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A 2-week, polysomnographic, safety study of sodium oxybate in obstructive sleep apnea syndrome

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Abstract

Purpose Sodium oxybate (SXB) is approved for cataplexy and excessive daytime sleepiness in narcolepsy. Obstructive sleep apnea syndrome (OSAS) affects ~9–50% of narcoleptics. Effects of 2-week SXB administration on apnea–hypopnea index (AHI), oxygen saturation (SaO_2), and sleep architecture were investigated in OSAS patients.

Methods OSAS patients ($n=48$) received 2-week SXB or placebo (PBO) treatment with polysomnography at baseline and day 14. The primary outcome measure was change from baseline in mean AHI. Secondary outcomes included changes from baseline in SaO_2, and sleep architecture.

Results Compared with PBO, SXB significantly increased reduction in mean AHI and obstructive apnea index with SXB (-0.8 ± 13.3 vs. -8.2 ± 10.0; $p=0.0327$ and 3.54 ± 11.1 vs. -4.72 ± 7.7; $p=0.0054$, respectively) and significantly increased change in slow wave sleep duration (5.2 ± 25.0 min vs. 29.4 ± 37.0 min; $p=0.0038$). There were no differences between treatments in SaO2, central apneic events, or other measures. Adverse events, most commonly headache, were noted in nine of 27 (33%) and six of 23 (26%) patients receiving SXB and PBO, respectively.

Conclusions Short-term use of 4.5 g/night SXB did not generate respiratory depressant effects in OSAS patients as measured by AHI, obstructive apnea events, central apneas, and SaO2. Extended use of SXB in higher therapeutic doses in OSAS has not been studied, and merits caution.

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Abbreviations

AHI	Apnea–hypopnea index
AEs	Adverse events
CPAP	Continuous positive airway pressure
EDS	Excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
GHB	Gamma-hydroxybutyrate
OSAS	Obstructive sleep apnea syndrome
PBO	Placebo
PSG	Polysomnography
REM	Rapid-eye movement
SaO_2	Oxygen saturation

SDB	Sleep disordered breathing
SXB	Sodium oxybate
SXB/MOD	Sodium oxybate+modafinil
SWS	Slow wave sleep
ZOL	Zolpidem

Introduction

Sodium oxybate (SXB), the sodium salt of gamma-hydroxybutyrate (GHB), was developed in France by Henri Laborit in 1960 and was initially used as an adjunct anesthetic agent [1, 2]. Since then, it has been developed for the treatment of narcolepsy and is approved in the USA for the treatment of excessive daytime sleepiness and cataplexy in narcolepsy and for narcolepsy and cataplexy in the European Union and Canada. It is also approved in Germany for intravenous anesthesia and in Italy and Austria for the treatment of alcoholism. Reports of efficacy of SXB in the treatment of fibromyalgia [3] have led to development of a phase III program. The effects of SXB on sleep architecture [4–6] and improvement of cataplexy and excessive daytime sleepiness (EDS) in narcolepsy [7–10] are well documented; however, its precise mechanism of action remains unknown. The continuous improvement in cataplexy observed over 6–12 months of narcolepsy treatment suggests durable effects of SXB therapy that might be mediated via long-term neuroplastic changes [8].

There are conflicting reports on the effects of SXB on respiration during sleep. Studies with GHB have demonstrated significant central nervous system depression without respiratory depression [1, 11]; however, there have been reports of respiratory depression with GHB abuse often in the presence of cointoxicants such as alcohol [12], and respiratory depression was reported during clinical trials with SXB in narcolepsy [4, 13].

Although the incidence of co-occurring obstructive sleep apnea syndrome (OSAS) in narcolepsy patients has not been well studied, estimates range from 9–50% [13–15]. The incidence of OSAS in narcolepsy may be related to an association between the high risk of OSAS with obesity [16–18], the higher body-mass-index found in narcoleptics compared with the general population, and binge-eating seen in childhood-onset narcolepsy [19, 20].

Significant concern regarding the effects of long-term use of SXB on sleep disordered breathing in narcoleptic patients with co-occurring OSAS remains despite no demonstrable acute effects of SXB on mean apnea–hypopnea index (AHI) or SaO_2 [21]. In the continuation phase of the previously reported study [21], the effects of administration of an additional two weeks of outpatient SXB on AHI and other measures of sleep disordered breathing (SDB), sleep architecture, and EDS are described here.

