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SCIENTIFIC INVESTIGATIONS

Treatment for patients with sleep apnea on opioids for chronic pain: results of the OpSafe trial

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Study Objectives: Approximately 20% of North Americans are afflicted with chronic pain with 3% being opioid users. The objective was to determine whether patients on opioids for chronic pain with newly diagnosed sleep apnea attended sleep clinic review and followed treatment recommendations.

Methods: The study was a post hoc analysis from a multicenter perspective cohort study. Inclusion criteria included adults taking opioid medications for chronic pain for >3 months. Demographic data and daily opioid dose were collected. Sleep apnea was diagnosed via level 1 polysomnography. Patients who attended sleep clinic review were grouped based on the types of treatment they received.

Results: A total of 204 patients completed polysomnography and 58.8% were diagnosed to have sleep apnea (apnea-hypopnea index ≥5 events/h). Of those with sleep apnea, 58% were recommended to have an evaluation by a sleep physician. Body mass index and age were 29.5 ± 6 kg/m^2 and 56 ± 12 years, respectively. Of those with newly diagnosed sleep apnea, 25% received treatment, with the majority being treated with positive airway pressure therapy, whereas the rest received positional therapy and opioids/sedative reduction. The adherence rate of positive airway pressure therapy was 55% at 1 year. Over 50% of participants on opioids for chronic pain with newly diagnosed sleep apnea declined attendance for sleep clinic review or treatment.

Conclusions: There was a high refusal rate to attend clinic for treatment. Adherence to positive airway pressure therapy was low at 55%. This sheds light on the high rate of treatment nonadherence and the need for further research.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: Opioid Safety Program in Pain Clinics (Op-Safe); URL: https://www.clinicaltrials.gov/ct2/show/NCT02513836; Identifier: NCT02513836.

Keywords: sleep apnea, PAP therapy, positional therapy, opioids, chronic pain

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Many North Americans have chronic pain that is treated with opioids. This study aimed to determine whether patients on opioids for chronic pain with newly diagnosed sleep apnea attended sleep clinic review and followed treatment recommendations.

Study Impact: Treatment recommendations for patients with sleep apnea on opioids for chronic pain were predominantly positive airway pressure therapy, positional therapy, and opioids/sedative dose reduction. Over 50% of participants on opioids for chronic pain with newly diagnosed sleep apnea declined attendance for sleep clinic review or treatment. Adherence to positive airway pressure therapy was low at 55%.

