ORIGINAL ARTICLE
SLEEP

Concomitant benzodiazepine and opioids decrease sleep apnoea risk in chronic pain patients

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ABSTRACT

Background: The concurrent use of sedating centrally acting drugs and opioids by chronic pain patients occurs routinely despite concerns of negative impacts on respiration during sleep. The effects of centrally acting drugs and opioids on sleep apnoea have not been well characterised. The objective of this study was to assess the effect of concomitant centrally acting drugs and opioids on the prevalence and severity of sleep apnoea in chronic pain patients.

Methods: We conducted a prospective cohort study at five chronic pain clinics. Each participant underwent an in-laboratory polysomnography and daily morphine milligram equivalents were calculated. Participants were grouped into centrally acting drugs and opioid users *versus* sole opioid users.

Results: Of the 332 consented participants, 204 underwent polysomnography and 120 (58.8%) had sleep apnoea (72% obstructive, 20% central, and 8% indeterminate sleep apnoea). Overall, 35% (71 of 204) were taking opioids alone, and 65% (133 of 204) were taking centrally acting drugs and opioids. There was a 69% decrease in the odds of having sleep apnoea (apnoea–hypopnoea index $\geqslant$5 events·h^{-1}) in participants taking benzodiazepine/opioids *versus* sole opioid users (OR 0.31, 95% CI:0.12–0.80, p=0.015). Additionally, concomitant benzodiazepine/opioids *versus* sole opioid use was associated with a decrease in respiratory arousal index scores (p=0.03). Mean overnight S_{PO_2} was approximately 1% lower in the concomitant benzodiazepine/opioids group *versus* sole opioid users (93.1±2.5 *versus* 94.4±2.1%, p=0.01).

Conclusion: In chronic pain patients on opioids, administration of certain benzodiazepine sedatives induced a mild respiratory depression but paradoxically reduced sleep apnoea risk and severity by increasing the respiratory arousal threshold.

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There may be potential to reduce sleep apnoea risk and severity in specific chronic pain patients on opioids using certain benzodiazepine sedatives by selecting those with a low respiratory arousal threshold in whom sleep promotion may stabilise breathing https://bit.ly/2Zj4WX1

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Introduction

Over the past two decades, there has been a continuous escalation in the use of opioids for the management of chronic noncancer pain [1, 2]. Approximately 70% of chronic noncancer pain patients on opioid therapy may have a sleep breathing disorder, such as sleep apnoea [3]. Opioids can suppress breathing frequency, tidal volume, chest, and abdominal wall compliance, upper airway patency, cough reflex, and the response to hypercapnia and hypoxia [2, 4]. In 2011, a panel of US experts indicated that one of the potential root causes of opioid-related deaths may be sleep apnoea [5]. Recently, the American Academy of Sleep Medicine released a position statement highlighting that chronic opioid use is associated with both central sleep apnoea (CSA) and obstructive sleep apnoea (OSA) and appropriate screening, diagnostic testing, and treatment of opioid-associated sleep-disordered breathing can improve patients' health and quality of life [6].

Chronic pain is commonly associated with sleep loss, anxiety, and depression; as a result, centrally acting drugs, such as benzodiazepines, zopiclone, antidepressants, gabapentinoids (gabapentin/pregabalin), and muscle relaxants, are often co-prescribed with opioid analgesics [7]. Concomitant use of centrally acting drugs, such as sedatives and hypnotics by opioid patients may further compromise breathing. This combination may increase the risk of respiratory depression and have a deleterious effect on sleep apnoea and oxygenation [2, 8]. However, the causes of sleep apnoea vary between individuals [9]. Similarly, the effects of these agents on the propensity of sleep apnoea and severity vary between patients [10, 11]. Although there is concern that centrally active drugs may have a deleterious effect on sleep apnoea, the magnitude of the concomitant effects between centrally acting drugs and opioids on sleep apnoea has not been well characterised [8, 12].

Benzodiazepines, a class of sedative-hypnotic drugs, commonly prescribed for anxiety disorders, are contraindicated in patients who are prescribed opioids due to concerns of increased risk for respiratory events [13–15]. Despite these concerns, its co-prescription with opioids has only increased from 2003 to 2015 [15]. Benzodiazepines may have an additive effect for respiratory depression and sleep apnoea in patients on opioids through its blunting effect on the arousal response to hypoxia and hypercapnia [16, 17]. On the other hand, benzodiazepines and other nonbenzodiazepine hypnotics may also have positive sleep effects, such as increases in sleep efficiency, reductions in sleep-onset latency and arousal frequency and in certain individuals with sleep apnoea (*i.e.* those with a low respiratory arousal threshold), reduction in severity of sleep apnoea [10, 18, 19]. Accordingly, the objective of this study was to assess the effect of concomitant centrally acting drugs and opioids (centrally acting drugs/opioids) on sleep apnoea, compared to sole opioid use in patients with chronic noncancer pain. We hypothesised that the concomitant use of centrally acting drugs/opioids would exacerbate the risk for opioid-associated sleep apnoea. Knowledge of these interactions will help to adopt safer prescribing practices and increase vigilance for patients co-prescribed centrally acting drugs with opioids.

