CHEST

Acetazolamide Plus Atomoxetine for Obesity Hypoventilation Syndrome Treatment

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BACKGROUND: A subgroup of patients with obesity exhibits hypoventilation as a result of, among other mechanisms, a narrow, collapsible upper airway (UA), a reduced ventilatory drive during both wakefulness and sleep, and the loss of pharyngeal muscle tone during sleep. These features characterize obesity-hypoventilation syndrome (OHS). If left untreated, OHS is associated with significant morbidity and mortality. Besides lifestyle modifications, positive airway pressure (PAP) is the only available treatment, and it is often not well tolerated. Drugs designed to activate UA muscles such as atomoxetine and to stimulate breathing such as acetazolamide represent a potential novel strategy for treating OHS.

RESEARCH QUESTION: Is 2 weeks of 500 mg acetazolamide plus 100 mg atomoxetine daily effective for OHS severity (reduction in mean nocturnal CO_2 as the primary outcome)?

STUDY DESIGN AND METHODS: In a randomized, double-masked crossover trial, we compared 2 weeks of acetazolamide plus atomoxetine with placebo in patients with OHS not treated with PAP. Patients with a BMI of $\geq$ 35 kg/m^2 underwent polysomnography with transcutaneous overnight measurement of CO_2 ($Ptcco_2$) and morning blood test to evaluate sleep-related and diurnal hypercapnia at baseline and after each treatment sequence.

RESULTS: Fifteen patients with a median age of 53 years (interquartile range [IQR], 36-59 years; 8 female patients; median BMI, 44 kg/m^2 [IQR, 42-53 kg/m^2]; baseline median $Ptcco_2$, 49 mm Hg [IQR, 44-55 mm Hg]; median apnea-hypopnea index (AHI), 64 events/h [IQR, 36-83 events/h], and median nocturnal peripheral capillary oxygen saturation (Spo_2), 84% [IQR, 79%-89%]) were randomized. Acetazolamide plus atomoxetine decreased nocturnal $Ptcco_2$ by a mean of −5.8 mm Hg (95% CI, −7.8 to −3.7 mm Hg; $P < .001$) and diurnal CO_2 compared with placebo. Median AHI decreased by −20.9 events/h (95% CI, −26.7 to −15.1 events/h; $P < .001$) and mean overnight Spo_2 increased by 4.3% (95% CI, 2.8%-5.7%; $P < .001$). No serious adverse events occurred.

INTERPRETATION: Our results show that the administration of acetazolamide plus atomoxetine significantly improved sleep-related hypoventilation, oxygen parameters, and AHI in treatment-naive patients with OHS. This proof-of-concept study provides encouraging results for a potential pharmacotherapy for OHS.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov; No.: NCT05448443; URL: www.clinicaltrials.gov

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KEY WORDS: acetazolamide; atomoxetine; hypercapnia; pharmacotherapy; obesity hypoventilation syndrome; sleep apnea

Take-Home Points

Research Question: Is the acetazolamide plus atomoxetine drug combination effective in treating obesity-hypoventilation syndrome (OHS)?

Results: The combination of acetazolamide plus atomoxetine was shown to reduce nocturnal transcutaneous overnight measurement of CO_2 by 5.8 mm Hg compared with placebo, lower apnea-hypopnea index by approximately 21 events/h with a 4.3% improvement in overnight peripheral capillary oxygen saturation, and was well tolerated without serious adverse events.

Interpretation: Acetazolamide plus atomoxetine was shown to be safe and effective in improving hypoventilation and sleep-related breathing in patients with OHS not receiving positive airway pressure.

Hypercapnia during both wakefulness and sleep among patients affected by obesity defines obesity-hypoventilation syndrome (OHS).[1,2] OHS is the most severe form of obesity-induced respiratory disease and, if left untreated, leads to serious sequelae, including pulmonary hypertension, heart failure, and increased rates of mortality and hospitalization resulting from acute-on-chronic hypercapnic respiratory failure.[1] Multiple mechanisms have been implicated in OHS development such as alterations in ventilatory drive and chemoresponsiveness, obesity-related modifications in the respiratory system, hormonal and metabolic derangements, and breathing disorders during sleep.[3-6] Most patients with OHS demonstrate concomitant OSA primarily because of a collapsible upper airway (UA) and reduced pharyngeal muscle tone during sleep.[7]

Although OHS is alleviated effectively with the use of positive airway pressure (PAP) devices, these are often poorly tolerated by patients and compliance is relatively low.[8,9] Weight management strategies represent a valid intervention for OHS; however, significant time is required for lifestyle changes or pharmacotherapy to lead to a clinically meaningful weight loss, and the possible risks related to bariatric surgery mitigate the enthusiasm for this treatment option.[10,11]

Considering the respiratory drive alteration and particularly the blunted respiratory response to CO_2 as 1 of the main mechanisms of hypoventilation in patients with OHS, drugs designed to stimulate ventilation such as acetazolamide, a carbonic anhydrase inhibitor, might be proposed to increase respiratory drive.[12,13] A concern with respiratory stimulants is that they can increase negative intrathoracic pressure, which may promote UA collapse.[13] This might be clinically relevant because most patients with OHS have concomitant OSA. Recently, it has been demonstrated that combinations of noradrenergic and antimuscarinic drugs are able to mitigate OSA by reactivating UA dilator muscles, thereby reducing sleep-related UA muscle relaxation during sleep.[14,15] The noradrenergic agent atomoxetine has shown the ability to reduce UA obstruction during sleep both in combination with antimuscarinics and as a standalone therapy.[15] However, when administered alone at high doses before bed to patients with OSA, it negatively impacts both objective and subjective sleep quality. In an effort to improve treatment success, we proposed the combination of acetazolamide plus atomoxetine to stimulate breathing and to activate UA muscles during sleep. Accordingly, the current randomized, double-masked, placebo-controlled cross-over trial tested the effect of 2 weeks of 500 mg acetazolamide plus 100 mg atomoxetine daily, equally divided in 2 doses administered in the morning and before bedtime, as strategy to mitigate OHS severity in outpatients naive or intolerant to PAP treatment.