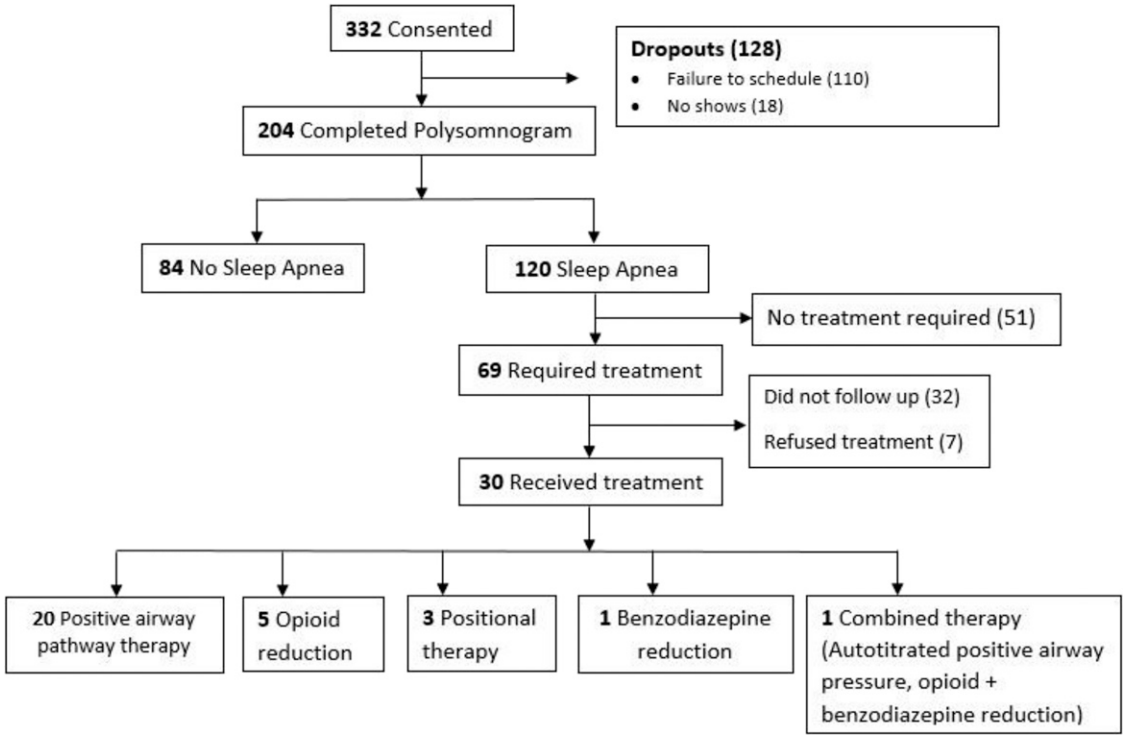
INTRODUCTION

Sleep and pain are interrelated, with a bidirectional relationship between the 2, where pain disrupts sleep and sleep disturbances exacerbate pain.[1] Impaired sleep is a predictor of pain[2] and increases the risk of developing chronic pain.[3] Approximately 50–80% of patients with chronic pain report sleep disturbances resulting in increased hyperalgesia.[3–5]

Sleep apnea is one of the most common sleep breathing disorders. Obstructive sleep apnea (OSA) involves respiratory effort in the absence of airflow as a result of an obstruction or narrowing of the upper airway.[6,7] Central sleep apnea (CSA) is the cessation of respiratory effort in the absence of airflow.[6,7] Sleep apnea in patients on opioids for chronic noncancer pain is often unrecognized.[8] One in five North Americans live with chronic pain, 3% of whom are opioid users.[9] In 2018, 47,590 total deaths in United States were reported to be the result of opioid overdose with 4,614 deaths reported in Canada. Approximately 70% of patients on opioids for chronic pain were reported to have sleep apnea.[10] The American Academy of Sleep Medicine recently released a position statement warning patients and medical providers that chronic opioid use is associated with both CSA and OSA. Screening, testing, and treatment of opioid-associated sleep-disordered breathing were recommended.[11]

Although evidence exists to confirm the association between chronic pain, opioids, and sleep apnea, the current therapeutic modalities for sleep apnea in patients on opioids for chronic pain

Figure 1—Study flow chart.



have not been properly explored in a pragmatic fashion. The objective of our study was to determine whether patients on opioids for chronic noncancer pain with newly diagnosed sleep apnea attend sleep clinic review and follow treatment recommendations. These patients were previously enrolled in the Opioid Safety Program in Pain Clinics (OpSafe) trial.[12]

METHODS

The study was a planned, post hoc analysis from a multicenter prospective cohort study "Development of an Innovative Opioids Safety Program in Pain Clinics."[12] This prospective cohort study was conducted at 5 university-affiliated tertiary care pain clinics in Canada. Detailed methods had been reported previously.[12] In brief, adults aged 18 years or older taking opioid medications for chronic pain for more than 3 months with a stable daily dose for more than 4 weeks were eligible to participate. Patients with a prior diagnosis of sleep apnea, active neurological or psychiatric disorders, cancer, and those in whom an urgent sleep evaluation was deemed necessary for safety reasons were excluded.

The research ethics board of each participating institution approved the research protocol (research ethics board approval numbers: 14-8611-AE, 15-0004-A, 2014-0122, and 106620) and all patients provided written informed consent. All patients' demographic characteristics, comorbidities, morphine milligram equivalents (MME), and medications were documented. Daily opioids doses were converted to approximate MME according to the US Centers for Disease Control and Prevention.[13] Patients were invited to undergo in-laboratory polysomnography.

Patients were invited to undergo in-laboratory level 1 polysomnography to diagnose sleep apnea. The polysomnography recordings were scored by experienced technologists and reviewed by 2 sleep physicians. Both technologists and sleep physicians were blinded to the clinical information. The recording montage included electroencephalography, bilateral electrooculograms, a chin electromyography, single lead electrocardiography, thoracic and abdominal respiratory inductance plethysmography, airflow measured by thermocouple and nasal pressure cannula, finger pulse oximetry, and bilateral limb movements. All of the signals were recorded on a computerized sleep scoring system (Sandman; Natus Medical, Inc, Middleton, WI), Sleep stages and electroencephalography (cortical) arousals were scored according to published guidelines.[6] Sleep apnea, central/obstructive apneas and hypopneas, arousal, and severity were scored and defined according to the American Academy of Sleep Medicine. Sleep apnea was defined as an apnea-hypopnea index (AHI) of 5 or more events/h of sleep.[6,12]

Sleep clinic review was recommended following the polysomnography for participants with an AHI of 10 or more events/h or an AHI of 5 or more events/h, with a score of Epworth sleep scale of more than 10 or greater than 10% of total sleep time with an oxygen saturation less than 90%.[14] Thus, patients with these criteria were recommended for a consultation with a sleep physician for further treatment. Decisions regarding treatment for these patients were made by the treating sleep physicians, which were based on the clinical history

Table 1—Demographic parameters of patients grouped by AHI and CAI.