Methods

Study design

This was a prospective cohort study. This study was a secondary analysis from the Opioid Safety Program in Pain Clinics (Op-Safe), a prospective cohort study, designed to examine the effect of opioids on sleep apnoea in patients with chronic pain (Clinical Trials.gov identifier: NCT02513836) [20]. The primary outcome was the apnoea–hypopnoea index (AHI), a polysomnography derived parameter indicating the severity of sleep apnoea. The secondary outcome measures were other polysomnography parameters, such as the central apnoea index (CAI), respiratory arousal index, and other sleep parameters.

Study participants

This prospective multicentre cohort study consisted of participants at five university-affiliated tertiary care pain clinics in Canada. The inclusion criteria were: 1) aged 18 years and older; 2) the use of opioids for chronic noncancer pain >3 months; 3) on stable dose of opioids for ⩾4 weeks; and 4) signed written informed consent [20]. The exclusion criteria were: 1) participants who had a previous diagnosis of sleep-disorder breathing with or without treatment within the last 3 years; 2) participants with chronic pain secondary to a neoplasm or metastasis; 3) known neurological or psychiatric conditions; and 4) the need for an urgent clinical sleep assessment due to serious medical conditions or safety-critical occupations [20].

Ethics approval

The research ethics board of each participating institution approved the research protocol. All participants provided written informed consent (research ethics board approval numbers: 14-8611-AE, 15-0004-A, 2014-0122, and 24 106620).

Study procedures

Eligible study participants were consented by a research assistant in the chronic pain clinics. Demographic data, daily opioid dose, and concomitant medication usage were collected. Participants were invited to undergo in-laboratory overnight polysomnography. Participants taking sedating centrally acting drugs were grouped based on the classification of drugs: benzodiazepines, zopiclone, antidepressants, gabapentinoids, and muscle relaxants. Participants taking opioids alone were grouped separately as the control comparators. Sleep apnoea, central/obstructive apnoea and hypopnoea, respiratory arousal threshold, and severity were scored and defined according to the American Academy of Sleep Medicine [21]. AHI $\geqslant$5 events·h^{-1} indicated the presence of sleep apnoea.

Data analysis

All statistical analyses were performed with Stata version 14.2 (StataCorp) [22]. To determine the effects of medication on the severity of sleep apnoea, the AHI, and other polysomnographic data were analysed. Daily opioid doses were converted to approximate morphine milligram equivalents (MMEs) according to the US Centers for Disease Control and Prevention [23], the benzodiazepines were converted to diazepam-equivalent daily dose [16], and the antidepressants were converted to fluoxetine-equivalent daily dose [24]. The muscle relaxants could not be converted to equivalent doses due to the absence of dose-equivalent factors. The positively skewed polysomnography parameters (AHI, CAI, respiratory arousal index), MME, benzodiazepine (diazepam equivalent), antidepressant (fluoxetine equivalent), zopiclone and gabapentinoid doses were logarithmically transformed ($\log_{10}(x+1)$) to conform more closely to a normal distribution. For continuous data, t-tests, Wilcoxon rank-sum tests, ANOVA, or Kruskal–Wallis tests were used where appropriate to test differences among the characteristics of sleep apnoea for the drug groups. For categorical data, a chi-squared test or Fisher's exact test were used where appropriate. To investigate the potential for a dose–response relationship on the AHI and other sleep apnoea indices, multivariable linear regression was used. To determine the effect of medications on the AHI and other sleep apnoea indices, logistic regression was used. The regression models were adjusted for potential confounding factors: age, sex, body mass index (BMI), cannabis, MME, and use of $\geqslant$2 centrally acting drugs. A p-value <0.05 was considered significant. The respiratory arousal threshold was calculated from polysomnography data according to established methodology [25]. To identify participants with a low arousal threshold (ArTH), a score of 1 was allocated if each of the following criteria were met: AHI <30 events·h^{-1}, nadir S_{pO_2} >82.5% and fraction of hypopnoea to apnoea >58.3% [25]. Each participant received a score ranging from 0 to 3, and a low ArTH ($\geqslant$15 cmH_2O) was defined as a score of $\geqslant$2 [25].

