AI)	NR	NR	33.3% paresthesia and released after dose reduced
Obstructive							
Eskandari et al, 2018 ²¹	64 ± 7	100	29 ± 4	37 ± 23	NR	NR	46% paresthesia, 31% dyspepsia
Whyte et al, 1988 ³²	51.50 ± 11.21	80	NR	50 ± 26	NR	NR	80% paresthesia
Unknown and Mixed Type							
Apostolo et al, 2014 ¹⁹	69.1 ± 1.9	100	24.5 ± 3.33	30.8 ± 13.8	NR	NR	NR
Inoue et al, 1999 ²³	55.2	88.0	25.6	27.1 ± 17.4	NR	NR	NR
Sakamoto et al, 1995 ²⁶	54.6	100	NR	34 ± 23.9 (AI)	NR	NR	50% numbness, 10% pollakiuria and 5% thirst
Sharp et al, 1985 ²⁷	53.6 ± 10.99	NR	33.55 ± 8.81	OSA: 89 ± 4.9 CSA: 83 ± 35.36 MSA: 64.75 ± 17.39	NR	NR	NR
Tojima et al, 1988 ²⁸	58 ± 4	55.6	29.86 ± 6.15	25 ± 6.7	NR	NR	22.2% dysesthesia and 11.1% pollakiuria

AHI = apnea-hypopnea index, AI = apnea index, BMI = body mass index, CSA = central sleep apnea, MSA = mixed sleep apnea, NR = not reported, OAI = obstructive apnea index, OSA = obstructive sleep apnea.

(MD -1.29, 95% CI: -3.10 to 0.53, $Z = 1.39$, $P = .16$) (**Figure S17**), slow-waveform sleep (MD 0.22, 95% CI: -0.88 to 1.33, $Z = 0.40$, $P = .69$) (**Figure S18**), and rapid eye movements (**Figure S19**) (MD 2.73, 95% CI: -0.28 to 5.75, $Z = 1.78$, $P = .08$). The change in N2 (MD 3.34, 95% CI: 0.12–6.56, $Z = 2.03$, $P = .04$) was small and clinically meaningless (**Figure S20**). High heterogeneity was found in sleep efficiency ($I^2 = 61\%$, $\chi^2 = 17.97$, $P = .01$), rapid eye movements ($I^2 = 86\%$, $\chi^2 = 28.52$, $P < .00001$) analysis, but not in total sleep time ($I^2 = 47\%$, $\chi^2 = 9.47$, $P = .09$), N1 ($I^2 = 31\%$, $\chi^2 = 2.90$, $P = .23$), N2 ($I^2 = 0\%$, $\chi^2 = 0.98$, $P = .61$), or slow-waveform sleep ($I^2 = 0\%$, $\chi^2 = 0.29$, $P = .87$).

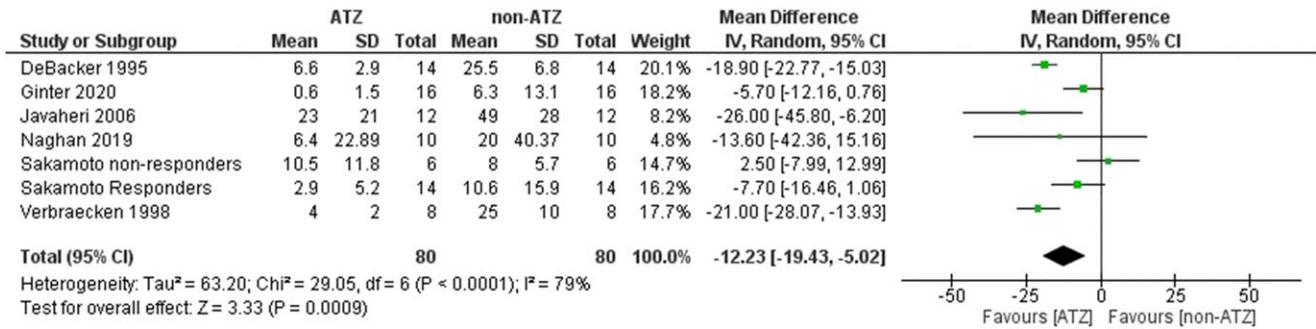
Hypercapnic ventilatory response

ATZ increased the hypercapnic ventilatory response (MD 0.70, 95% CI: 0.06–1.35, $Z = 2.13$, $P = .03$). Significant statistical heterogeneity was found in this analysis ($I^2 = 72\%$, $\chi^2 = 25.36$, $P = .0007$) (**Figure S21**).

