Effect of Acetazolamide and AutoCPAP Therapy on Breathing Disturbances Among Patients With Obstructive Sleep Apnea Syndrome Who Travel to Altitude: A Randomized Controlled Trial

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Obstructive sleep apnea syndrome (OSA) is a highly prevalent disease affecting at least 2% to 4% of middle-aged adults in Western countries. Patients with OSA experience excessive sleepiness, cognitive impairment, and other symptoms that impair quality of life. In addition, they are at increased risk of being involved in traffic accidents and having cardiovascular disease. Nocturnal application of continuous positive airway pressure (CPAP) is currently the most effective therapy.

As travel to the mountains for professional and recreational activities is increasingly popular, involving millions of persons worldwide, the estimated number of patients with OSA among mountain tourists is also very high, several hundred thousand to several million persons each year. Recently, we reported that untreated patients with OSA living near sea level travel to altitude, but this may expose them to hypoxemia and exacerbation of sleep apnea. The treatment in this setting is not established.

Objective To evaluate whether acetazolamide and autoadjusted continuous positive airway pressure (autoCPAP) control breathing disturbances in OSA patients at altitude.

Design, Setting, and Participants Randomized, placebo-controlled, double-blind, crossover trial involving 51 patients with OSA living below an altitude of 800 m and receiving CPAP therapy who underwent studies at a university hospital at 490 m and resorts in Swiss mountain villages at 1630 m and 2590 m in summer 2009.

Interventions Patients were studied during 2 sojourns of 3 days each in mountain villages, 2 days at 1630 m, 1 day at 2590 m, separated by a 2-week washout period at less than 800 m. At altitude, patients either took acetazolamide (750 mg/d) or placebo in addition to autoCPAP.

Main Outcome Measures Primary outcomes were nocturnal oxygen saturation and the apnea/hypopnea index; secondary outcomes were sleep structure, vigilance, symptoms, adverse effects, and exercise performance.

Results Acetazolamide and autoCPAP treatment was associated with higher nocturnal oxygen saturation at 1630 m and 2590 m than placebo and autoCPAP: medians, 94% (interquartile range [IQR], 93%-95%) and 91% (IQR, 90%-92%) vs 93% (IQR, 92%-94%) and 89% (IQR, 87%-91%), respectively. Median increases were 1.0% (95% CI, 0.3%-1.0%) and 2.0% (95% CI, 2.0%-2.0%). Median night-time spent with oxygen saturation less than 90% at 2590 m was 13% (IQR, 2%-38%; \( P < .001 \)). Acetazolamide and autoCPAP resulted in better control of sleep apnea at 1630 m and 2590 m than placebo and autoCPAP: median apnea/hypopnea index was 5.8 events per hour (5.8/h) (IQR, 3.0/h-10.1/h) and 6.8/h (IQR, 3.5/h-10.1/h) vs 10.7/h (IQR, 5.1/h-17.7/h) and 19.3/h (IQR, 9.3/h-29.0/h), respectively; median reduction was 3.2/h (95% CI, 1.3/h-7.5/h) and 9.2 (95% CI, 5.1/h-14.6/h).

Conclusion Among patients with OSA spending 3 days at moderately elevated altitude, a combination of acetazolamide and autoCPAP therapy, compared with autoCPAP alone, resulted in improvement in nocturnal oxygen saturation and apnea/hypopnea index.

Trial Registration clinicaltrials.gov Identifier: NCT00928655

See also Patient Page.
level) experienced pronounced hypoxemia and an exacerbation of sleep-related breathing disturbances with frequent central apneas/hypopneas during a stay at moderate altitude for a few days. Compared with low altitude, patients performed poorly in driving simulator tests, showed an increase in arterial blood pressure, and had more frequent cardiac arrhythmias. Thus, exposure to even moderate altitude has undesirable health effects in untreated patients with OSA.

A randomized, placebo-controlled, double-blind trial revealed that the respiratory stimulant acetazolamide, a carbonic-anhydrase inhibitor used to treat acute mountain sickness and high-altitude periodic breathing, increased nocturnal oxygen saturation and partially improved sleep apnea in otherwise untreated OSA patients at altitude. Although acetazolamide was superior to no treatment at all, the drug did not adequately control breathing disturbances. Because CPAP alone does not optimally control central sleep apnea and other potentially effective treatments, such as adaptive servo-ventilation or CPAP combined with supplemental oxygen, are impractical to carry along during altitude travel and entail considerable additional costs, a simple treatment of OSA at altitude is needed.