Results

Of the 332 eligible participants, 204 (61.4%) participants underwent polysomnography, and 128 (38.6%) dropped out due to failure to complete polysomnography and were excluded from the analysis (figure 1). The average age of participants who underwent polysomnography was 52 (SD 13.1) years with an average BMI of 28.6 kg·m^{-2} (SD 6.4) and 41% were male (table 1). Overall, 22% of the study participants were

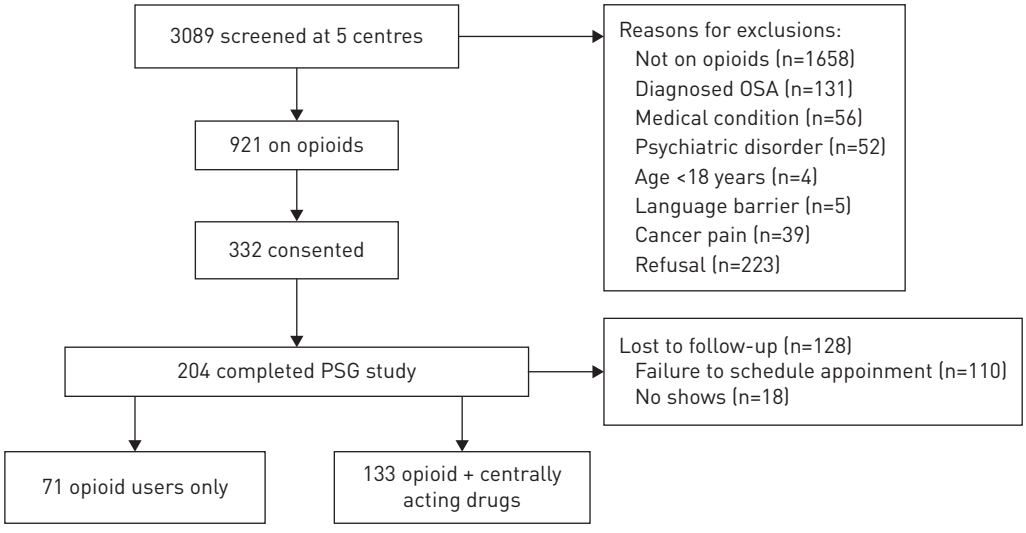

FIGURE 1 Study flow chart.

TABLE 1 Demographics and polysomnographic characteristics of participants taking opioids only *versus* centrally acting drugs/opioids

Variable	Opioids alone	Opioid+concomitant medications
Total (n=204)	71 (35)	133 (65)
Age years	52.7±13.4	51.7±12.9
Male sex	32 (45)	52 (39)
Body mass index kg·m^{-2}	28.8±6.1	28.4±6.5
MME mg per day	72 (22–135)	68.8 (30–180)
Neck circumference cm	39 (36–42)	38 (34–42.5)
Active smoker	9 (13)	36 (27)*
Cannabis user	3 (4)	12 (9)
Medical conditions		
Asthma	8 (11)	12 (9)
COPD	3 (4)	4 (3)
Osteoarthritis	25 (35)	29 (22)
Sleep parameters		
Apnoea–hypopnoea index events·h^{-1}	8 (3.2–17.8)	5.3 (1.5–19.4)
Obstructive apnoea index events·h^{-1}	5.6 (2.0–12.9)	4.2 (1.3–14.2)
Central apnoea index events·h^{-1}	0.4 (0–1.7)	0.4 (0–2.6)
Mixed apnoea index events·h^{-1}	0 (0–0)	0 (0–0)
Hypopnoea index events·h^{-1}	5.7 (2.0–13.1)	3.7 (1.1–9.8)
Total arousal index	15.9 (8.9–26.6)	12.9 (8.4–23.1)
Mean SpO_2 %	94.5 (92.9–96.2)	94.2 (93–95.7)
Nadir SpO_2 %	87 (84–91)	87 (83–91)
CT90 %	0.2 (0–3.1)	0.2 (0–4.8)
Oxygen desaturation index (⩾3%)	11.2 (3.9–26.5)	8.7 (2.1–26.2)
Total sleep time min	334 (276.5–372)	335.5 (278.3–375.7)
Sleep efficiency %	79.8 (71.6–90.2)	86.5 (76.0–91.7)#
Sleep stage N1 %	7.5 (4.0–12.1)	6.0 (3.2–11.1)
Sleep stage N2 %	67.9 (59.5–75.2)	66.0 (59.4–74.7)
Sleep stage N3 %	8.0 (2.6–15.9)	9.7 (2.0–18.8)
REM %	12.6 (74–18.0)	12.4 (5.5–19)

Values are expressed as mean±SD, median (interquartile range), or frequency (percentage) as appropriate. A t-test, Wilcoxon rank-sum test, chi-squared test or Fisher's exact test were conducted to examine differences in the characteristics of participants taking centrally acting drugs *versus* sole opioid users. MME: morphine milligram equivalent; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; SpO_2: oxyhaemoglobin saturation; CT90: cumulative time SpO_2 <90%; REM: rapid eye movement. *: p<0.05.