pH, PaCO₂, and HCO⁻

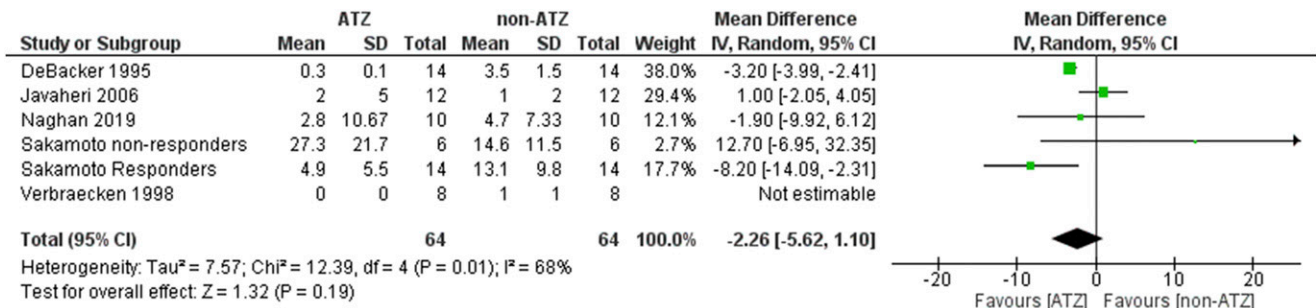
ATZ lowered blood pH (MD -0.07, 95% CI -0.08 to -0.05, $Z = 8.97$, $P < .00001$) (**Figure S22**), PaCO₂ (MD -4.59, 95% CI: -5.80 to -3.39, $Z = 7.46$, $P < .00001$) (**Figure S23**), and HCO⁻ (MD -5.65, 95% CI -6.81 to -4.49, $Z = 9.54$, $P < .00001$) (**Figure S24**). Significant heterogeneity was found in the analysis

Figure 2—CAHI.



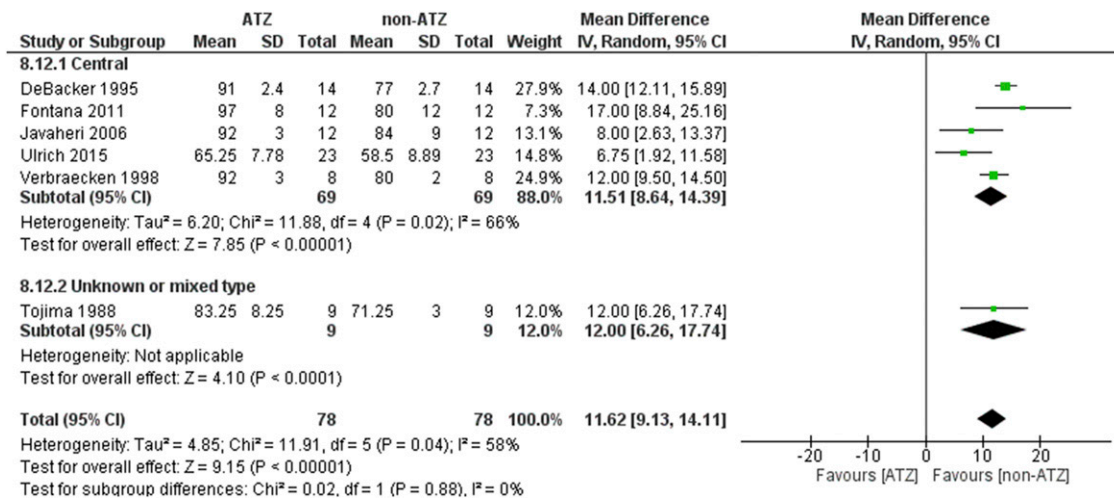
ATZ = acetazolamide, CAHI = central apnea-hypopnea index, CI = confidence interval, SD = standard deviation.