Therefore, the current study was designed to evaluate the hypothesis that acetazolamide combined with autoadjusted CPAP (autoCPAP, computer-controlled continuous mask pressure adjustment) provides a better oxygenation and control of sleep-related breathing disturbances than autoCPAP alone in patients with OSA spending a few days at moderate altitude.

**METHODS**

This randomized, placebo-controlled, double-blind crossover trial evaluated the efficacy of acetazolamide in patients with OSA receiving autoCPAP therapy at altitude. The study was performed in Zurich and Davos, Switzerland, from July to November 2009. Participants underwent baseline studies at low altitude (Zurich, 490 m [1608 ft]; barometric pressure [PB], 719 mm Hg) receiving autoCPAP and on the last of 4 nights of CPAP withdrawal (to confirm OSA and assess severity). Further studies were performed during two 3-day sojourns at moderate altitude, one during which patients received acetazolamide plus autoCPAP and the other during which patients received placebo plus autoCPAP, in random order, separated by a 2-week washout period at less than 800 m with patients receiving CPAP. Altitude studies were carried out in the Swiss Alps at Davos Wolfgang, 1630 m (5348 ft; PB, 630 mm Hg), and Davos Jakobshorn, 2590 m (8497 ft; PB, 562 mm Hg). An illustration of the design (eFigure) and further details of methods are provided in the eAppendix.

**Participants**

Patients of both sexes with OSA receiving CPAP therapy, aged 20 to 80 years, and living below 800 m were invited to participate. Patients had to be nonsleepy (Epworth score ≤10) with regular CPAP use. A prior diagnosis of OSA based on excessive sleepiness and an elevated apnea/hypopnea index (AHI) prior to initiation of treatment had to be documented and verified by a current polysomnography at 490 m in the fourth night of a CPAP withdrawal showing an AHI greater than 10 events per hour (10/h) with predominant obstructive events. Further inclusion and exclusion criteria are listed in the eAppendix. The study was approved by the local ethics committee, and patients gave written informed consent.

**Interventions**

During altitude sojourns, patients took acetazolamide capsules (one 250-mg dose every morning and two 250-mg doses every evening), or identically looking placebo capsules, before meals while supervised by an investigator. After study inclusion, patients were switched from their own CPAP device to a CPAP device operated in autoadjusting mode (RemStar M-Series, Philips Respironics) using their own nasal mask or face mask. The mask pressure range was set at 5 to 15 cm H2O. Randomization of the order of treatment with acetazolamide and placebo was performed by letting patients select a medication set from a box containing 6 sets labeled with a code and dispensed in balanced blocks by an independent pharmacist. A balanced design in regard to the order of altitude exposure was obtained by letting patients choose among available study time slots without being aware of the corresponding predefined order of altitude exposure. Patients and investigators were blinded to the study medication until all analyses were completed, and analyses were performed blinded in regard to altitude.

**Assessments**

Polysomnography included standard measurements, calibrated respiratory inductance plethysmography, diaphragmatic surface electromyography to better differentiate obstructive from central apneas/hypopneas, transcutaneous PCO2 (PtCO2), mask pressure, and airflow.

Morning examinations comprised questionnaires to assess current sleepiness (Karolinska sleepiness scale), symptoms of acute mountain sickness (environmental symptoms questionnaire cerebral score and Lake Louise score), estimated time spent awake during the previous night, and adverse effects of study drugs. Blood pressure and body weight were measured. Vigilance was evaluated between 9 AM and 10 AM by the psychomotor vigilance test and the divided attention steering simulator test. Spirometry, single-breath carbon monoxide diffusing capacity, and 6-minute walk distance were assessed.

**Outcomes**

Primary outcomes were nocturnal oxygen saturation and the AHI. Additional outcomes were sleep structure, vigilance measures, applied mask pressure, symptoms, adverse effects, blood pressure, pulmonary function variables, and 6-minute walk distance.
Minimally important differences were assumed as 2% (SD, 4%) in oxygen saturation and 10 events per hour (SD, 20/h) in AHI, respectively, based on previous studies,6,7 corresponding to moderate effect sizes of 0.5.24 To detect these differences with a 2-sided significance level of .05 and a power of 80%, the required sample size including 10 withdrawals was estimated to be 50 participants.