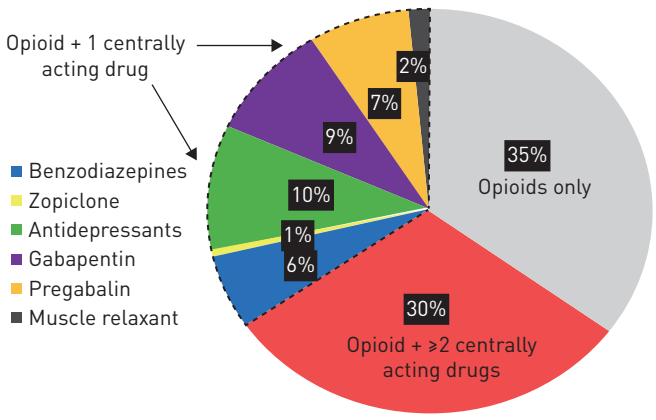

FIGURE 2 Medication usage of the participants presented as a percentage of the population (n=204). About 30% of participants were on opioids only, serving as controls. 35% of participants were on one concomitant sedating drug with opioids, while 30% were on at least two or more concomitant sedating drugs with opioids.

active smokers, 7% were cannabis users, 10% had asthma, and 3% had chronic obstructive pulmonary disease (COPD).

A total of 35% (71 of 204) of patients were taking opioids alone, and 65% (133 of 204) were taking centrally acting drugs/opioids (table 1). Participants were categorised based on their usage of six different centrally acting medications: benzodiazepines, zopiclone, antidepressants, gabapentin, pregabalin, and muscle relaxants (figure 2). The mean dose for each centrally acting drug and the frequency and percentage of participants taking each type of benzodiazepines are presented in table S1. The median (IQR) MME for patients taking opioids alone *versus* centrally acting drugs/opioids were similar, 72 (22–135) mg per day and 68.8 (30–180) mg per day respectively (table 1).

Effect of opioids and sedatives on sleep apnoea

A total of 41% of participants had no sleep apnoea and 59% had newly diagnosed sleep apnoea (72% obstructive, 20% central, and 8% indeterminate). There was no significant difference in the prevalence of sleep apnoea in participants taking centrally acting drugs/opioids compared to those taking opioids alone (68% (48 of 71) *versus* 54% (72 of 133), p=0.063). Of the 120 participants, 45.8% had mild, 23.3% had moderate, and 30.8% had severe sleep apnoea with no difference between those taking centrally acting drugs/opioids *versus* those taking only opioids (p=0.057) (Table S2). Additionally, there were no significant differences in the AHI (p=0.16), CAI (p=0.636), or respiratory arousal index (p=0.272) between those on centrally acting drugs/opioids *versus* opioids alone (table 2).

Multivariable logistic regression adjusted for confounding variables (age, sex, BMI, MME, cannabis use, use of ⩾2 centrally acting drug) demonstrated that the effect of centrally acting drugs/opioids on the prevalence of sleep apnoea (table 3). A significant increase in the odds of sleep apnoea (AHI ⩾5 events·h^{-1}) was associated with age (OR 1.06, 95% CI: 1.03–1.095, p<0.001), BMI (OR 1.08, 95% CI: 1.03–1.14, p=0.004) and MME (OR 2.10, 95% CI: 1.14–3.87, p=0.017). The concomitant use of benzodiazepines and opioids (benzodiazepine/opioids) was associated with a significant decrease in the odds of sleep apnoea (OR 0.31, 95% CI: 0.12–0.80, p=0.015) (table 3). No significant effect on the prevalence of CSA was found with centrally acting drugs/opioids.

Effect of opioids and sedatives on sleep architecture, oxygenation, and arousal threshold

After multivariable regression adjusted for all confounding variables, the use of benzodiazepine/opioids was associated with a decrease in the respiratory arousal index (p=0.03) (table 4). Increasing age (p<0.001), male sex (p=0.026), and BMI (p=0.005) was also associated with an increase in the respiratory arousal index (table 4). The MME (p=0.023) and cannabis use (p=0.008) decreased the percentage of rapid eye movement (REM) sleep (table S3). The use of gabapentinoids (p=0.009) with opioids was associated with an increase in the percentage of REM sleep, whereas the use of muscle relaxants with opioids was associated with a decrease in the percentage of REM sleep (p=0.03) (table S4).