Methods

Subjects

Sixty patients with OSAS were recruited from two centers (St. Petersburg, FL and London, Ontario, Canada). Inclusion criteria included a history of OSAS, AHI ≥10 and ≤40, and SaO_2 nadir ≥75% (AASM Task Force 1999 criteria for OSAS [23]). Exclusion criteria included a recent history of substance abuse or shift work, or experiencing any major illness, including unstable cardiovascular, endocrine, neoplastic, gastrointestinal, hematologic, hepatic, immunologic, metabolic, neurological, pulmonary, and/or renal disease. Sixteen patients were using continuous positive airway pressure (CPAP) prior to screening and discontinued use during the study. Patients were withdrawn from the study if they failed to comply with the protocol or had any serious adverse events (AEs).

Study design

Following screening, patients had one baseline overnight polysomnography (PSG). This allowed the participants to acclimatize to the laboratory and ensured that the inclusion criteria were met. During this baseline PSG, ten patients experienced oxygen desaturation below 75% lasting less than 10 s. These were judged by the investigators to be artifacts and the patients continued in the study. Prior to entering the 2-week randomized outpatient continuation phase reported here, patients received the following four treatments in a crossover design on four consecutive nights: (1) 9 g SXB, (2) 9 g sodium oxybate/modafinil 200 mg (SXB/MOD), (3) Zolpidem 10 mg (ZOL), and (4) placebo (PBO). These results are reported elsewhere [21].

Following the end of the acute phase, patients were randomized to one of two treatment groups: (1) SXB: Xyrem® 500 mg/ml oral solution, Jazz Pharmaceuticals, Inc. in a dose of 4.5 g per night for 13 days and 9 g for day 14 (taken in divided doses at bedtime and 2.5–4 h after their first dose) or (2) placebo (sodium citrate solution, equimolar to Xyrem® with respect to sodium and indistinguishable by taste, Jazz Pharmaceuticals, data on file), taken in divided doses at bedtime and 2.5–4 h after their first dose. A lower dose of SXB was administered in the outpatient setting (4.5 g) due to the potential risk of respiratory depression in the unmonitored home setting. To provide a more relevant evaluation of potential SXB-induced risk, sleep breathing events and sleep architecture were studied using the highest approved dose of SXB (9 g) in subjects who had become accustomed to receiving a lower dose at home. Eight patients in each group used CPAP during the outpatient phase of the study and none used CPAP during the final PSG visit on day 14. The results for the patients who used CPAP were not analyzed separately.

Data analysis

The primary outcome variable was the change in mean AHI from baseline to the final PSG visit on day 14. AHI was defined as the number of apneas (obstructive, mixed, and central) plus hypopneas per hour of sleep. Secondary outcomes included the mean changes in sleep architecture, oxygenation variables and Epworth Sleepiness Scale (ESS) scores [22]. Events were defined using standard criteria [23] and studies were manually scored by one registered polysomnographic technologist. Criteria for scoring hypopneas followed standard criteria of: (1) A clear decrease (>50%) from baseline in the amplitude of a valid measure of breathing during sleep. Baseline is defined as the mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event (in individuals who have a stable breathing pattern during sleep) or the mean amplitude of the three largest breaths in the 2 min preceding onset of the event (in individuals without a stable breathing pattern); (2) A clear amplitude reduction of a validated measure of breathing during sleep that does not reach the above criterion but is associated with either an oxygen desaturation of >3% or an arousal; and (3) The event lasts 10 s or longer [23]. Sleep was scored per Rechtschaffen and Kales criteria [24]. The data were analyzed by the two-sample t test. If the normality assumption was not met, Wilcoxon's rank-sum test was used. A significance level of 0.05 was used. All tests were two-sided. Due to the nonparametric nature of the data, Spearman's rank-order correlation coefficients were computed for changes in slow wave sleep (SWS; stages 3 and 4 nonrapid eye-movement sleep), AHI, and ESS. A correlation was accepted as significant if the p value was <0.05; the sign of the correlation coefficient indicates whether the variable pairs positively or negatively correlated.