ABBREVIATIONS: AHI = apnea-hypopnea index; HCO_3^- = serum bicarbonate; IQR = interquartile range; OHS = obesity-hypoventilation syndrome; PAP = positive airway pressure; $Ptco_2$ = transcutaneous overnight measurement of CO_2; REM = rapid eye movement; Sao_2 = arterial oxygen saturation; Spo_2 = peripheral capillary oxygen saturation; UA = upper airway

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Study Design and Methods

Patients

Both male and female patients between 18 and 75 years of age with a BMI of $\geq$ 35 kg/m^2 and presence of sleep-related or diurnal hypoventilation were eligible for study enrollment. According to the European Respiratory Society guidelines, the broader OHS spectrum includes not only patients with obesity and established daytime hypercapnia, but also those with earlier phases of the syndrome who demonstrate sleep-related hypoventilation, referred as pre-OHS. Sleep-related hypoventilation was defined according to the European Respiratory Society and the American Academy of Sleep Medicine guidelines as (1) transcutaneous overnight measurement of CO_2 ($Ptcco_2$) of $>$ 55 mm Hg or (2) $>$ 50 mm Hg if $Ptcco_2$ increases by $>$ 10 mm Hg for $>$ 10 minutes of sleep compared with awake supine value, or (3) presence of serum bicarbonate (HCO_3^-) levels of $\geq$ 27 mEq/L and $Ptcco_2$ with an additional criterion of $Ptcco_2$ reaching at least 48 mm Hg at any time overnight that was added according to clinical experience.[16,17] Diurnal hypercapnia was defined as a $Paco_2$ of $\geq$ 45 mm Hg at morning arterial blood gas test. Patients treated with PAP were included in the study only if they showed poor compliance (use of PAP $<$ 4 h/night for 70% of nights) and they were asked to stop the treatment completely at least 2 weeks before the in-laboratory polysomnography performed at screening. Exclusion criteria included any clinically significant neurologic, respiratory, renal, psychiatric, or cardiovascular disorder; untreated narrow-angle glaucoma; hypertension requiring $>$ 3 drugs to be controlled; use of respiratory stimulants or depressants; or other medications known to interact with study drugs. In particular, a history of respiratory diseases was evaluated to exclude any other cause of hypoventilation.

Participants were enrolled from June 2022 through May 2024 at our sleep clinic (Istituto Auxologico Italiano, Milan, Italy), and the trial ended when the target sample size was reached. The study (European Union Drug Regulating Authorities Clinical Trials Database Identifier: 2022-000693-26) was approved by the ethics committee and by the Italian Medicines Agency (Agenzia Italiana del Farmaco) on May 2, 2022. Informed consent in writing was obtained from all study participants. The study was registered at ClinicalTrials.gov (Identifier: NCT05448443).

Study Design

This was a randomized, double-masked, placebo-controlled, crossover, phase 2a, single-center proof-of-concept study testing the combination of acetazolamide plus atomoxetine in adults with OHS and pre-OHS. Sequential randomization for the active drug and placebo order was performed. More details about data analyses and measurements of outcomes are available in e-Appendix 1.

Study participants underwent eligibility screening with a 1-night in-laboratory baseline polysomnography (Embla) with $Ptcco_2$ evaluation, which served as the baseline for CO_2 and other polysomnography end points. Overnight polysomnography recordings and scoring were performed in accordance with the American Academy of Sleep Medicine rules.[18] Participants were eligible for randomization if $Ptcco_2$ at baseline identified sleep-related hypoventilation. Eligible participants then were randomized equally to receive first 500 mg acetazolamide plus 100 mg atomoxetine daily (acetazolamide plus atomoxetine) or matching placebo. The primary outcome was the change in $Ptcco_2$ in the treatment group compared with the placebo group. Secondary outcomes were: (1) the proportion of participants showing sleep-related hypoventilation with acetazolamide plus atomoxetine vs placebo and (2) the change in apnea-hypopnea index (AHI) with acetazolamide plus atomoxetine vs placebo. We also evaluated the change in overnight arterial oxygen saturation (Sao_2) parameters, including the mean, nadir, proportion of the night spent with Sao_2 $<$ 90%, hypoxic burden, change in $Paco_2$, PaO_2, HCO_3^- and blood pH during wakefulness from the arterial blood gas analysis, the change in subjective sleepiness measured with the Epworth Sleepiness Scale, the short Sleep Apnea Quality of Life Index, the Patient Global Impression of Disease Severity questionnaires, and Psychomotor Vigilance Test findings as exploratory outcomes.

Statistical Analysis

The study was powered to detect a difference in nocturnal mean (SD) $Ptcco_2$ of 5 (5) mm Hg between active and placebo treatments (α, 5%; power, 90%), based on the hypothesis of clinically relevant reduction given that no previous treatment with acetazolamide plus atomoxetine was tested in these patients. A dropout rate of 20% was assumed in the power calculation.