No significant dose–response relationship was found with the use of centrally acting drugs/opioids compared to sole opioids with any polysomnography parameters. Using linear regression, we found that concomitant use of benzodiazepines/opioids showed a decrease in the obstructive AHI (p=0.003),

TABLE 2 The apnoea–hypopnoea index, central apnoea–hypopnoea index and respiratory arousal index scores of patients taking opioids only *versus* centrally acting drugs/opioids

Variable	n	Apnoea–hypopnoea index		Central apnoea index		Respiratory arousal index (n=203)	
		Median (IQR)	p-value	Median (IQR)	p-value	Median (IQR)	p-value
Total	204	6.4 (2.3–19.1)	–	0.4 (0–1.9)	–	2.5 (0.9–7.7)	–
Opioids alone	71	8.0 (3.2–17.8)	–	0.4 (0–1.7)	–	3.0 (1.1–10.4)	–
Opioids+centrally acting drugs	133	5.3 (1.5–19.6)	0.163	0.4 (0–2.6)	0.636	2.2 (0.7–7.2)	0.272
Opioids+benzodiazepine	31	4.0 (1.0–13.6)	0.128	0.4 (0–5.2)	0.718	1.5 (0.2–5.5)	0.066
Opioids+zopiclone	12	4.8 (0.8–16.4)	0.450	0.7 (0.2–3.6)	0.424	2.7 (0.4–8.8)	0.881
Opioids+antidepressants	51	7.4 (2.3–22.5)	0.812	0.4 (0–2.8)	0.762	3.9 (0.8–7.6)	0.628
Opioids+gabapentinoids	79	6.4 (2.3–23)	0.652	0.4 (0–2.5)	0.819	2.5 (1.0–7.6)	0.101
Opioids+muscle relaxants	14	2.6 (1.2–15.0)	0.127	0.8 (0.1–5.6)	0.558	1.9 (0.5–5.6)	0.416

Mann–Whitney U-test was used to examine differences in the sleep apnoea index scores of participants taking centrally acting drugs *versus* opioids alone. All medication groups are dichotomously coded based on use. IQR: interquartile range.

TABLE 3 The effect of concomitant centrally acting drugs/opioids on the prevalence of sleep apnoea compared to sole opioid use

Variable	n	Apnoea–hypopnoea index ⩾5	
		OR (95% CI)	p-value
Age years	204	1.06 (1.03–1.09)	<0.001***
Male sex	84	1.78 (0.92–3.46)	0.085
Body mass index kg·m^{-2}	204	1.08 (1.03–1.14)	0.004*
MME mg per day	202	2.10 (1.14–3.87)	0.017*
Cannabis use	15	1.25 (0.37–4.21)	0.722
Opioids+benzodiazepines	31	0.31 (0.12–0.80)	0.015*
Opioids+zopiclone	12	0.64 (0.17–2.46)	0.516
Opioids+antidepressants	51	0.97 (0.47–2.00)	0.929
Opioids+gabapentinoids	80	0.91 (0.46–1.79)	0.787
Opioids+muscle relaxants	14	0.98 (0.26–3.68)	0.971

Multivariable logistic regression was used for the apnoea–hypopnoea index, adjusted for age (years), sex, body mass index (kg·m^{-2}), MME (mg per day), cannabis and use of ⩾2 centrally acting drugs. Use of centrally acting drugs, sex, and cannabis use were all dichotomously coded. Age, body mass index, and MME are continuous variables. AHI is also dichotomously coded: 0: score <5; 1: score ⩾5. MME was $\log_{10}$ (x+1) transformed. MME: morphine milligram equivalent; AHI: apnoea–hypopnoea index; OR: odds ratio; CI: confidence interval. *: <0.05; ***: <0.001.

hypopnoea index (p=0.009), and mean S_{pO_2} (p=0.036) after adjustment for confounding variables. The obstructive AHI was lower in the benzodiazepine/opioid group compared to the sole opioid users (median (IQR) 3.3 (0.3–6.7) *versus* 5.6 (2–12.9) events·h^{-1} (p=0.014)). Similarly, the hypopnoea index was lower in the benzodiazepine/opioid group *versus* the sole opioids users (median (IQR) 3.2 (0.5–5.8) *versus* 5.7 (2–13.1) events·h^{-1} (p=0.0421)). Mean S_{pO_2} was approximately 1% lower in the concomitant benzodiazepine/opioid group *versus* sole opioid users (93.1±2.5 *versus* 94.4±2.1%, p=0.01). The estimated respiratory arousal threshold in these participants was low, (median (IQR) −10.2 (−14.9– −6.3) cmH_2O). The respiratory arousal threshold was similar in the use of centrally acting drugs/opioids group *versus* sole opioid users, (median (IQR) −10.4 (−15.3– −6.4) and −9.03 (−13.9– −6.2), respectively (p=0.362)).