Figure 3—OAHl.



ATZ = acetazolamide, OAHl = obstructive apnea-hypopnea index, CI = confidence interval, SD = standard deviation.

Figure 4—PaO₂.



ATZ = acetazolamide, CI = confidence interval, PaO₂ = partial arterial pressure of oxygen, SD = standard deviation.

of pH (I² = 71%, $\chi^2 = 27.71$, P = .0005) and PaCO₂ (I² = 79%, $\chi^2 = 43.79$, P < .00001). All the results remained consistent when divided by the type of sleep apnea (Figure S25).

DISCUSSION

ATZ had beneficial effects in CSA but not OSA. There was improvement in PaO₂ and mean SaO₂, but no impact on

respiratory event duration. No improvement in the lowest SaO₂ was found overall. The respiratory related arousal index was reduced and total sleep time and sleep efficiency increased, consistent with improvements in sleep quality. However, slow-wave sleep was not impacted.

ATZ is a drug with complex effects, including powerful carbonic anhydrase inhibition.³⁷ In our included studies, the causes of CSA were mainly heart failure and opioid drugs.²⁵ However, the mechanisms of CSA in patients with heart failure

and opioids were different and also the mechanisms of ATZ are different in these 2 types of CSA. It would be expected that the entire spectrum of high loop gain sleep apnea (heart failure, OSA with high loop gain as a driving mechanism, treatment-emergent central) would show a key hyperventilatory feature, that of hypocapnia; opioids induce hypercapnia.

In the patients with heart failure, a model of hyperventilatory CSA increased left atrial/pulmonary capillary wedge pressure,³⁸ and compromised vasodilatory/vasoconstrictive cerebrovascular response to transient hypercapnia/hypocapnia will increase the CO₂ response slope sensitivity and narrow the CO₂ reserve.^{38–40} Prolonged circulation time and enhanced carotid chemosensitivity, which increases loop gain, also contributes.^{10,41} Although ATZ can cause a mild metabolic acidosis and lower PaCO₂, the apneic threshold decreases to a larger extent and eupneic PaCO₂ also increased.⁴² Through these mechanisms, the net effect is that the CO₂ reserve increases, reducing instability to minor fluctuations in CO₂. ATZ increases ventilatory drive and causes mild hyperventilation.⁴³ For a given change in ventilatory volume, the change of PaCO₂ is smaller during hyperventilation.⁴² Thus, the ventilatory response to arousal and plant gain is reduced. The change in PaCO₂ to induce instability/apnea is increased by more than 30% and the ventilatory volume required is increased 3-fold when given ATZ.⁴² The diuretic effect of ATZ⁴⁴ also improves pulmonary congestion and increases CO₂ reserve. Another mechanism for ATZ's stabilizing effect on ventilatory drive response to hypoxia and hypercapnia could be by reducing chemosensitivity of the peripheral chemoreflex.^{45,46} The drug can also reduce the slope of hypoxic ventilatory response, in one study from 1.03 to 0.78 (L/min/mm Hg).²² Our analysis found that ATZ increased the ventilatory response change in PaCO₂, while Edward's et al¹⁸ showed that the drug reduced the ventilatory response to arousal from sleep. All our included studies measured the hypercapnic response during wake, and thus are not directly comparable to sleep state assessments. Systemic metabolic acidosis, which is a long-term effect of ATZ, can inhibit the hypoxic ventilatory response.⁴⁷