Data are presented as median (interquartile range [IQR]) unless otherwise specified. Linear mixed-model analysis was used to assess differences in continuous end points with acetazolamide plus atomoxetine vs placebo, adjusting for baseline values, period, and sequence effects and including the patient as a random effect. Mixed-effects models were assessed for convergence and reliability, and model residuals were assessed for normality. Outcomes with categorical data were analyzed using the Fisher exact test. Participants were required to have at least 1 assessment after baseline to be included in analysis. Missing data were not imputed. A P value of $< .05$ was considered statistically significant. Statistical analyses were performed using Graph Pad Prism version 10.2 software (McKiev Software) and MATLAB (MathWorks).

Results

Patients

Thirty-two patients underwent baseline polysomnography with $Ptcco_2$ analyses for eligibility evaluation. Of these, 15 individuals were eligible for randomization based on the presence of sleep-related or diurnal hypoventilation (Fig 1). One patient dropped out before starting the first treatment period (personal reasons). One patient dropped out at the beginning of the first treatment period (active drug period) because of adverse events (asthenia).

Data from 13 participants were available for analysis of OHS severity at baseline and on both nights after the week of drug or placebo intake. Our population included 8 patients with both diurnal and sleep-related hypoventilation consistent with OHS and 5 patients with only sleep-related hypoventilation consistent with pre-OHS. The characteristics of these patients are shown in Table 1.

Objective Outcomes of Acetazolamide Plus Atomoxetine Therapy

As hypothesized, acetazolamide plus atomoxetine reduced $Ptcco_2$ compared with placebo (difference, −5.8 mm Hg [95% CI, −7.8 to −3.7 mm Hg]; $P = 3 \times 10^{-6}$) (Table 2, Fig 2). Secondary efficacy outcomes also were significant. Sleep-related hypoventilation was reduced in 6 of 13 participants receiving acetazolamide plus atomoxetine compared with 1 of 13 participants receiving placebo (OR, 0.097 [95% CI, 0.010-0.983]; $P = .037$, Fisher exact

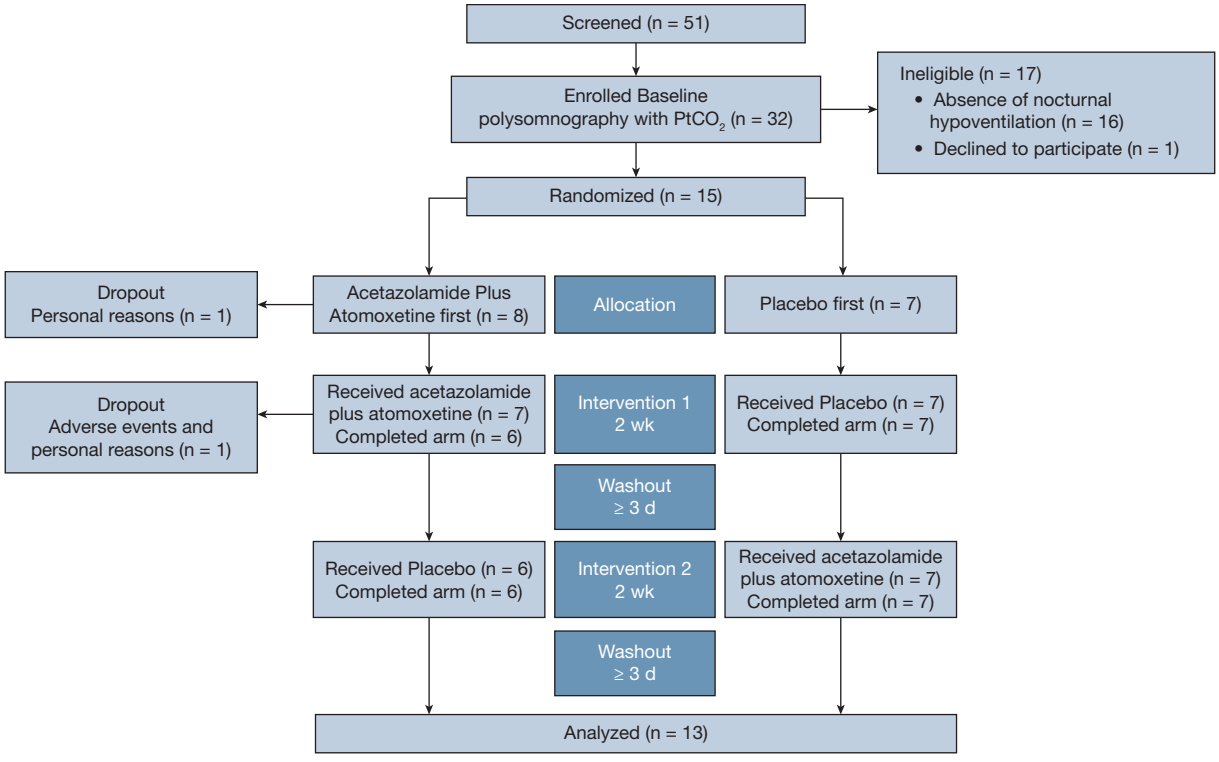

Figure 1 – *Consolidated Standards of Reporting Trials diagram of the trial. $PtcCO_2$ = transcutaneous overnight measurement of CO_2.*

TABLE 1] Patient Characteristics (N = 13)