Ethics

The protocol used in this study was approved by the Institutional Review Board/Ethics Board of each participating trial center. Written informed consent was obtained from each patient prior to initiation of the study. This study was conducted in accordance with the Helsinki Declaration, revised 1997. Clinical trial registry: ClinicalTrials.gov; clinical trial registration number: NCT00086281.

Results

Demographics

Fifty patients (83%) were randomized and 48 (80%) completed the outpatient phase of the trial (Fig. 1). Two patients (4%) withdrew due to adverse events prior to receiving any study drug. Demographic characteristics are presented for all randomized patients in Table 1. There were no differences between groups in mean age, weight, height, BMI, race, or sex. Results are presented for patients who completed the trial in Table 2.

Sleep disordered breathing

There were no differences in respiratory PSG measurements between groups at baseline (see Table 1). The mean AHI was significantly reduced from baseline in the SXB treatment group compared with PBO at day 14 (−8.2± 10.0 vs. −0.8±13.3; p=0.0327). In addition, the number of obstructive apneic events per hour (obstructive apnea index) was also significantly reduced from baseline in the SXB group compared with PBO (−4.72±7.68 vs. 3.54± 11.08; p=0.0054). There were no differences between
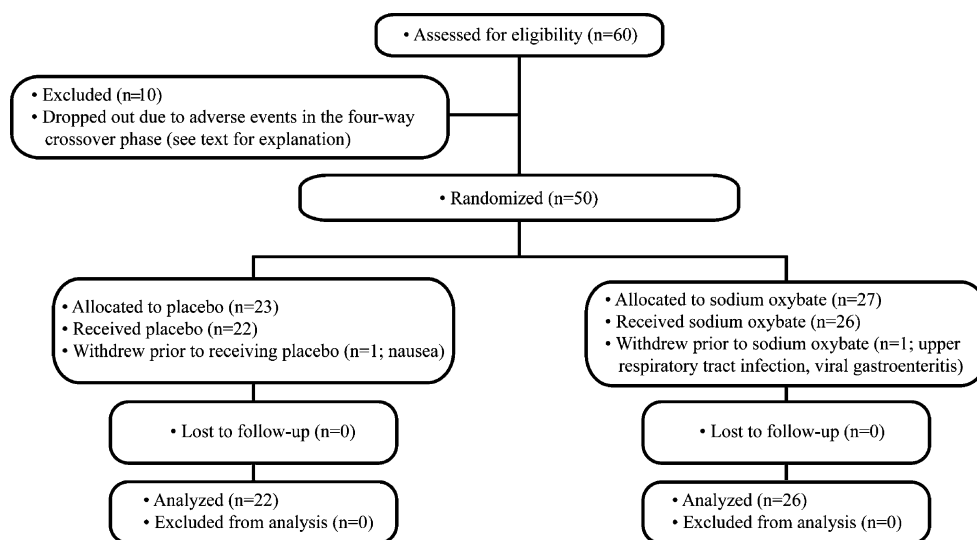
Fig. 1 Subject flow diagram

Table 1 Study demographics

Characteristic	Placebo (*n*=23), mean (SD)	SXB (*n*=27), mean (SD)
Age (years)	49.7 (11.1)	49.7 (8.0)
Weight (kg)	100.7 (16.6)	102.7 (18.3)
Height (cm)	174.7 (4.5)	175.9 (9.7)
BMI (kg/m^2)	33.0 (5.4)	33.2 (5.0)
Race—counts (%)		
Caucasian	21 (91.3)	24 (88.9)
Black	1 (4.3)	2 (7.4)
Asian	1 (4.3)	0 (0)
Hispanic	0 (0)	1 (3.7)
Other	0 (0)	0 (0)
Sex—counts (%)		
Male	20 (87)	21 (77.8)
Female	3 (13)	6 (22.2)

SXB sodium oxybate, *BMI* body mass index

treatment groups noted in SaO2 or central apneic events per hour. The proportion of patients at the final visit with an AHI<10 for SXB was numerically greater than PBO (2/22 (9.1%) vs. 8/26 (30.8%)) and opposite trend was seen for the proportion with SaO_2 nadir <85% for SXB compared with PBO (18/26 (69.2%) vs. 12/22 (54.6%)); however, these differences were not statistically significant.