ATZ may be beneficial in opioid-induced sleep-disordered breathing,²⁵ which is characterized by obstructive and central respiratory abnormality, ataxic breathing, and mild hypercapnia.⁴⁸ Thus, this is a model of hypoventilatory CSA. Opioids have complex respiratory effects, not only depressing respiration but also disrupting respiratory rhythm. In animal models, experimental instillation of μ -opioid agonists into the pre-Böttinger complex suppresses ventilation.^{49,50} Opioids decrease the mean frequency of inspiratory motor nerve output. This type of opioid-induced quantal slowing results from transmission failure of rhythmic drive from preinspiratory neurons to pre-Böttinger complex inspiratory neurons, depressed below threshold for spontaneous rhythmic activity.⁵¹ Genetic deletion of μ -opioid receptors in a glutamatergic pre-Böttinger complex subpopulation abolishes opioid-mediated depression of inspiratory burst firing by reducing burstlet frequency.⁵² Activation of μ -opioid receptors in the Kölliker-Fuse nucleus eliminates the post-inspiration phase of the respiratory cycle.⁵³ Opioid drugs increase the sensitivity to hypoxia of the peripheral chemoreflex but blunt the sensitivity of the hypercapnic response.^{54,55} Patients using opioids are exposed to some hypoventilation

and elevated PaCO₂ during sleep.⁵⁴ In patients with opioids, the apneic threshold increases by about 6 mm Hg.⁵⁶ Under this condition, a small change in ventilation will cause a larger change in PaCO₂ and interact with the apneic threshold,⁴² in essence increasing plant gain. The increase in inspiratory drive caused by ATZ through metabolic acidosis and effects on both the central and peripheral chemoreceptors may offset the opioid effects.²⁴ ATZ can reduce fluid overload,⁵⁷ lower the PaCO₂ level, and reduce plant gain,⁵⁸ all beneficial effects.

A general effect on high loop gain is also suggested by a report on benefits for persistent CPAP treatment associated CSA.⁵⁹ Our study found that pH and bicarbonate were lower in the ATZ group in both types of sleep apnea. The studies that reported the level of bicarbonate administered ATZ for 7 to 30 days. This indicated that the effect of ATZ in inducing metabolic acidosis might persist for at least 1 month.⁶⁰ However, more studies should be done to explore whether this effect can persist since renal adaptation could occur.⁶¹ The analysis cannot exclude an acute effect of ATZ such as reducing the chemosensitivity of the peripheral chemoreflex. Studies are required to determine the magnitude of peripheral chemoreflex inhibition and impact on AHI.

ATZ was not beneficial for patients with OSA in our analysis. High loop gain may drive part of the AHI in a subset of otherwise labeled patients with OSA, but the likely heterogeneity of pathophysiology possibly did not allow any benefit to show. It is not surprising that ATZ can “change” central to obstructive sleep apnea.²⁷ ATZ improves only high loop gain but not the other endotypes driving sleep apnea.¹⁷ Disease drivers frequently coexist, thus the airway is narrow or occluded during the nadir of periodic breathing.^{62,63} It can be difficult to distinguish OSA and CSA with conventional scoring, thus the studies summarized likely had admixtures of disease beyond that estimated by the scored indices. Some of the included studies did not provide obstructive AHI and central AHI separately, which made it difficult to define the role of ATZ in OSA. ATZ might have a potential role in reducing OAI in patients without heart failure; perhaps it was those with high loop gain who benefitted.

A recent meta-analysis reported that ATZ was effective in both OSA and CSA.⁶⁴ There are some important differences in the tabulated studies and exclusion criteria. The authors included 28 studies (13 OSA/15 CSA, ATZ = 542 and controls = 553 patients). The AHI reduction was similar in OSA vs CSA, but significantly greater with higher doses (at least up to 500 mg/day). These results differ from ours as 1) physiological studies in OSA patients were included, 2) non-peer-reviewed studies were included, and 3) studies were at both high altitude and sea level, while our study only focused on sleep apnea at sea level. Our results better reflect what may occur when used at sea level.