Baseline Characteristic	Data
Age, y	53.0 (36.0-59.3)
BMI, kg/m^2	43.9 (41.5-52.9)
Weight, kg	116.0 (107.5-160.8)
Sex, male to female ratio	6:7
Hypertension	6 (46)
Diabetes	1 (8)
Dyslipidemia	4 (31)
Mean overnight $Ptcco_2$, mm Hg	48.7 (44.0-55.2)
$Paco_2$, ABG, mm Hg	47.0 (42.1-49.4)
Pao_2, ABG, mm Hg	73 (64.9-86.6)
Bicarbonates, ABG, mEq/L	29.8 (27.5-31.3)
Arterial blood pH	7.43 (7.39-7.44)
AHI, events/h	64.1 (36.4-83.3)
Mean overnight Sao_2, %	84.4 (79.3-89.3)
Minimum overnight Sao_2, %	62.0 (51.5-69)
T90, % TST	68.9 (52.5-96.5)
Hypoxic burden, % min/h	279.8 (114-854.1)
Arousal index, events/h	37.1 (17.6-57.7)
PLM index, events/h	3.2 (0.0-13.1)
Total sleep time, min	382.5 (306.5-408.9)
Non-REM sleep, % TST	
N1	4.2 (2.8-6.3)
N2	68.4 (56.2-78.6)
N3	10.7 (2-20.9)
REM sleep, % TST	15.4 (14.5-19.7)
Sleep efficiency, % TST	77.5 (67.6-85.1)
Wake after sleep onset , min	88.2 (65.6-110.3)
ESS	11.0 (8.5-15.5)
Short SAQLI	47.0 (38.8-58.3)
PGI-S	8.0 (5.0-9.0)
PVT response time, ms	288.0 (248.5-339.5)
BP, mm Hg	
Systolic	131.0 (120.8-138.5)
Diastolic	83.0 (77.5-89.3)
Heart rate, wake, beats/min	80.0 (74.0-93.5)
Overnight heart rate, beats/min	74.5 (66.3-79.9)

Data are presented as No. (%) or median (interquartile range) unless otherwise indicated. Bicarbonates were sampled from ABG. ABG = arterial blood gas; AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale; PGI-S = Patient Global Impression of Disease Severity; PLM = periodic leg movements; $Ptcco_2$ = transcutaneous overnight measurement of CO_2; PVT = Psychomotor Vigilance Test; Sao_2 = arterial oxygen saturation; SAQLI = Sleep Apnea Quality of Life Index; T90 = percentage of time with oxygen saturation of < 90%; TST = total sleep time.

test). AHI also was reduced significantly with acetazolamide plus atomoxetine vs placebo (difference, −20.9 events/h [95% CI, −26.7 to −15.1 events/h]; $P = 2 \times 10^{-8}$) (Table 2, Fig 2). Findings did not change when models were adjusted for body position during sleep (e-Table 1).

In additional analysis, acetazolamide plus atomoxetine significantly improved overnight Sao_2 metrics (Fig 2). The mean and minimum overnight Sao_2 both were increased with acetazolamide plus atomoxetine vs placebo (+4.3% [95% CI, 2.8%-5.7%] and +6.6% [95% CI, 3.2%-10.0], respectively) (Table 2). The proportion of the night spent with Sao_2 of < 90% was reduced by −19.6% (95% CI, −28.9% to −10.3%) with acetazolamide plus atomoxetine vs placebo ($P = .0001$) (Table 2, Fig 2). The hypoxic burden also was reduced with acetazolamide plus atomoxetine vs placebo (–119.1% min/h [95% CI, –148.4% to –84.1% min/h]; $P = 1.6 \times 10^{-6}$) (Table 2, Fig 2). Total sleep time was not different between acetazolamide plus atomoxetine and placebo (Table 2); however, a small but significant increase was found in the fraction of time spent in N3 (non-rapid eye movement [REM]) sleep with acetazolamide plus atomoxetine (+5.3% [95% CI, 0.6%-10.0%]; $P = .028$) (Table 2). Other measures of sleep architecture were not different across arms. Arterial blood pH was reduced significantly in the acetazolamide plus atomoxetine arm compared with the placebo arm (−0.07 [95% CI, −0.09 to −0.04]; $P = 6 \times 10^{-7}$) (Table 2). Acetazolamide plus atomoxetine also was associated with a significantly greater reduction in body weight from baseline compared with placebo (−3.8 kg [95% CI, −5.1 to −2.6 kg]; $P = 4.8 \times 10^{-7}$). Also no difference was found in results from the Psychomotor Vigilance Test in either arm.

Subjective Outcomes of Acetazolamide Plus Atomoxetine Therapy

No perceived differences in sleepiness were found per the Epworth Sleepiness Scale questionnaire or sleep apnea-specific quality of life according to the short Sleep Apnea Quality of Life Index questionnaire between the acetazolamide plus atomoxetine and placebo arms (Table 2). We also observed a trend toward improved Patient Global Impression of perceived severity of disease with acetazolamide plus atomoxetine compared with placebo (difference, −0.9 [95% CI, −1.7 to 0.0]; $P = .056$) (Table 2), but this did not reach significance most likely because of the low sample size.