Of 204 participants, 78% had a low arousal threshold. Of the 133 participants taking centrally acting drugs/opioids, 80% (106 of 133) had a low arousal threshold. Of the 31 patients taking benzodiazepine/opioids, 84% (26 of 31) had a low arousal threshold. Multivariable logistic regression was used to determine the effect of centrally acting drugs/opioids on the prevalence of a low arousal threshold *versus*

TABLE 4 The effect of concomitant centrally acting drug use with opioids on the respiratory arousal index compared to sole opioid use

Variable	n	Respiratory arousal index		
		Coefficient	Standard error	p-value
Age years	203	0.011	0.003	<0.001***
Male sex	83	0.142	0.063	0.026*
Body mass index kg·m^{-2}	203	0.014	0.005	0.005*
MME mg per day	202	0.053	0.057	0.344
Cannabis use	14	0.083	0.126	0.511
Opioids+benzodiazepines	30	−0.200	0.091	0.030*
Opioids+zopiclone	12	−0.003	0.130	0.982
Opioids+antidepressants	51	0.015	0.071	0.833
Opioids+gabapentinoids	79	−0.056	0.065	0.392
Opioids+muscle Relaxant	14	0.108	0.127	0.397

Multivariable regression was used for the respiratory arousal index adjusted for age (years), sex, body mass index (kg·m^{-2}), MME (mg per day), and cannabis and use of ⩾2 centrally acting drugs. Use of centrally acting drugs, sex, and cannabis use were all dichotomously coded. Age, body mass index, and MME are continuous variables. Respiratory arousal index and MME are continuous variables and have been $\log_{10}$ (x+1) transformed due to skewness. MME: morphine milligram equivalent. *: p<0.05; ***: p<0.001.

sole opioid use (table S4). No significant difference was found for the odds of having a low arousal threshold with centrally acting drugs/opioids *versus* opioid use alone after adjusting for all confounding variables (table S5).

Demographics and sleep parameters of participants taking opioids alone *versus* benzodiazepine/opioid users are presented in table S6. The median (IQR) MME was significantly higher in the concomitant benzodiazepine/opioid group *versus* sole opioid users (115 (50.5–495) *versus* 72 (22.5–135) mg per day, p=0.02). The distribution of AHI, mean nadir S_{pO_2}, MME, and cumulative time S_{pO_2} <90% of participants on opioids alone *versus* participants on benzodiazepine/opioids is shown in figure 3. When considering participants with mean nadir S_{pO_2} <92%, there was a significant difference in median (IQR) MME for participants taking benzodiazepine/opioids *versus* participants taking opioids only, (180 (120–620) *versus* 55.5 (24–120) mg per day, p=0.003). Two of the participants taking benzodiazepine/opioids with mean nadir S_{pO_2} of 90% and 88.5%, respectively had MMEs >700 mg per day.

Discussion

In this study, we found that in patients with chronic pain on opioids, concomitant benzodiazepine/opioids *versus* opioid use alone was associated with a 69% decrease in the odds of having sleep apnoea and a decrease in respiratory arousal index. However, concomitant use was associated with a minor (~1%) nonclinically significant reduction in mean overnight oxygenation. Additionally, the reported concurrent use of cannabis was associated with a decrease in the percent of REM sleep in these chronic opioid users.