Characteristics	AHI ≥5 events/h (n = 120)	CAI ≥5 events/h (n = 33)
Body mass index, kg/m^2	29.5 ± 6	29 ± 7
Age, years	56 ± 12	54 ± 13
Neck circumference, cm	39.7 ± 5	40 ± 5
Male sex, n (%)	58 (48.3)	18 (54.5)
Epworth Sleepiness Scale	9.1 ± 5	9.8 ± 5
Daytime SpO_2, %	94.5 ± 2	93.3 ± 3
MME, mg/d	75 (30, 187.5)	172.5 (50, 735)
Medical conditions, n (%)		
Hypertension	21 (17.5)	4 (12.1)
Cardiovascular diseases*	10 (8.3)	3 (9.1)
Diabetes	13 (10.8)	3 (9.1)

Data are presented as frequency (percentage) where indicated, mean ± SD, or median (interquartile range). AHI = apnea-hypopnea index; CAI = central apnea index; MME = morphine milligram equivalents; SpO_2 = oxyhemoglobin saturation. *Cardiovascular diseases include angina, myocardial infarction, arrhythmia, valvular disease, peripheral vascular disease, or stroke; no participant had history of heart failure.

and polysomnography results. Patients who attended for a sleep clinic review were grouped based on the treatment they received (**Figure 1**). The different types of treatment included the following: positive airway pressure (PAP) therapy, positional therapy, and reduction of medication such as opioid or benzodiazepine. Positional therapy was conducted with the traditional devices (eg, tennis ball technique or similar commercial sleep-position modification devices). Positional OSA is defined as a reduction in AHI by 50% when sleeping in the nonsupine position.[6]

All statistical analyses were performed with Stata version 14.2 (StataCorp, College Station, TX).[15] The continuous data are presented with means (standard deviations) or medians (interquartile ranges). The categorical data are presented using frequencies (percentages). Repeated-measure *t* test was conducted to compare AHI before and after PAP therapy treatments. The *t* tests or Wilcoxon rank-sum tests and Fisher's exact tests or chi-square tests were used to test differences in the characteristics of patients who attended sleep clinic and those who refused to attend/refused treatment. A *P* value less than .05 was considered significant, but no data were found as to why a proportion of the patients refused to attend the sleep clinic.

RESULTS

Of the 332 eligible patients, 204 (61.4%) completed polysomnography. One hundred and twenty patients (59%) had an AHI of 5 or more events/h and were diagnosed with sleep apnea. The mean age and body mass index were 56 ± 12 years and 29.5 ± 6 kg/m^2, respectively. Of the 120 patients with sleep apnea, 33 had a central apnea index (CAI) of 5 or greater. The median MME for AHI of 5 or more events/h and CAI of 5 or greater were 75 (30, 187.5) mg/d and 172.5 (50, 735) mg/d, respectively (**Table 1**).

From the 120 patients with an AHI of 5 or more event/h, a sleep clinic review was recommended in 69 patients (57.5%), while 51 patients (42.5%) required no further evaluation (**Table 2**). The decision that participants required no further evaluation was based on the study protocol. This protocol indicated no follow-up was required if the AHI was less than 10 and or the Epworth Sleepiness Scale was less than 10 and there was no evidence of sleep-related hypoxia or hypoventilation as determined by the sleep physician.