Adverse Events of Acetazolamide Plus Atomoxetine Therapy

Adverse events associated with each treatment period are shown in Table 3. The most common adverse events

TABLE 2] Study Outcomes

Variable	Placebo	Acetazolamide Plus Atomoxetine	Acetazolamide Plus Atomoxetine vs Placebo	
			Difference	*P* Value
Primary outcome				
Mean overnight $Ptcco_2$, mm Hg	48.6 (45.6-51.7)	42.9 (39.9-45.9)	**−5.8 (−7.8 to −3.7)**[a]	
Secondary outcome				
AHI, events/h	67.9 (47.9-87.8)	47.0 (27.0-67.0)	**−20.9 (−26.7 to −15.1)**[a]	
Arterial blood gas analysis				
Arterial blood pH	7.43 (7.41-7.45)	7.36 (7.34-7.38)	**−0.07 (−0.09 to −0.04)**[a]	
$Paco_2$, mm Hg	45.2 (41.6-48.8)	40.2 (36.7-43.8)	**−5.0 (−7.9 to −2.0)**[b]	
Pao_2, mm Hg	80.8 (71.5-90.1)	77.3 (68-86.7)	**−3.5 (−13.3 to 6.3)**	.5
Bicarbonates, mEq/L	29.6 (28-31.3)	22.6 (20.9-24.2)	**−7.0 (−8.6 to −5.4)**[a]	
Polysomnographic characteristics				
Mean overnight Sao_2, %	84.7 (81-88.3)	88.9 (85.3-92.6)	**4.3 (2.8-5.7)**[a]	
Minimum overnight Sao_2, %	61.4 (56.7-66.2)	68.0 (63.3-72.8)	**6.6 (3.2-10.0)**[a]	
T90, % TST	59.6 (44.4-74.9)	40.0 (24.8-55.3)	**−19.6 (−28.9 to −10.3)**[a]	
Hypoxic burden, % min/h[c]	297.9 (178.8-496.2)	178.7 (107.3-297.8)	**−119.1 (−148.4 to −84.1)**[a]	
Arousal index, events/h	46.6 (27.3-65.9)	32.0 (12.7-51.4)	**−14.6 (−20.2 to −8.9)**[a]	
PLM index, events/h	7.9 (0.3-15.4)	8.9 (1.1-16.6)	1.0 (−5.4 to 7.5)	
Total sleep time, min	347.8 (305.1-390.5)	346.3 (303.6-389)	−1.5 (−34.2 to 31.3)	
Non-REM sleep, % TST				
N1	6.2 (2.8-9.6)	5.2 (1.8-8.6)	−1.0 (−3.1 to 1.1)	
N2	66.3 (60.2-72.4)	65.1 (59-71.2)	−1.2 (−6 to 3.6)	
N3	11.7 (6.5-17.0)	17 (11.7-22.3)	**5.3 (0.6-10)**[b]	
REM sleep, % TST	15.8 (12.5-19.0)	12.7 (9.5-15.9)	−3.1 (−6.9 to 0.8)	
Sleep efficiency, % TST	74.2 (65.8-82.6)	75.6 (67.1-84)	1.4 (−4.4 to 7.2)	
Wake after sleep onset, min	97.0 (57.7-136.3)	96.7 (57.4-136.0)	−0.3 (−24.9 to 24.4)	.98
Patient-reported outcomes and psychomotor vigilance				
ESS	9.2 (6.0-12.5)	8.3 (5.0-11.5)	−1.0 (−3.3 to 1.4)	
Short SAQLI	38.9 (27.4-50.4)	40.5 (29.0-52.0)	1.6 (−9.3 to 12.5)	
PGI-S	6.8 (5.6-7.9)	5.9 (4.8-7.0)	−0.9 (−1.7 to 0.0)	
PVT reaction time, ms	302.7 (264.3-341.1)	294.0 (255.6-332.4)	−8.7 (−51.4 to 34)	
Safety measurements				
BP, mm Hg				
Systolic	124.7 (118.2-131.3)	121.7 (115.2-128.3)	−3.0 (−11.0 to 5.0)	
Diastolic	82.6 (76.9-88.4)	84.7 (79.0-90.5)	2.1 (−4.0 to 8.2)	
Heart rate	86.9 (80-93.8)	89.4 (82.5-96.2)	2.4 (−2 to 6.8)	
Overnight heart rate	74.5 (68.5-80.4)	80.7 (74.8-86.6)	**6.2 (0.8-11.7)**[b]	
Change in weight from baseline, kg	−0.6 (−1.5 to 0.3)	−4.4 (−5.3 to −3.5)	**−3.8 (−5.1 to −2.6)**[a]	

Data are presented as estimate (95% CI) unless otherwise indicated. Mixed-model analysis included all data for patients that completed both arms (N = 13). Models were adjusted for baseline values, sequence, and period, with patient included as a random effect. For the primary outcome model, intraclass correlation coefficient = 0.77, indicating substantial between-patient variability, and $R^2 = 0.86$. Boldface values indicate a significant difference between acetazolamide plus atomoxetine and placebo. ABG = arterial blood gas; AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale; PGI-S = Patient Global Impression of Disease Severity; PLM = periodic leg movements; $Ptcco_2$ = transcutaneous overnight measurement of CO_2; PVT = Psychomotor Vigilance Test; REM = rapid eye movement; Sao_2 = arterial oxygen saturation; SAQLI = Sleep Apnea Quality of Life Index; T90 = percentage of time with oxygen saturation of < 90%; TST = total sleep time.

[a] $P < .001$.

[b] $P < .05$.

[c] First transformed for normality using the transformation $y = \log10(x)$; values were backtransformed for presentation. Bicarbonates were sampled from ABG.