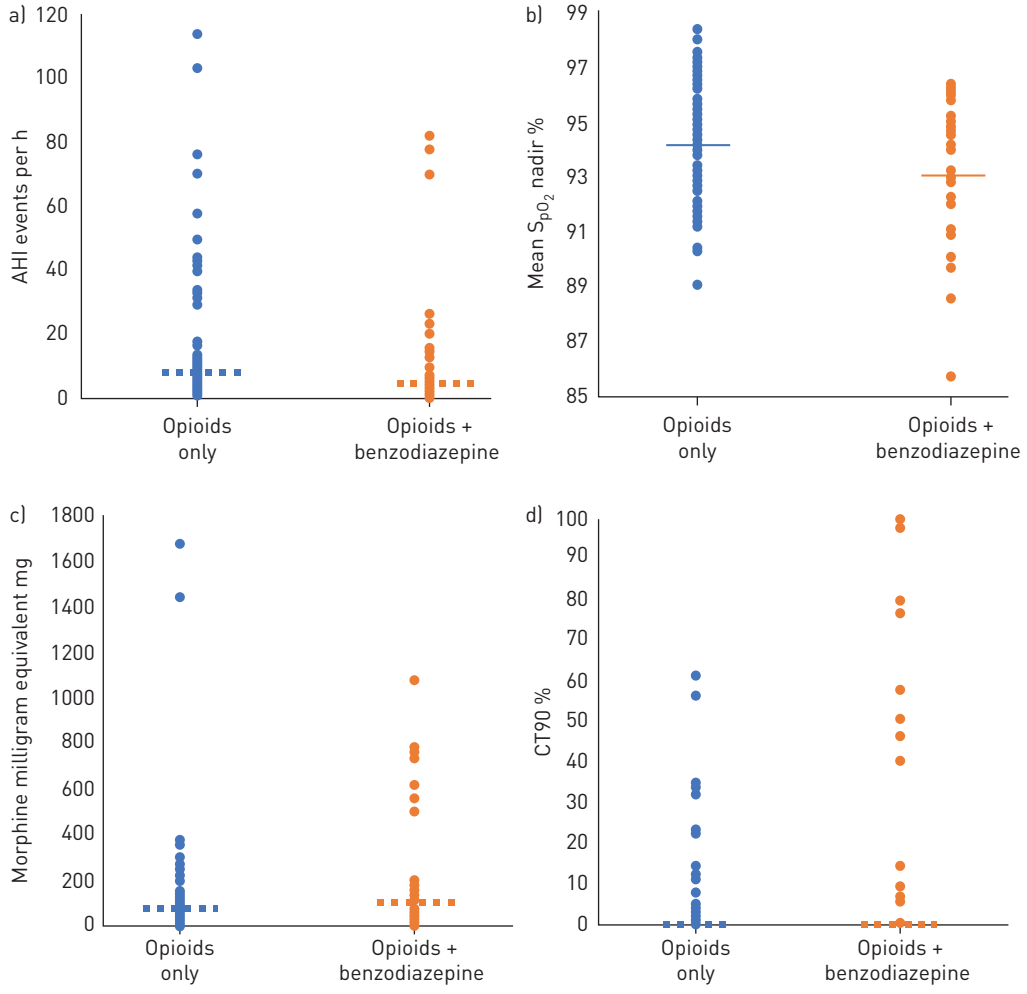

FIGURE 3 Distribution of a) apnoea–hypopnoea index (AHI), b) mean S_{pO_2} nadir, c) morphine milligram equivalent and d) cumulative time percentage with S_{pO_2}<90% (CT90%). for participants taking opioids only (n=71) *versus* opioids+benzodiazepine (n=31). There was a significant difference in mean S_{pO_2} nadir and MME for participants taking opioids compared to those taking opioids with benzodiazepine. Horizontal plain lines represent means and dotted lines represent medians as appropriate.

Similar to previous studies, we found a high prevalence of sleep apnoea (59%) in patients using chronic opioids [12, 16]. While chronic high-dose opioid use is consistently associated with high rates of sleep apnoea, a recent randomised trial indicated that an acute, modest dose of morphine does not systematically worsen OSA [11]. Rather, in some cases, morphine can reduce OSA severity by reducing "high loop gain" in people who are overly sensitive to small changes in CO_2 without worsening the other key causes of OSA [11, 26]. Centrally acting drugs such as sedatives and hypnotics are commonly believed to have a deleterious additive effect on sleep apnoea when combined with opioid use. Data to support these concerns are limited [2, 16, 27, 28]. We found no significant difference in the prevalence or the severity of sleep apnoea in participants taking centrally acting drugs/opioids *versus* participants on an opioid medication alone. In addition, the prevalence of sleep apnoea did not differ between patients taking zopiclone, antidepressants, gabapentinoids, or muscle relaxants with opioids *versus* sole opioid users.