Figure 1. Patient Flow

Patients assessed for eligibility

121

70 Excluded
47 Refused to participate
16 Had ODI <15/h without CPAP
2 Had chronic pain
2 Had other medical conditions
1 Used CPAP <4 h per night
1 Had skin allergy
1 Could not discontinue CPAP

51 Allocated to altitude sequence and to baseline 1 study with or without CPAP

12 Allocated to altitude sequence
1630 m then 2590 m and baseline study with CPAP

13 Allocated to altitude sequence
2590 m then 1630 m and baseline study with CPAP

13 Allocated to altitude sequence
1630 m then 2590 m and baseline study without CPAP

13 Allocated to altitude sequence
2590 m then 1630 m and baseline study without CPAP

1 Withdrawn (atrial fibrillation at 1630 m)

1 Withdrawn during washout (bicycle accident)

5 Randomized to receive placebo then acetazolamide

7 Randomized to receive acetazolamide then placebo

6 Randomized to receive placebo then acetazolamide

7 Randomized to receive acetazolamide then placebo

25 Participants in baseline study 1 with CPAP

26 Participants in baseline study 1 without CPAP

24 Participants in baseline study 2 without CPAP

25 Participants in baseline study 2 with CPAP

26 Participants included in intention-to-treat analysis

Altitude study 1 placebo group

5 at 1630 m then 2590 m
7 at 2590 m then 1630 m

12 Randomized to study drug sequence

Altitude study 1 acetazolamide group

7 Randomized to receive acetazolamide then placebo

6 Randomized to receive acetazolamide then placebo

7 Randomized to receive acetazolamide then placebo

2-wk washout period at <800 m with CPAP

Altitude study 2 placebo group

Altitude study 2 acetazolamide group

6 at 1630 m then 2590 m
7 at 2590 m then 1630 m

Altitude study 2 acetazolamide group

6 at 1630 m then 2590 m
7 at 2590 m then 1630 m

13 Randomized to study drug sequence

6 at 2590 m then 1630 m

Altitude study 2 placebo group

Altitude study 2 acetazolamide group

7 at 1630 m then 2590 m
5 at 2590 m then 1630 m

Altitude study 2 placebo group

Altitude study 2 acetazolamide group

7 at 1630 m then 2590 m
6 at 2590 m then 1630 m

Altitude study 2 placebo group

Altitude study 2 acetazolamide group

7 at 1630 m then 2590 m
6 at 2590 m then 1630 m

2-wk washout period at <800 m with CPAP

4 Patients were allocated to 1 of 4 altitude exposure sequences by letting them select 1 of the available study time slots according to preference. Neither the patient nor the coordinator was aware of the sequence details at the time of allocation. CPAP indicates continuous positive airway pressure; /h, events per hour; ODI, oxygen desaturation index.
Statistical Analysis
Data are summarized as medians and interquartile ranges to account for the nonnormal distribution. Analyses were performed on an intention-to-treat basis. Missing data were replaced by corresponding values on the alternative drug assuming no effect of acetazolamide. Friedman analysis of variance (ANOVA) was applied to data grouped according to altitude and treatment. If ANOVA indicated a significant overall effect, Wilcoxon matched pairs tests were performed between data on acetazolamide and placebo at corresponding altitude and between data at different altitudes on corresponding drugs. Drug effects were additionally assessed by computing median differences with 95% confidence intervals of data on acetazolamide and placebo.

Multivariable, random-effects, generalized least square regression models were fitted to primary outcomes to assess potential effects of altitude exposure sequence, drug order, time effects (including acclimatization), age, and sex (eAppendix). The number of patients needed to treat with acetazolamide to prevent 1 patient from having an AHI greater than 10/h and a mean nocturnal oxygen saturation less than 90% at altitude was computed. Performance of low-altitude baseline characteristics in predicting patients with the largest AHI reduction by acetazolamide was assessed by Spearman rank order correlations and receiver operating characteristics. Statistical significance was assumed at a 2-sided \( P < .05 \) applying a Bonferroni correction where appropriate. (Details on the statistical analysis are in the eAppendix.)

RESULTS
Of 121 screened patients, 51 met inclusion criteria and were randomized (FIGURE 1). Study participants were predominantly male (48/51), aged 37 to 75 years, and not sleepy with regular CPAP use (TABLE 1). Polysomnography on the last of 4 nights of CPAP withdrawal at 490 m revealed moderate to severe OSA and virtually no central apneas/hypopneas. The reintroduction of CPAP at 490 m (TABLE 2) increased the oxygen saturation by a median of 1% (95% CI, 1%-2%) and reduced the AHI by 48.8/h (95% CI, 42.9/h-54.8/h).