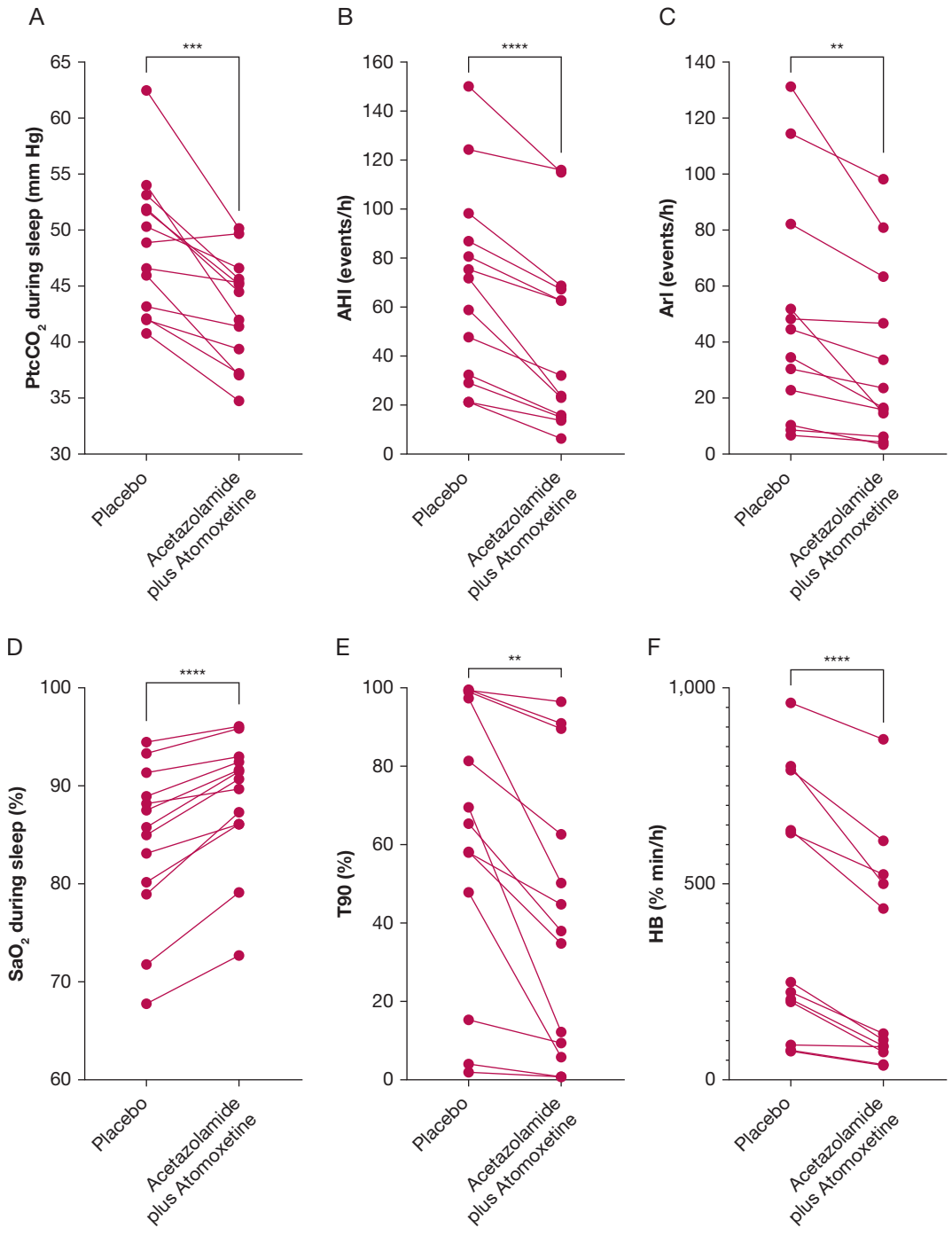

Figure 2 – *A-F, Graphs showing individual data for changes in $Ptco_2$ during sleep (A), AHI (B), ArI (C), and oxygen-related metrics during sleep from placebo to acetazolamide plus atomoxetine treatment: mean overnight Sao_2 (D), T90 (E), and HB (F). *P < .05, **P < .01, ***P < .001, ****P <.0001, respectively. AHI = apnea-hypopnea index (3% desaturation or arousal definition for hypopneas); ArI = arousal index; HB = hypoxic burden; $Ptco_2$ = transcutaneous overnight measurement of CO_2; Sao_2 = arterial oxygen saturation; T90 = percentage of time with oxygen saturation of < 90%.*

reported in the acetazolamide plus atomoxetine arm were paresthesia (n = 6/13), fatigue (n = 3/13), and dysgeusia (n = 2/13), and those in the placebo arm were paresthesia (n = 2/13), dysgeusia (n = 2/13), and insomnia (n = 2/13). No participants experienced severe adverse events in either arm. No differences were found in terms of resting BP or daytime heart rate among the visits; however, mean overnight heart rate was elevated in the acetazolamide plus atomoxetine arm vs placebo arm (+6.2 beats/min [95% CI, 0.8-11.7 beats/min]; $P = .027$).

TABLE 3] Adverse Events

Adverse Event	Acetazolamide Plus Atomoxetine	Placebo
Paresthesia	6 (40.0)	2 (13.3)
Fatigue	3 (20.0)	0 (0)
Dysgeusia	2 (13.3)	2 (13.3)
Insomnia	1 (6.7)	2 (13.3)
Nocturia	1 (6.7)	1 (6.7)
Constipation	1 (6.7)	1 (6.7)
Tinnitus	1 (6.7)	0 (0)
Difficult digestion	1 (6.7)	0 (0)
Dyspnea	0 (0)	1 (6.7)
Feeling of swollen throat	1 (6.7)	0 (0)
Vomiting	1 (6.7)	0 (0)
Fall	0 (0)	1 (6.7)
Headache	1 (6.7)	1 (6.7)
Diarrhea	1 (6.7)	0 (0)
Chest pain	0 (0)	1 (6.7)
Legs edema	0 (0)	1 (6.7)
Lack of appetite	1 (6.7)	0 (0)
Postural instability	1 (6.7)	0 (0)
Sweating	0 (0)	1 (6.7)

Data are presented as No. (%).