Sleep architecture

As shown in Table 1, there were no differences in sleep architecture characteristics between groups at baseline. There was an increased duration of SWS with SXB treatment, which was significantly greater than the change from baseline seen in PBO (29.4±37.0 min vs. 5.2± 25.0 min; *p*=0.0038). There were no differences between groups in incremental changes in time spent in stage 1 or stage 2 sleep, or rapid eye movement (REM) sleep, total sleep time, wake after sleep onset, or arousal index.

Excessive daytime sleepiness

Epworth sleepiness scale scores decreased in both treatment groups, but this difference was not significant (−3.5±5.3 with SXB vs. −0.6±3.3 with PBO; *p*=0.09).

Correlational analysis

As indicated in Fig. 2, the change from baseline in SWS was negatively and significantly correlated with the change from baseline in AHI for all patients (*r*=−0.38; *p*=0.0074) but not for SXB (*r*=−0.252, ns) or PBO (*r*=−0.274, ns) alone. No significant correlations between change from baseline in SWS and either change in obstructive apneas or ESS were seen.

Safety

Of the 50 patients who were randomized and for whom AEs are reported in Table 3, two patients withdrew before receiving drug in this study. These two patients reported AEs at the end of the prior study which are reported elsewhere [21]. No other patients withdrew during the double-blind phase. As shown in Table 3, nine of 27 (33.0%) and 6/23 (26.1%) patients experienced AEs in the SXB and PBO groups, respectively. The most common individual event was headache (4/23 in PBO and 2/27 in SXB). There were no serious AEs or deaths reported during the study.

Discussion

There is a compelling clinical need to determine whether therapeutic agents with the potential to cause respiratory depression such as SXB can be safely used in patients with OSAS, especially since CPAP treatment compliance is generally poor, typically less than 50% in patients with OSAS [25]. SXB is currently a standard treatment for narcolepsy, where a potentially large proportion (9–50%) of patients may also have diagnosed or undetected OSAS [13, 15, 16]. Patients with OSAS have compromised respiration during sleep due to an increased mechanical load on the airway combined with the normal decrease in respiratory drive. In normal subjects, reduced facilitatory drive to the upper respiratory muscles occurs as sleep progresses through deeper stages of sleep (stages 1–4) and then to REM. This reduced drive is accompanied by decreases in minute ventilation and ventilatory drive and lung volumes, leading to increased upper airway resistance and increased respiratory events [26].

Table 2 Treatment effects of SXB on SDB and sleep architecture

	Baseline			Night 14		
	PBO (n=22)	SXB (n=26)	p value	PBO (n=22)	SXB (n=26)	p value
Respiratory parameters—mean (SD)						
AHI	25.0 (8.1)	23.5 (10.0)	NS	24.2 (13.9)	15.3 (8.5)	
AHI Change from baseline				−0.79 (13.3)	−8.2 (10.0)	0.0327
Central Apneas Index	0.55 (1.34)	0.68 (1.84)	NS	0.74 (1.52)	1.20 (2.30)	
Central Apneas Index Change from baseline				0.19 (0.69)	0.51 (1.09)	NS
Obstructive Apneas Index	7.62 (7.79)	9.02 (9.94)	NS	11.16 (10.72)	4.30 (4.40)	
Obstructive Apneas Index Change from baseline				3.54 (11.08)	−4.72 (7.68)	0.0054
SaO_2 (Mean)	95.3 (1.2)	94.6 (1.6)	NS	94.9 (1.5)	94.6 (1.6)	
SaO_2 (Mean) Change from baseline				−0.4 (1.6)	0.1 (2.0)	NS
$SaO_2 < 90\%$ (in min)	1.0 (1.2)	1.5 (2.2)	NS	1.4 (1.5)	1.6 (2.0)	
$SaO_2 < 90\%$ (in min), change from baseline				0.5 (1.5)	0.1 (2.7)	NS
$SaO_2 < 80\%$ (in min)	0.02 (0.04)	0.04 (0.12)	NS	0.2 (0.6)	0.1 (0.3)	
$SaO_2 < 80\%$ (in min) Change from baseline				0.2 (0.6)	0.1 (0.3)	NS
Sleep Architecture (min)—Mean (SD)						
Stage 1	19.5 (10.9)	15.7 (11.7)	NS	10.2 (6.5)	8.7 (8.4)	
Stage 1 Change from baseline				−9.3 (11.0)	−7.0 (12.0)	NS
Stage 2	233.5 (54.6)	240.5 (44.8)	NS	254.8 (55.2)	265.6 (34.5)	
Stage 2 Change from baseline				21.3 (43.3)	25.1 (52.4)	NS
SWS (Stage 3&4)	37.5 (25.4)	43.7 (19.8)	NS	42.7 (24.4)	73.1 (40.0)	
SWS Change from baseline				5.2 (25.0)	29.4 (37.0)	0.0038
REM Sleep	73.6 (28.3)	74.7 (27.6)	NS	84.2 (28.8)	71.3 (30.4)	
REM Sleep Change from baseline				10.6 (26.0)	−3.4 (39.2)	NS
WASO	98.7 (66.3)	91.1 (66.2)	NS	80.8 (58.3)	56.8 (25.5)	
WASO Change from baseline				−18.0 (49.3)	−34.3 (65.0)	NS
TST	364.2 (65.8)	374.7 (65.5)	NS	392.0 (55.9)	424.5 (31.9)	
TST Change from baseline				27.8 (55.8)	49.8 (64.6)	NS
Arousal index (n/hr)	4.5 (7.0)	2.4 (3.6)	NS	4.9 (10.3)	1.5 (2.7)	
Arousal index Change from baseline				0.4 (5.6)	−0.8 (4.2)	NS
Epworth Sleepiness Score						
ESS	11 (5.8)	12.2 (5.1)	NS	10.5 (6.6)	8.6 (4.8)	
ESS Change from baseline				−0.6 (3.3)	−3.5 (5.3)	NS