Sleep Studies
Results are summarized in Table 2. At 1630 m and 2590 m, combined acetazolamide and autoCPAP treatment was associated with higher oxygen saturation and a lower AHI compared with placebo and autoCPAP. AutoCPAP and acetazolamide increased the median nocturnal oxygen saturation by 1.0% (95% CI, 0.3%-1.0%) at 1630 m and by 2.0% (95% CI, 2.0%-2.0%) at 2590 m. Correspondingly, the median reduction in the AHI was 3.2/h (95% CI, 1.3/h-7.3/h) at 1630 m and 9.2/h (95% CI, 5.1/h-14.6/h) at 2590 m. The favorable effects of acetazolamide were even greater at the higher altitude (FIGURE 2). The reduction in the AHI was mainly related to a lower number of central apneas/hypopneas, particularly during non–rapid eye movement (NREM) sleep (eTable 1), but obstructive apneas/hypopneas were slightly reduced as well (at 2590 m).

Multivariable, random-effects, generalized least square regression analysis confirmed a significant increase of nocturnal oxygen saturation and a reduction of the AHI by acetazolamide compared with placebo (eTables 2 through 4). A significant interaction of drug \times \text{ altitude} indicated a greater efficacy of acetazolamide in increasing oxygen saturation and reducing the AHI at 2590 m compared with 1630 m. There was no effect of the drug order, altitude exposure sequence, or consecutive test number on nocturnal oxy-

Table 1. Characteristics of Patients (N = 51)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Men/women, No.</td>
<td>48/3</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>63 (59-66)</td>
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<tr>
<td>BMI, median (IQR)</td>
<td>33.0 (30.1-35.8)</td>
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<tr>
<td>Epworth score (with CPAP), median (IQR)</td>
<td>7 (5-9)</td>
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<tr>
<td>CPAP use per night, median (IQR), h</td>
<td>6.6 (5.4-7.2)</td>
</tr>
<tr>
<td>Mask pressure 90th percentile, median (IQR), cm H2O</td>
<td>10.1 (8.7-11.2)</td>
</tr>
<tr>
<td>Sleep study after 4 nights CPAP withdrawal at 490 m, median (IQR)</td>
<td>1.3/h-7.5/h at 1630 m and 9.2/h (95% CI, 5.1/h-14.6/h) at 2590 m.</td>
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</table>
gen saturation (eTable 2). Regression analysis did not show an effect of the drug order on the AHI, but there was a negative association of the consecutive test numbers 3 and 5 (day 3 of altitude sojourns compared with day 2) consistent with a time effect, possibly related to acclimatization (eFigure). Regression model predictions for a 60-year-old man revealed higher values of mean nocturnal oxygen saturation and lower AHI on acetazolamide vs placebo at both altitudes (eTable 4). To prevent 1 patient from experiencing an increase of the AHI to greater than 10/h or a decrease of the oxygen saturation to less than 90% at 2590 m, 2 patients (95% CI, 2-4) or 3 patients (95% CI, 2-6), respectively, had to be treated with acetazolamide (eTable 5).

The use of acetazolamide was associated with a reduced PtcCO2 (Table 2). Sleep efficiency and the amount of deep sleep (NREM stages 3 and 4) with acetazolamide and autoCPAP exceeded corresponding values with placebo and autoCPAP. The mask pressure applied by autoCPAP devices was lower with acetazolamide than with placebo.

Altitude effects were evaluated by comparing results from autoCPAP at 490 m with corresponding values from placebo and autoCPAP at 1630 m and 2590 m, respectively. This revealed an altitude-dependent decrease in nocturnal oxygen saturation associated with a progressive increase in the AHI due to central apneas/hypopneas, while the obstructive AHI remained unchanged. Regression analysis confirmed that the higher altitude (2590 m vs 1630 m) was associated with lower nocturnal oxygen saturation and a higher AHI (Tables 2 and 3).

The mask pressure applied by autoCPAP devices during placebo treatment increased significantly at altitude (Table 2, Figure 2).

### Daytime Evaluation

Patients reported that they spent less time awake during the nights they received acetazolamide and autoCPAP at 1630 m and 2590 m compared with placebo and autoCPAP, but subjective sleepiness remained unchanged. Lake Louise acute mountain sickness scores were significantly lower with acetazolamide vs placebo at 2590 m. However, scores on the environmental symptoms questionnaire (cerebral subscore) were unchanged, and the prevalence of clinically relevant acute mountain sickness did not exceed 1 or 2 patients at any altitude (Table 3, eTable 6). The performance in the psychomotor vigilance test reaction time and in the steering simulator test was similar with acetazolamide and placebo (Table 3).

Acetazolamide and autoCPAP therapy was associated with a significant reduction in weight and blood pressure and a slight increase in spirometric volumes at 2590 m (Table 3). Although the 6-minute walk distance was similar with acetazolamide and placebo, acetazolamide increased arterial oxygen saturation at the beginning and end of the walk tests, both at 1630 m and 2590 m.