Discussion

In this study, for the first time to our knowledge we tested acetazolamide in combination with atomoxetine for OHS outpatients, including those with both daytime hypercapnia and sleep related-hypoventilation and those naïve or intolerant to PAP treatment. We showed that: (1) acetazolamide plus atomoxetine greatly reduced nocturnal and diurnal CO_2 and improved nighttime Sa_{O_2} parameters, (2) the drug combination significantly reduced AHI by about 21 events/h, (3) the drug combination also improved sleep quality as demonstrated by improvements in arousal index and the time spent in deep sleep, and (4) after 2 weeks of acetazolamide plus atomoxetine treatment, a weight reduction of approximately 4 kg was noted.

Atomoxetine is a selective norepinephrine reuptake inhibitor approved for the treatment of attention deficit hyperactivity disorder in adults and children. Studies in humans have shown a decrease in OSA severity with the administration of noradrenergic drugs such as atomoxetine or reboxetine in combination with antimuscarinic drugs such as oxybutynin or its R-enantiomer aroxybutyinin.[14,15,19] Increasing the concentration of norepinephrine during sleep in the brainstem could stimulate the UA motoneurons to similar levels as wakefulness.[20] Although atomoxetine administered alone has been shown to reduce UA obstruction in previous trials, its wake-promoting effects at the most effective doses make it unsuitable as a standalone therapy because it has been found to worsen sleep quality both subjectively and objectively. However, our population did not experience worsened sleep quality during drug administration.

Acetazolamide is a nonselective carbonic anhydrase inhibitor that inhibits renal tubular reabsorption of HCO_3^-, thereby causing a hyperchloremic metabolic acidosis that lowers pH in the brain and increases central ventilatory drive and minute ventilation. Acetazolamide has other sites of action, including the CNS, as evidenced by increased ventilation after acute IV dosing, before a change in arterial pH occurs. Administration for 24 hours increased hypercapnic ventilatory response in healthy people.[13] In patients with OSA, acetazolamide improved AHI and overnight minimum Sa_{O_2}[21] through reduction in ventilatory instability or loop gain. Loop gain has 2 major components: controller gain (chemoresponsiveness, that is, the change in ventilation for a given change in Pa_{CO_2}) and plant gain (change in Pa_{CO_2} for a given change in ventilation).[22] Carbonic anhydrase inhibitors, by stimulating ventilation, can lower plant gain and thus reduce overall loop gain.[21] In a study of patients with obesity with OSA, an 8-week treatment with the carbonic anhydrase inhibitor topiramate combined with phentermine significantly reduced the AHI compared with placebo.[23] Another drug in this class, zonisamide, also has demonstrated a beneficial effect on OSA severity.[24] Although these effects likely are the result in part of weight reduction, the concurrent impact on loop gain may contribute to the enhanced efficacy of these drug combinations. More recently, sulthiame, another carbonic anhydrase inhibitor, was shown to lower AHI in patients with OSA.[25] Despite differences in patient populations, our findings in patients with OHS support the positive impact of acetazolamide plus atomoxetine on OSA severity, with a reduction of 21 events/h compared with placebo. In patients with OSA, acetazolamide has been tested together with atomoxetine plus oxybutynin and shown to be more effective on AHI reduction vs placebo or acetazolamide alone.[26] However, the combination of acetazolamide plus atomoxetine plus oxybutynin had no better benefit on AHI compared with atomoxetine plus oxybutynin, suggesting overlapping physiologic mechanisms in patients with OSA.[26]

Acetazolamide previously was administrated to patients with OHS only in studies conducted in the ICU setting with mechanically ventilated patients for hypercapnic respiratory failure.[12,27] Although the use of acetazolamide alone did not shorten the time of mechanical ventilation,[27] in 1 study the drug administered for 1 to 4 days decreased plasma HCO_3^- and increased CO_2 response, thereby enhancing central ventilatory drive.[12] We observed a reduction of nocturnal $Ptcco_2$ and diurnal $Paco_2$ in nearly all patients. Ventilatory control is very sensitive to changes in $Paco_2$ and pH; when the respiratory system is unable to adjust $Paco_2$ and pH, the kidneys compensate to maintain normal pH. Hypercapnia is responsible for impaired immune function in animal models,[28] and most importantly, chronic hypercapnia is associated with increased mortality.[29-31] Thus, the improvement of hypercapnic status in outpatients with OHS might prevent the evolution toward respiratory failure and consequently improve morbidity and mortality, as recently shown in a large epidemiologic data set.[4,31,32]

Our findings suggest a synergistic potential of acetazolamide and atomoxetine in modulating both central ventilatory drive and UA tone, 2 key pathophysiologic mechanisms implicated in OHS. The dual action—stimulating ventilation via metabolic acidosis and enhancing airway patency through noradrenergic tone—may help to correct both sleep-related hypoventilation and obstructive events, providing a strong physiologic basis for their combined use in this clinical context (Fig 3).