SXB=sodium oxybate; PBO=placebo; AHI=apnea-hypopnea index; SaO2=oxygen saturation; SWS=slow wave sleep; REM=rapid eye movement; WASO=wake after sleep onset; TST=total sleep time; ESS=Epworth Sleepiness Scale

This 2-week outpatient continuation phase of a trial of SXB in mild to moderate OSAS demonstrated that SXB 4.5 g in two divided doses nightly over 13 nights followed by a final night of 9 g challenge did not increase the risk of respiratory depression. Instead, compared with baseline PSG values obtained prior to the crossover phase of the study, an improvement in AHI and a reduction in the number of obstructive apnea events were seen at day 14 with 9 g SXB treatment. These results are similar to other trials of SXB which demonstrated a decrease in duration of obstructive apneas and increased SWS and no worsening of AHI in doses of approximately 4–9 g nightly [27–29].

Limitations of this study

Interpretation of these results are limited both by the small sample size (n=50) and the analysis of only one final PSG night with SXB treatment. Although an overall decrease of AHI with SXB treatment was demonstrated, significant

Fig. 2 Correlation analysis of SWS and AHI. The change from baseline in SWS was negatively correlated with the change from baseline in AHI for all patients ($r=-0.38$; $p=0.0074$) but not for SXB ($r=-0.252$, ns) or PBO ($r=-0.274$, ns) alone
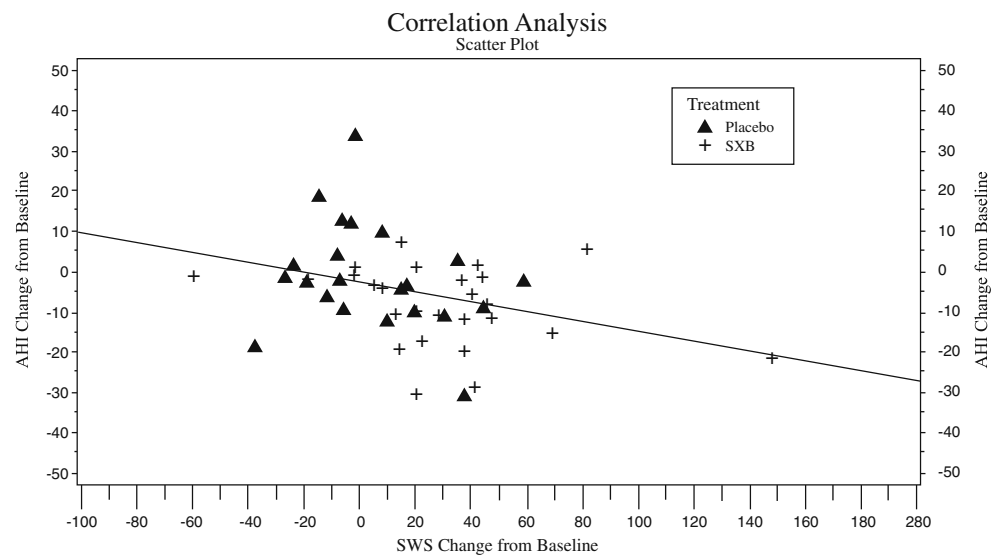
night-to-night variability in AHI has been noted in the literature [30–32]. Furthermore, the dosing scheme of SXB 9 g on the night of the final attended PSG and 4.5 g for 2 weeks at home was chosen to maximize patient safety but