Adverse effects of acetazolamide were limited to unpleasant taste or paresthe-

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### Table 2. Sleep Studies (N = 51)

<table>
<thead>
<tr>
<th></th>
<th>Median (IQR)</th>
<th>490 m (With CPAP)</th>
<th>Placebo</th>
<th>Acetazolamide</th>
<th>1630 m (With CPAP)</th>
<th>Placebo</th>
<th>Acetazolamide</th>
<th>2590 m (With CPAP)</th>
<th>Placebo</th>
<th>Acetazolamide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nocturnal oxygen saturation, %</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>95 (84-96)</td>
<td>93 (82-94)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>94 (93-96)&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>89 (87-91)&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>91 (90-92)&lt;sup&gt;c,e&lt;/sup&gt;</td>
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<tr>
<td><strong>% time with oxygen saturation &lt; 90%</strong></td>
<td>0 (0-3)</td>
<td>0 (0-3)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0 (0-2)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>57 (28-82)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13 (2-38)&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td><strong>Arousal index, 1/h</strong></td>
<td>16.2 (9.2-27.3)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.4 (2.6-11.9)&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>16.2 (9.2-27.3)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.4 (2.6-11.9)&lt;sup&gt;c,d&lt;/sup&gt;</td>
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<td><strong>REM, %</strong></td>
<td>19 (14-22)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>17 (14-23)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>17 (13-21)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>17 (13-21)&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td><strong>NREM stages 3 and 4, %</strong></td>
<td>3.5 (1.6-2.6)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.1 (1.0-3.6)&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>2.1 (1.0-3.6)&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>2.1 (1.0-3.6)&lt;sup&gt;c,d&lt;/sup&gt;</td>
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<td><strong>Apnea/hypopnea index, total, 1/h</strong></td>
<td>1.6 (0.5-4.3)</td>
<td>4.3 (1.3-13.8)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.8 (0.7-6.2)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>12.6 (5.6-23.0)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.0 (1.2-7.6)&lt;sup&gt;c,d,e&lt;/sup&gt;</td>
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<td><strong>Total sleep time, min</strong></td>
<td>382 (326-414)</td>
<td>427 (389-465)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>451 (393-486)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>412 (354-465)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>446 (405-474)&lt;sup&gt;c,d&lt;/sup&gt;</td>
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<td><strong>Sleep efficiency, %</strong></td>
<td>80 (74-88)</td>
<td>81 (72-89)</td>
<td>87 (79-91)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>79 (67-88)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>85 (81-91)&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td><strong>NREM stages 3 and 4, %</strong></td>
<td>15 (10-21)</td>
<td>13 (8-19)</td>
<td>15 (9-20)</td>
<td>10 (6-16)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13 (9-19)&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td><strong>REM, %</strong></td>
<td>19 (14-24)</td>
<td>23 (18-28)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>19 (14-22)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>17 (14-23)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17 (13-21)&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td><strong>Arousal index, 1/h</strong></td>
<td>15.8 (9.7-28.8)</td>
<td>17.4 (11.4-26.3)</td>
<td>16.4 (9.3-25.5)</td>
<td>16.3 (10.6-25.8)</td>
<td>14.1 (9.1-24.5)</td>
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<td><strong>Heart rate, 1/min</strong></td>
<td>60 (50-68)</td>
<td>60 (54-65)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>59 (54-68)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>64 (58-70)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>61 (59-69)&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td><strong>Median CPAP, cm H2O</strong></td>
<td>8.4 (7.5-10.9)</td>
<td>9.0 (8.0-11.7)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.3 (7.2-10.8)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10.0 (8.9-13.2)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.9 (7.1-10.8)&lt;sup&gt;d&lt;/sup&gt;</td>
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**Abbreviations:** CPAP, continuous positive airway pressure; IQR, interquartile range; NREM, non–rapid eye movement; PtcCO2, transcutaneous carbon dioxide pressure; REM, rapid eye movement.

<sup>a</sup>P values were computed by Friedman analysis of variance (ANOVA) for overall effects.

<sup>b</sup>Values are median (IQR) of the individual mean oxygen saturation during time in bed.

<sup>c</sup>P < .05 vs 490 m (Wilcoxon matched pairs tests).

<sup>d</sup>P < .05 vs placebo (Wilcoxon matched pairs tests).

<sup>e</sup>P < .05 vs 1630 m within treatment (Wilcoxon matched pairs tests).

<sup>f</sup>Total sleep time divided by time in bed.

<sup>g</sup>Percentage of total sleep time spent in NREM or REM sleep.
sias of mild to moderate intensity (reported as “somewhat disturbing”) (Table 3, eTable 7). None of the patients discontinued the therapy because of adverse effects.