The concomitant use of opioids and benzodiazepines demonstrated a significant decrease in the obstructive apnoea index and hypopnoea index scores. This finding is inconsistent with concerns that benzodiazepine use increases the risk of sleep apnoea *via* a blunting effect on the arousal response to hypoxia, hypercapnia, and respiratory effort during sleep [16, 17, 27]. Very few experimental studies have examined the effect of benzodiazepines on sleep in chronic opioid users. Studies reported an increase in the respiratory arousal threshold with benzodiazepines such as flurazepam and triazolam [19, 29, 30]. Lorazepam, a benzodiazepine, can delay arousals and produce a dose-dependent increase in genioglossus muscle activity in rats [31]. Contrary to these studies, we found that 78% of the participants have a low respiratory arousal threshold, which has been shown to be a key contributor to OSA in one-third of patients [9, 25, 32]. A premature arousal in patients with a low respiratory arousal threshold phenotype, results in inadequate build-up of respiratory stimuli, precluding recruitment of upper airway dilator muscles [19, 33, 34]. If sleep can be maintained in these patients using a sedative or a hypnotic without impairing pharyngeal muscle activity, the accumulation of stimuli (CO_2 and negative pharyngeal pressure) may allow for recruitment of upper airway pharyngeal dilator muscles to enable stable breathing in many cases [10, 19]. The severity of sleep apnoea is usually worse in the lighter stages of sleep compared to slow-wave sleep [35, 36]. In this population of opioid users, most of whom were not obese, the low arousal threshold may explain the reduced risk of sleep apnoea with concomitant use of a sedative. Indeed, ~85% of people with OSA who are not obese are estimated to have a low respiratory arousal phenotype [32]. However, benzodiazepines may be potentially detrimental to sleep and breathing in those with a high arousal threshold [37, 38] or in those with a highly collapsible airway irrespective of the arousal threshold [25]. Indeed, there was a modest ~1% reduction in mean overnight oxygenation in concomitant benzodiazepine/opioid users. Although this reduction in overnight oxygenation may not be clinically relevant, we must bear in mind that benzodiazepine use with opioids may indeed increase the risk of respiratory depression in certain patients [14, 15]. In 2016, the US Food and Drug Administration issued a strong warning against the concurrent use of opioids and benzodiazepines and highlighted risks (including respiratory depression) associated with their combined use [13].

Nonetheless, the current findings suggesting that sleep promotion strategies may be beneficial in reducing sleep disruption and respiratory event frequency in predominantly nonobese people with chronic pain are intriguing. However, caution is warranted as this may not extend to other patient populations (*i.e.* those who are obese). This requires further investigation. Interestingly, a recent study challenged the traditional thinking that opioid use worsens sleep apnoea by genotyping their patients and demonstrating that opioids did not worsen OSA in men with the OPRM1 genotype [11]. Detailed phenotyping and genotyping of sleep apnoea is necessary to determine the impact of the combination of sedatives and opioids on the airway.

While dronabinol has recently been shown to modestly reduce obstructive apnoea severity [39], the effect of cannabis on sleep apnoea requires further research. Our results have demonstrated no significant effect on the prevalence of sleep apnoea in 16 patients using cannabis together with their opioid medications. We did find a significant decrease in the percentage of REM sleep associated with cannabis use, which is consistent with other cannabinoid studies [40]. Further research is needed to determine the mechanism and its significance in altering the proportion of REM sleep.

Use of antidepressants and gabapentinoids showed no significant effect on the sleep apnoea indices. This finding is inconsistent with the literature, which warns of an additive effect of opioid-related respiratory abnormalities with gabapentin [41]. Additionally, antidepressant use has been reported to promote CSA in patients with chronic pain [12, 28]. One such study reported a significant increase in CSA with concomitant antidepressant/opioid use [28].

Our study has several limitations. Of the consented participants, 61% completed a polysomnogram, leading to possible selection bias, as those with sleep complaints may be more likely to consent to an

overnight polysomnogram. Additionally, compliance with medications or screening for substance use disorder was not assessed. Thus, documented medication use may not be reflective of actual consumption. Alcohol consumption data were not available for the participants in this study. Thus, its effect as a confounding factor could not be controlled in the analysis. The study sample for subanalyses investigating certain centrally acting drugs was relatively small. Within the benzodiazepine class there may be differential effects of each individual medication on opioid-related sleep apnoea. However, this study was insufficiently powered to investigate these specific effects and thus this is an area that requires further investigation. Future studies are required to have a greater understanding of the interaction between specific benzodiazepines and chronic opioid use and their subsequent effect on sleep-disordered breathing and respiration.

Conclusions

In patients with chronic pain taking opioids, administration of certain benzodiazepine sedatives induced a mild respiratory depression but paradoxically a reduced sleep apnoea risk and severity by increasing the respiratory arousal threshold. There may be potential to reduce the risk and severity of sleep apnoea in specific patients with chronic pain taking opioids with the use of certain benzodiazepine sedatives by selecting those with a low respiratory arousal threshold in whom sleep promotion may stabilise breathing.

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