A response to ATZ was not universal. One included study showed that about 30% of the patients did not respond to ATZ and both CAS and OSA indices increased after ATZ.²⁶ No significant changes were found in arterial blood values such as pH and PaCO₂. It is possible that the probability of a response to ATZ is reflected in a change (reduction) of PaCO₂ or end-tidal CO₂. A different study showed that 54.7% of patients receiving ATZ had no response, and these patients had a higher body mass index (27 \pm 6.5 vs 23.8 \pm 4.2) and higher AHI (32.5 \pm 16.5 vs

20.7 ± 16.5).²³ The body mass index association suggests confounding obstructive elements.

Only 1 study compared the results of ATZ and ATZ plus CPAP.²¹ This study showed that the usage of ATZ plus CPAP was more effective in improving AHI but not SpO₂. ATZ did not impact CPAP adherence (usage time: 4.8 ± 2.2 hours when using CPAP vs 5.0 ± 2.0 hours when using CPAP plus ATZ). Five patients used ATZ after uvulopalatopharyngoplasty, and the results showed that ATZ improved the effect of uvulopalatopharyngoplasty.²³ These 2 studies suggest that ATZ might have a role as adjunctive therapy, especially if there is residual apnea during therapy for OSA. However, CSA emerging after treatment initiation might not be persistent,⁶⁵ thus the role for long-term use of ATZ in these patients remains uncertain. Improvements in sleep quality occurred with ATZ—a reduced arousal index and an increase in total sleep time and sleep efficiency. This was likely from an improvement in respiration. ATZ did improve the minimum PaO₂ and mean SaO₂, but only a trend toward rising nadir SaO₂. All the above effects of ATZ were more significant in patients with CSA instead of patients with OSA, unknown, or mixed apnea. This further supports the likelihood that ATZ did benefit CSA, while OSA phenotyping is probably needed to optimize assessment of the drug.

The most common adverse effect of ATZ was paresthesia, whose rates varied from 33.3 to 80%; a dose reduction reduced this effect.³¹ Other side effects included dyspepsia and increased urination. One study showed that if 2 doses are taken, the effect of ATZ could last for 24 hours.²² A single dose is expected to last a whole night. Thus, 1 report described an acute confusional syndrome in a patient with OSA, possibly from metabolic acidosis induced by ATZ.²⁶ A meta-analysis of adverse events from ATZ had 42 studies and over 1,200 participants.⁶⁶ The most common side effects, which were dose dependent, were paresthesia, dysgeusia, polyuria, and fatigue.

Three studies reported that ATZ was effective in reducing clinical symptoms of severe sleep apnea, such as snoring, headache, and excessive daytime sleepiness, and improving cognition.^{26,28,30} However, another study showed no subjective or objective improvements in clinical symptoms.³²

Our analysis has some limitations. There were a relatively small number of studies. Most included studies had small sample. Respiratory event scoring standards have changed over the decades and introduced errors in quantification. Significant heterogeneity existed in most of our analysis due to age, body mass index, and AHI, all of which might influence responsiveness to ATZ. Moreover, the administration of ATZ such as dose (varied from 250 mg/day to 1000 mg/day) and length of administration (varied from 3 days to 115 days) were significantly different between studies. Optimal dosing remains undefined, as when used with CPAP, single bedtime 250 mg dosing may be sufficient.⁶⁰ The studies were not long-term trials, which is an important consideration for sleep apnea treatment.

CONCLUSIONS

ATZ seems effective in partially reducing CSA. Improved phenotyping may be better able to identify patients who may

respond. Despite the general consistency of results across the reviewed studies, ready clinical application of our results is limited due to the existence of high heterogeneity.

ABBREVIATIONS

AHI, apnea-hypopnea index
 ATZ, acetazolamide
 CI, confidence interval
 CPAP, continuous positive airway pressure
 CSA, central sleep apnea
 OAI, obstructive apnea index
 OSA, obstructive sleep apnea
 MD, mean difference
 PaO₂, arterial partial oxygen pressure
 PaCO₂, arterial partial carbon dioxide pressure
 PAP, positive airway pressure
 SaO₂, saturation of oxygen

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