Comparing outcomes at 490 m with autoCPAP with corresponding values for the group taking placebo and autoCPAP at the higher altitudes revealed that patients perceived that they had spent a greater portion of the night awake at 2590 m compared with 490 m, but they did not feel sleepier or experience more symptoms of acute mountain sickness (Table 3, eTable 6).

At 2590 m, for patients receiving placebo and autoCPAP, blood pressure was increased (Table 3), and there were decreases in forced vital capacity, forced expiratory volume in the first second of expiration, and diffusing capacity compared with values at 490 m with autoCPAP. The 6-minute walk distance remained unchanged with placebo and autoCPAP at 1630 m and 2590 m compared with values for autoCPAP at 490 m, but the oxygen saturation at the beginning and end of walk tests was lower at altitude and patients rated the required effort as higher than at 490 m (Table 3).

A residual AHI greater than 5/h recorded in the memory of the autoCPAP device during home therapy at 490 m identified “good responders” to acetazolamide at 2590 m, ie, patients with an AHI reduction greater than 10/h with the drug, with a specificity of 0.72 and a sensitivity of 0.65 (eAppendix).

COMMENT

The current randomized, placebo-controlled, double-blind trial provides several novel findings that are clinically relevant for patients with OSA traveling to altitude. First, the data show that combined therapy with acetazolamide and autoCPAP provides a better oxygenation during sleep and wakefulness, prevents an exacerbation of sleep apnea at altitude, and reduces the time spent awake during nights compared with autoCPAP alone. Second, the results demonstrate that autoCPAP alone is an effective therapy for obstructive apneas/hypopneas even at altitude where central apneas/hypopneas emerge. Our study provides important information for patients with OSA planning a stay at altitude because they can continue using their CPAP in autoadjusting mode during altitude travel and enhance this treatment with acetazolamide if they want to spend less time awake at night, to achieve a higher arterial oxygen saturation and an optimal control of sleep apnea.

Despite their sleep-related breathing disturbances, many patients with OSA are professionally and socially active and enjoy recreational activities. Being able to undergo altitude travel with minimal adverse health effects is an important aspect of their quality of life. Until recently, no robust scientific evidence has been available to counsel OSA patients planning a trip to altitude. Observations in 5 patients with OSA exposed to normobaric hypoxia simulating an altitude of 2750 m revealed frequent central sleep apneas.23

In a randomized controlled trial, we previously confirmed that untreated OSA patients residing at less than 800 m experience exacerbated sleep-related breathing disturbances, pronounced hypoxemia, impaired driving simulator performance, cardiac arrhythmias, blood pressure elevation, and weight gain during a stay at 1680 m and 2590 m.9

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In the current trial, we evaluated the combined treatment with acetazolamide and autoCPAP because acetazolamide alone did not adequately control obstructive apneas/hypopneas in a previous study in OSA patients at altitude, although it prevented central apneas/hypopneas. Conversely, CPAP alone did not consistently suppress central apneas associated with heart failure, and central apneas may even emerge during CPAP therapy of OSA. We used the autoadjusting mask pressure mode because autoCPAP is increasingly prescribed as a long-term therapy for OSA, and we assumed patients would continue their usual autoCPAP therapy during altitude travel. The combined therapy with acetazolamide and autoCPAP provided an almost complete control of sleep apneas/hypopneas.