Of the 69 patients, 30 (43.5%) patients attended a consultation with a sleep physician and agreed to treatment, while 39 (56.5%) patients refused consultation (n = 32) or PAP therapy (n = 7) after consultation (**Figure 1** and **Table 2**). When comparing the demographic characteristics and sleep parameters of patients who attended sleep clinic review with those who refused consultation, the first group had significantly higher Epworth Sleepiness Scale (11.0 ± 4.8 vs 7.8 ± 5.0; $P < 0.05$) and CAI (4.8 [0.9–30.9] vs 0.9 [0–6.2]; $P < .05$). There was no significant difference in other demographic characteristics (sex, age, body mass index, MME) and sleep parameters (oxygen desaturation index, low SpO_2 [oxyhemoglobin saturation], mean SpO_2, and CT90 [cumulative time SpO_2 <90%]) between those who attended sleep clinic review and treatment and those who refused. No data are available on why these patients refused to attend/follow-up for their sleep clinic review.

Of the 30 patients who attended sleep clinic, 20 (66.7%) patients were recommended PAP therapy (17 continuous PAP [CPAP]/auto-titrated PAP, 1 bilevel PAP, and 2 adaptive servoventilation) (**Table 2**). The mean baseline AHI score and ODI was 41.9 ± 24 and 37 ± 22 events/h for PAP therapy, respectively (**Table 3**). Of the 2 patients who received adaptive servoventilation, residual AHI information was available for 1 patient after 1 year. Pretreatment baseline AHI was 77.7 events/h and residual AHI after treatment decreased to 7.4 events/h. Of the 20 patients who received PAP therapy, 11 (55%) adhered to treatment at 1 year. In the PAP-adherent patients, the mean AHI was significantly reduced after treatment at 1 year vs baseline (3.5 ± 2.7 vs 40.7 ± 21.2 events/h, $t(10) = 6.3$, $P < .01$).

Following a sleep consultation, the decision for positional therapy was made in conjunction with the patient and sleep physician. Three patients received positional therapy. The mean baseline AHI score and ODI were 11.2 ± 6.9 and 12.5 ± 2.4 events/h, respectively (**Table 3**). The baseline mean supine and nonsupine AHIs were 24.2 ± 2 and 1.3 ± 1 events/h, respectively.

Five patients had solely dose reduction of opioids, with a baseline AHI score of 49 ± 26 events/h and CAI score of 31.9 ± 13.0 events/h. The median (interquartile range) MME was 270 (135, 750) mg/d (**Table 2**). The other sleep parameters of the patients in each treatment group are shown in **Table 2** and **Table 3**.

DISCUSSION

Our prospective study provides significant insights into the types of treatment that are recommended for patients with

Table 2—Recommendations for sleep apnea treatment in patients on opioids for chronic pain.

	n (%)	MME, mg/d	AHI, events/h	Obstructive AHI, events/h	Central AHI, events/h	AHI 5 to <15, mild	AHI 15 to <30, moderate	AHI ≥30, severe
Sleep apnea (AHI ≥ 5)	120	75 (30, 87.5)	25.8 ± 23.5	17.5 ± 17.9	7.8 ± 15.6	55	28	37
Required no treatment	51 (42.5)	94 (24, 214)	13.4 ± 18.1	10.7 ± 18.2	2.6 ± 4.8	40 (72.7)	8 (28.6)	3 (8.1)
Required treatment	69 (57.5)	60 (30, 83.8)	35.0 ± 22.9	22.5 ± 16.1	11.6 ± 19.3	15 (27.3)	20 (71.4)	34 (91.9)
Refused treatment (7) or attendance (32)	39 (32.5)	70 (20, 87.5)	31.6 ± 21.4	22.7 ± 17.6	8.7 ± 18.4	9 (16.4)	14 (50)	16 (43.2)
Treatment	30 (25)	55 (40, 135)	39.4 ± 24.4	22.4 ± 14.2	15.5 ± 20.0	6 (10.9)	6 (21.4)	18 (48.6)
PAP therapy (20), CPAP/APAP (17), ASV (2), BPAP (1)	20 (16.7)	45 (30, 65)	41.9 ± 23.6	25.7 ± 12.4	14.5 ± 21.5	3 (5.5)	4 (14.2)	13 (35.1)
Positional therapy	3 (2.5)	135 (45, 365)	11.2 ± 6.9	9.7 ± 5.5	1.5 ± 1.6	2 (3.6)	1 (3.6)	0
Opioid reduction	5 (4.2)	270 (135,750)	49.0 ± 26.0	14.2 ± 12.1	31.9 ± 13.0	0	1 (3.6)	4 (10.8)
Benzodiazepine reduction	1 (0.8)	55	13.6	4.5	9.1	1 (1.8)	0	0
Combined therapy*	1 (0.8)	196	54	53.2	0.8	0	0	1 (2.7)

MME are presented as median (interquartile range). Sleep parameters are presented as mean ± SD. Categorical variables are presented as frequency (%). *Combined therapy: APAP, opioid + benzodiazepine reduction. AHI = apnea-hypopnea index; APAP = autotitrated positive airway pressure; ASV = adaptive servo-ventilation; BPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; MME = morphine milligram equivalents; PAP = positive airway pressure.