Besides the improvement in the respiratory pattern, we detected an increase in stage 3 sleep during the active

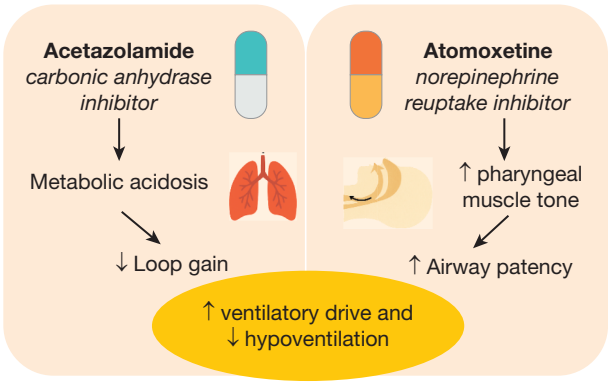

Figure 3 – *Diagram showing hypothesized mechanism of action of the combination of acetazolamide and atomoxetine. Acetazolamide induces a transient metabolic acidosis, which reflexively enhances ventilatory drive and stabilizes ventilatory control, thereby reducing loop gain. Atomoxetine increases upper airway dilator muscle activity, attenuating upper airway obstruction.*

treatment weeks compared with placebo. Although atomoxetine alone reduced REM sleep, carbonic anhydrase inhibitors have been shown to improve sleep architecture by increasing REM sleep in patients with OSA.[15,25] Patients with OHS are known to demonstrate fragmented sleep with an altered macroarchitecture and microarchitecture characterized by reduced deep and REM sleep.[7] Improvement in hypercapnic status, combined with reduced sleep apneas and fewer arousals, likely promoted better sleep continuity during the acetazolamide plus atomoxetine period, contributing to an increase in stage 3 sleep.

No major safety issues were experienced during the 2 weeks of drugs administration. The main adverse event was intermittent paresthesia, which is expected from the use of acetazolamide. Fatigue emerged in 3 patients and might be expected from previous reports of acetazolamide use in clinical trials.[33] Although nocturnal heart rate increased during acetazolamide plus atomoxetine administration, diurnal heart rate and BP did not change after 2 weeks of treatment. As a consequence of the bicarbonaturia induced by acetazolamide, we observed metabolic acidosis in 4 patients (1 patient with moderate and 3 with mild metabolic acidosis) after 2 weeks of drug administration that was not associated with typical symptoms. This effect might be mitigated with long-term administration and probably could be avoided by administering lower doses of acetazolamide, to be tested in new trials.

We noted a significant reduction of body weight after 2 weeks of acetazolamide plus atomoxetine administration. This effect might be attributable not only to the diuretic action of acetazolamide, but also to the metabolic role of carbonic anhydrase inhibitor enzymes,[34] which are involved in processes like fatty acid biosynthesis and de novo lipogenesis.[35] Moreover, acetazolamide has been shown to alter the taste of carbonated drinks, significantly reducing intake and thereby promoting weight loss.[36] The use of acetazolamide or similar agents, such as zonisamide or topiramate, was demonstrated to induce weight loss in many patients with obesity, also improving blood glucose levels.[37,38] However, considering the high baseline BMI of our population, the observed weight loss is unlikely to be the main driver of the improvements seen in $Ptcco_2$, hypoxic burden, and AHI.[32] These changes are related more plausibly to the direct ventilatory and respiratory effects of the pharmacologic intervention.

Although our results strongly suggest an important effect of acetazolamide plus atomoxetine on hypercapnia in OHS, our study is a proof-of-concept trial in a limited number of patients without cardiorespiratory comorbidities. To ensure representation of all stages of OHS, including pre-OHS, we included criterion 3—based on clinical and empirical considerations—which applied to only 1 patient. Although OHS is a relatively rare condition in the general population,[4,39] larger and longer trials need to be performed to confirm the efficacy and the safety of these drugs in a broad range of patients with OHS and to explore any potential modifiers of treatment efficacy. Moreover, the safety of acetazolamide plus atomoxetine in patients with cardiac comorbidities also needs to be studied carefully, including heart rate nocturnal evaluation and arrhythmia monitoring. Although acetazolamide plus atomoxetine reduced hypercapnia and improved nocturnal oxygenation, AHI, and arousal index, its impact on subjective sleep quality was not statistically significant in this small trial. Given the administration of the drug combination for only 2 weeks, the period was probably not long enough to achieve effects on subjective outcomes. This reason is supported by the absence of a worse sleep architecture and subjective sleep quality in the questionnaire results. Finally, we did not assess the individual effects of acetazolamide or atomoxetine on CO_2 or oxygen levels and did not explore the specific contribution of each drug to the overall clinical efficacy.

Interpretation

In this study of adults with OHS, acetazolamide plus atomoxetine demonstrated clinically meaningful improvement in hypercapnia and OSA severity and generally was well tolerated over a 2-week treatment period. OHS is a disorder that is associated with considerable morbidity and mortality. Many patients are untreated or treated inadequately because of poor tolerance to or adherence to PAP therapy, or both. These data suggest that acetazolamide plus atomoxetine may be an effective treatment option for some patients. However, further evaluation of efficacy and safety in larger populations for a longer period are needed, along with identification of phenotypic and endotypic traits that predict better response to treatment. Specifically, it will be of interest to focus on the effect of the drug's respiratory stimulant and related iatrogenic metabolic acidosis over time. Future studies also should explore the potential role of these pharmacologic agents in relationship to PAP therapy, considering the diversity of clinical presentations and pathophysiologic mechanisms underlying OHS, such as those without coexisting OSA. Stratified approaches may help to identify patient subgroups most likely to benefit from pharmacologic interventions, either as alternatives or complements to existing treatments.

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