Table 3. Daytime Evaluation

<table>
<thead>
<tr>
<th>Median (IQR)</th>
<th>Placebo</th>
<th>Acetazolamide</th>
<th>Placebo</th>
<th>Acetazolamide</th>
<th>P Value, ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated time spent awake of previous night, min</td>
<td>35 (10-80)</td>
<td>30 (15-75)</td>
<td>20 (8-60)c</td>
<td>60 (30-120)d,e</td>
<td>30 (10-90)c</td>
</tr>
<tr>
<td>Karolinska sleepiness score</td>
<td>3 (3-4)</td>
<td>3 (2-3)</td>
<td>3 (3-3)</td>
<td>3 (3-3)</td>
<td>3 (2-3)</td>
</tr>
<tr>
<td>Acute mountain sickness score</td>
<td>0.00 (0.00-0.09)</td>
<td>0.00 (0.00-0.08)</td>
<td>0.00 (0.00-0.00)</td>
<td>0.00 (0.00-0.18)</td>
<td>0.00 (0.00-0.08)</td>
</tr>
<tr>
<td>Lake Louise</td>
<td>1.00 (1.00-3.00)</td>
<td>1.00 (2.00-2.00)</td>
<td>1.00 (2.00-2.00)d</td>
<td>1.00 (2.00-4.00)</td>
<td>1.00 (2.00-2.00)c</td>
</tr>
<tr>
<td>Adverse effects, No. (%)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>4 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>96.1 (90.4-109.3)</td>
<td>97.1 (89.0-110.3)</td>
<td>95.5 (88.1-108.2)c,d</td>
<td>97.4 (89.6-109.2)</td>
<td>95.4 (88.0-108.3)c,d</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>100 (93-107)</td>
<td>101 (96-106)</td>
<td>96 (92-104)c</td>
<td>104 (99-112)d</td>
<td>99 (90-104)c</td>
</tr>
<tr>
<td>PVT reaction time, ms</td>
<td>233 (201-277)</td>
<td>223 (194-265)d</td>
<td>238 (212-270)e</td>
<td>223 (206-281)g</td>
<td>238 (270-281)</td>
</tr>
<tr>
<td>Vigilance</td>
<td>0.32 (0.26-0.43)</td>
<td>0.27 (0.22-0.35)d</td>
<td>0.28 (0.23-0.38)</td>
<td>0.28 (0.24-0.35)</td>
<td>0.31 (0.25-0.41)</td>
</tr>
<tr>
<td>Pulmonary Function</td>
<td>4.27 (3.88-4.73)</td>
<td>NA</td>
<td>NA</td>
<td>3.97 (3.71-4.54)d</td>
<td>4.00 (3.65-4.58)c,d</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>107 (102-116)</td>
<td>NA</td>
<td>NA</td>
<td>100 (92-109)d</td>
<td>101 (97-112)d</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>3.00 (2.63-4.34)</td>
<td>NA</td>
<td>NA</td>
<td>3.00 (2.72-3.28)d</td>
<td>3.00 (2.82-3.40)c</td>
</tr>
<tr>
<td>PEF, L/min</td>
<td>8.85 (8.07-9.80)</td>
<td>NA</td>
<td>NA</td>
<td>9.25 (7.97-10.15)d</td>
<td>9.15 (8.08-10.36)d</td>
</tr>
<tr>
<td>DLCO adjusted, mmol x min^-1 x kPa^-1</td>
<td>9.2 (7.8-10.2)</td>
<td>NA</td>
<td>NA</td>
<td>8.7 (7.4-9.9)d</td>
<td>8.6 (7.2-9.5)d</td>
</tr>
<tr>
<td>DLCO adjusted, % predicted</td>
<td>100 (91-111)</td>
<td>NA</td>
<td>NA</td>
<td>95 (86-104)d</td>
<td>93 (84-102)d</td>
</tr>
</tbody>
</table>

Abbreviations: CPAP, continuous positive airway pressure; DASS, divided attention steering simulator test; DLCO, diffusing capacity test; FEV1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; IQR, interquartile range; NA, not applicable (no pulmonary function tests were performed at 1630 m); PEF, peak expiratory flow rate; PVT, psychomotor vigilance test; SpO2, pulse oximeter oxygen saturation.

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nea at altitude and a better oxygenation than autoCPAP alone with a major reduction in the time spent with an oxygen saturation less than 90% (Table 2). Acetazolamide has been shown to stabilize ventilation by reducing both the PCO₂ during eupnea and the apnea threshold for CO₂, thereby maintaining the CO₂ reserve and increasing the ventilatory overshoot required to induce apnea.⁷ Accordingly, we found that the combined treatment with acetazolamide and autoCPAP was associated with a lower PtCO₂ and AHI as well as with a higher nocturnal oxygen saturation than autoCPAP alone (Table 2, Figure 2). The effect of acetazolamide on nocturnal oxygen saturation at 2590 m was similar to that of reintroducing CPAP after a 4-night withdrawal at 490 m (Table 1 and Table 2). Apart from the stabilizing effect on control of breathing, the better oxygenation with acetazolamide at altitude might potentially prevent adverse consequences of sympathetic overstimulation and cerebral tissue hypoxia.³⁰

We found that the amount of AHI reduction by acetazolamide at 2590 m was correlated with the AHI on CPAP at low altitude. This finding suggests that the residual AHI on CPAP at low altitude measured by polysomnography or recorded during home therapy in the internal memory of the CPAP device might help counsel patients regarding the expected benefit from using acetazolamide during an altitude sojourn.

Sleep efficiency and deep sleep (NREM stages 3 and 4) were also improved by the combined treatment. The clinical relevance of these changes in neurophysiologic measures of sleep induced by acetazolamide is supported by the associated improvement in subjective insomnia, although the performance in vigilance tests remained unchanged (Table 2).