Table 3—Additional sleep parameters for sleep apnea treatment in patients on opioids for chronic pain.

	n (%)	AHI, events/h	ODI, events/h	Lowest SpO_2, %	Mean SpO_2, %	CT90, %
Sleep apnea (AHI ≥ 5)	120	25.8 ± 23.5	27.7 ± 23.9	83.5 ± 6.5	93.6 ± 2.2	11.8 ± 22.3
Required no treatment	51 (42.5)	13.4 ± 18.1	18.5 ± 22.0	84.5 ± 6.7	93.6 ± 2.5	12.1 ± 22.7
Required treatment	69 (57.5)	35.0 ± 22.9	34.5 ± 23.1	82.8 ± 6.3	93.7 ± 2.0	11.6 ± 22.1
Refused treatment (7) or attendance (32)	39 (32.5)	31.6 ± 21.4	33.0 ± 22.2	82.8 ± 6.5	93.7 ± 2.4	14.7 ± 26.5
Treatment	30 (25)	39.4 ± 24.4	36.5 ± 24.7	82.8 ± 6.1	93.7 ± 1.4	7.5 ± 14.0
PAP therapy (20), CPAP/APAP (17), ASV (2), BPAP (1)	20 (16.7)	41.9 ± 23.6	37.0 ± 22.1	81.9 ± 6.2	93.9 ± 1.4	7.4 ± 13.7
Positional therapy	3 (2.5)	11.2 ± 6.9	12.5 ± 2.4	86 ± 1.7	93.0 ± 0.6	2.1 ± 1.0
Opioid reduction	5 (4.2)	49.0 ± 26.0	47.8 ± 28.6	82.6 ± 7.9	93.0 ± 1.8	13.6 ± 21.2
Benzodiazepine reduction	1 (0.8)	13.6	4.3	88.7	93.2	0
Combined therapy*	1 (0.8)	54	74	86	94.3	3.2

AHI = apnea-hypopnea index; APAP = autotitrated positive airway pressure; ASV = adaptive servo-ventilation; BPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CT90 = cumulative time SpO_2 <90%; ODI = oxygen desaturation index; PAP = positive airway pressure; SpO_2 = oxyhemoglobin saturation. *Combined therapy: APAP, opioid + benzodiazepine reduction.

differing sleep apnea profiles. The study also fills a knowledge gap regarding adherence to recommended treatment in patients with sleep apnea on opioids, with the largest dataset in this area. We recently showed that sleep apnea was greatly underdiagnosed in patients on opioids for chronic pain.[12] In 204 patients on opioids for chronic pain, 58.8% were diagnosed to have sleep apnea (AHI ≥5 events/h; 72% obstructive, 20% central, and 8% indeterminate sleep apnea), with a high prevalence of moderate (23.3%) and severe sleep apnea (30.8%).[12] In 120 patients who were diagnosed with sleep apnea, 57.5% were recommended for a sleep clinic review, while 42.5% were deemed not to require any further evaluation based on the results of the polysomnography. Unfortunately, there was a large drop-out rate as over 50% refused either evaluation or PAP treatment.

Twenty-five percent of those with newly diagnosed sleep apnea received treatment, with the majority receiving PAP therapy and a minority either positional therapy or isolated opioids/sedative reduction. The adherence rate of PAP therapy was 55% at 1 year, with 11 of the 20 patients who were recommended PAP therapy continuing to use it after 1 year.

All of the patients on opioids who received opioid reduction as their treatment had either severe CSA or predominantly CSA, with a mean CAI score of 32 events/h and a median MME of 270 mg/d. Four percent solely received opioid reduction as a therapy. Previous studies have shown that opioid use is associated with a high prevalence of CSA.[10,16,17] Opioids can suppress breathing frequency, tidal volume, chest, and abdominal wall compliance, the response to hypercapnia, hypoxia, and upper airway patency.[18] The 2019 American Academy of Sleep Medicine Position Statement acknowledged that there is a higher prevalence of CSA with chronic opioid use and its effect appears to be dose dependent.[11] Opioid reduction is an effective modality

for CSA as 2 previous case studies have reported complete resolution of CSA following discontinuation of opioids.[19,20]