may not accurately reflect the long-term effects of SXB on sleep disordered breathing.

Methodological issues such as the choice of baseline PSG values prior to the crossover phase of the study instead

Table 3 Summary of treatment-related post-dose adverse events (MedDRA classification)

System Organ Class Preferred term	Placebo (n=23) N (%)	Sodium oxybate (n=27) N (%)
Number of patients with any event	6 (26.1)	9 (33.3)
Eye disorders	1 (4.3)	0 (0)
Asthenopia	1 (4.3)	0 (0)
Eye pain	1 (4.3)	0 (0)
Vision blurred	0 (0)	1 (3.7)
Gastrointestinal disorders	0 (0)	1 (3.7)
Dyspepsia	0 (0)	1 (3.7)
Diarrhea	0 (0)	1 (3.7)
General disorders and administration site conditions	1 (4.3)	0 (0)
Fatigue	1 (4.3)	0 (0)
Infections and infestations	1 (4.3)	0 (0)
Bronchitis	1 (4.3)	0 (0)
Injury, poisoning, and procedural complications	0 (0)	1 (3.7)
Limb injury	0 (0)	1 (3.7)
Musculoskeletal and connective tissue disorders	1 (4.3)	1 (3.7)
Musculoskeletal stiffness	1 (4.3)	0 (0)
Rotator cuff syndrome	0 (0)	1 (3.7)
Nervous system disorders	4 (17.4)	3 (11.1)
Dizziness	0 (0)	1 (3.7)
Headache	4 (17.4)	2 (7.4)
Somnolence	1 (4.3)	0 (0)
Respiratory, thoracic, and mediastinal disorders	2 (8.7)	1 (3.7)
Dry throat	1 (4.3)	0 (0)
Epistaxis	1 (4.3)	0 (0)
Pharyngolaryngeal pain	0 (0)	1 (3.7)
Skin and subcutaneous disorders	0 (0)	1 (3.7)
Pruritis generalized	0 (0)	1 (3.7)

of following the crossover phase may not accurately reflect the true baseline values. Also, the effects of SXB seen in the present study in OSAS patient may differ from those in narcoleptic patients with concurrent OSAS.

Conclusion

It is not clear how SXB might reduce AHI in OSAS patients. Overall, the change from baseline in mean SWS was associated with the change in mean AHI for the whole sample studied but not for the SXB or PBO group alone. This is most likely due to smaller numbers in the individual groups. It is not clear if the increment of SWS is mechanistically associated with improvement of AHI. It is speculated that SXB may affect brainstem catecholaminergic systems [33] that may increase the facilitatory drive to stabilize the upper airway. SXB may also have additional more direct effects on muscle tone, as GHB administration-induced increased peripheral muscle EMG activity has been reported in animal studies [34].

The presence of sleep disordered breathing should be carefully evaluated in all patients who are candidates for SXB therapy. As indicated in the crossover study, nighttime administration of SXB 9 g resulted in more central apneas than PBO [21]. Therefore, further studies investigating the longer-term effects (>3 months) of higher doses of SXB (6 to 9 g) on sleep disordered breathing as well as studies investigating the respiratory effects of SXB on CPAP compliance and pressures in patients with co-occurring OSAS are recommended.

Short-term use of SXB at 4.5 g per night did not generate respiratory depressant effects in patients with OSAS as measured by AHI, obstructive apnea events, central apneas, and SaO_2. The effects of longer term use of SXB in higher therapeutic doses for patients with OSAS have not been rigorously studied and nocturnal oximetry monitoring or nocturnal polysomnography with SXB might be useful. SXB therapy in patients with co-occurring OSAS should be approached with caution.

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