The weight gain and reductions in spirometric volumes and in diffusing capacity we observed when patients received autoCPAP alone at 2590 m (Table 3) are consistent with interstitial pulmonary fluid accumulation, similar to findings in healthy subjects acutely exposed to a much higher altitude of 4559 m, but different mechanisms may be involved.³¹,³² Fluid accumulation and its rostral displacement may play a role in promoting upper airway collapse in patients with OSA,³³ and in this regard, the observed increase in mask pressure applied by autoCPAP devices seems appropriate. Acetazolamide may have contributed to reducing the AHI, with its diuretic effect preventing fluid retention, weight gain, and increases in blood pressure at altitude (Table 3).

The 6-minute walk distances at 490 m, 1630 m, and 2590 m were similar (Table 3), but patients perceived a greater required effort at the higher altitude associated with the lower oxygen saturation. Acetazolamide did not change exercise performance or perceived effort but mitigated the altitude-induced decrease in oxygen saturation at rest and during exercise, which may be relevant for OSA patients with cardiovascular comorbidities.

To achieve a maximal effect of acetazolamide, we used a relatively high dose of 750 mg per day. Although up to 30% of the patients perceived mild but not disturbing adverse effects, no severe adverse effects occurred. Compared with the dose of 500 mg per day used in our previous study,⁷ the prevalence and intensity of adverse effects were not increased (Table 3). Further studies are required to establish the optimal dose of acetazolamide.

The finding that autoCPAP alone prevented obstructive apneas/hypopneas even in the presence of altitude-induced central apneas/hypopneas is of particular interest (Table 2). In untreated OSA patients traveling from 490 m to 2590 m, we previously observed a considerable increase in AHI from 47.5/h to 90.9/h.³⁴ In the current study, in patients with OSA of similar severity treated with autoCPAP and placebo, the increase in AHI from 6.6/h at 490 m to 19.3/h at 2590 m was only modest and due exclusively to the emergence of central apneas/hypopneas (Table 2). Thus, autoCPAP effectively prevents obstructive apneas even at altitude. Whether the slight increase in applied mask pressure of approximately 1 cm H₂O (Table 2) was advantageous and whether operating the CPAP device with the same fixed pressure at all altitudes would have been superior to autoCPAP remains unknown. In 7 high-altitude residents with OSA living at 2255 m to 3080 m, the mask pressure applied by autoCPAP devices on descent to lower altitudes did not change, but the AHI decreased.³⁴ This raises the question whether the patients would have required a higher mask pressure at altitude.³⁴

Our study has several limitations that should be considered in its interpretation. We studied a typical cohort of patients with OSA consisting predominantly of middle-aged men with moderate obesity and stable comorbidities such as hypertension and diabetes during the first 3 days of an altitude sojourn. It is uncertain whether the results of the current trial are also valid in women and in patients of different age or with more severe comorbidities, during extended sojourns, or at higher altitudes. The data obtained in the current study with a particular autoCPAP machine may not necessarily apply to other machines operating with different proprietary pressure control algorithms. We did not evaluate the economic consequences of recommending acetazolamide to patients with OSA traveling to altitude, but the drug is relatively inexpensive (ie, $1.10 to $1.50 for a daily dose of 750 mg).

In conclusion, among patients with OSA spending 3 days at moderately elevated altitude, combined treatment with acetazolamide and autoCPAP, compared with autoCPAP alone, resulted in improvement in nocturnal oxygen saturation, better control of sleep apnea, and reduced insomnia. Alleviating hypoxemia at rest and during exercise at altitude by acetazolamide may potentially contribute to reducing the risk of adverse effects of altitude exposure, in particular in patients with OSA and cardiovascular comorbidities.
ACETAZOLAMIDE AND AUTOCPAP FOR PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME

Author Contributions: Dr Latshang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. 

Study concept and design: Nussbaumer-Ochsner, Kohler, Bloch. 

Acquisition of data: Latshang, Nussbaumer-Ochsner, Henn, Ulrich, Bloch. 

Analysis and interpretation of data: Latshang, Henn, Lo Casco, Ledergerber, Kohler, Bloch. 

Drafting of the manuscript: Latshang, Bloch. 

Critical revision of the manuscript for important intellectual content: Latshang, Nussbaumer-Ochsner, Henn, Ulrich, Lo Casco, Ledergerber, Kohler, Bloch. 

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Obtained funding: Kohler, Bloch. 

Administrative, technical, or material support: Latshang, Nussbaumer-Ochsner, Henn, Ulrich, Lo Casco, Bloch. 

Study supervision: Latshang, Bloch. 

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Online-Only Material: The eAppendix, eFigure, and eTables are available at http://www.jama.com. 

REFERENCES


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