Positional therapy was recommended in 3% of patients who had mild to moderate OSA that was positional in nature. Approximately 50% of patients with mild OSA and 19% with moderate OSA have positional OSA.[21] In mild to moderate positional OSA, positional therapy, as a primary treatment, was found to be as effective as CPAP with a higher adherence than PAP.[21,22] In our study, 1 patient was on a low opioid dose and was diagnosed with mild CSA. The patient was treated with a dose reduction of benzodiazepine. Sedatives like benzodiazepines may have an additive effect for sleep apnea in patients taking opioid medications[23]; 1 patient on high-dose opioids was diagnosed with severe OSA. A combination of PAP therapy, dose reduction in opioids, and benzodiazepine was recommended.

There is a high prevalence of sleep apnea in patients on opioids for chronic pain. In a study assessing the prevalence of sleep apnea among methadone users, 30% of patients were diagnosed with CSA.[17] Unusual breathing patterns have also been associated with patients with sleep apnea who currently use opioids, emphasizing the need for monitoring sleep-disordered breathing in these patients.[24] As suggested by the American Academy of Sleep Medicine, collaboration among medical providers, such as pain and sleep physicians, is essential for early identification of sleep disorders.[11] Cooperation between the 2 specialties allows optimal patient-centered care for patients on chronic opioids. Sleep apnea is a complex disorder and no standardized treatment fits every patient, and this also applies to patients on opioid therapy for chronic pain. Due to the varying underlying phenotypes among patients, personalized treatment is the best approach to successfully managing sleep apnea.[25–27]

We found a significant improvement in mean AHI in the PAP-adherent patients, including adaptive servo ventilation. Since adaptive servo-ventilation therapy is not covered by government insurance in Ontario, Canada, physician-prescribing practice is altered because it is not financially feasible for most patients. Untreated sleep apnea is associated with an increased risk of cardiovascular disease, stroke, accidents due to daytime sleepiness, and death.[28] Besides improving health, PAP therapy has been shown to increase pain threshold and decrease pain sensitivity.[29,30] Efforts to educate both patient and health care professionals regarding chronic pain and sleep apnea are greatly needed in order to optimize treatment and improve daily life.

Forty-five percent of patients were nonadherent to PAP therapy. Our results are consistent with previous reports of nonadherence to PAP therapy.[31] Despite previous efforts to improve CPAP efficacy and tailoring the CPAP toward the patient's individual needs through behavioral interventions, CPAP nonadherence still presents a big problem.[31] The main reason for lack of adherence was reported to be pressure intolerability.[30] Importantly, the results are also encouraging as they demonstrate that PAP therapy acceptance and tolerance by those on opioids do not differ greatly from the general population. Furthermore, it was shown to be highly effective in alleviating the sleep apnea. The high rate of nonattendance for sleep clinic review or refusal of treatment highlights a grave issue that sleep apnea therapy is not regarded as essential for optimal health. Education is needed to increase the PAP-adherent rate among patients with chronic pain.

Our study has some limitations. Of the consented patients from the OpSafe Trial, only 61% completed polysomnography, leading to possible selection bias, and over 50% who completed polysomnography subsequently refused attendance to a sleep clinic or treatment. As this was a pragmatic study, treatment regimens were not standardized and there was an absence of objective data on either the efficacy or adherence to positional therapy by patients. Additionally, we do not have information on whether or not opioids and benzodiazepine dose-reduction recommendations were implemented. We did not explore participant reasons for declining further sleep clinic review or treatment. Last, it is not clear if the failure to attend for sleep clinic review is a pattern seen across attendance for other medical specialists in this population.

CONCLUSIONS

Over 50% of participants on opioids for chronic pain from the OpSafe Trial with newly diagnosed sleep apnea declined attendance for sleep clinic review or treatment, and 25% completed specific sleep apnea–related treatment. Of those who pursued PAP therapy, adherence was similar to that in the general population at 1 year and was proven to be effective in abolishing the sleep apnea. Further studies are required to explore factors influencing this population's lack of engagement with sleep health providers and barriers to adherence to PAP therapy.

ABBREVIATIONS

AHI, apnea-hypopnea index
CAI, central apnea index
CPAP, continuous positive airway pressure
CSA, central sleep apnea
MME, morphine milligram equivalents
OSA, obstructive sleep apnea
PAP, positive airway pressure

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