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SCIENTIFIC INVESTIGATIONS

The influence of opioids and nonopioid central nervous system active medications on central sleep apnea: a case-control study

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Study Objectives: Opioids are known to contribute to central sleep apnea (CSA), but the influence of nonopioid central nervous system active medications (CNSAMs) on CSA remains unclear. In light of the hypothesized impact of nonopioid CNSAMs on respiration, we examined the relationships between the use of opioids only, nonopioid CNSAMs alone, and their combination with CSA.

Methods: Among all adults who underwent polysomnography testing at the University of Michigan's sleep laboratory between 2013 and 2018 (n = 10,606), we identified 212 CSA cases and randomly selected 300 controls. Participants were classified into four groups based on their medication use: opioids alone, nonopioid CNSAMs only, their combination, and a reference group, including those who did not use any of these medications. We defined CSA as a binary outcome and as a continuous variable using central apnea index data. Logistic and linear regression were used to examine associations between medication use, CSA diagnosis, and central apnea index.

Results: Study participants included 58% men, and mean age was 50 (± 14 standard deviation years. Nearly half of the study participants did not use opioids or nonopioid CNSAMs, 6% used opioids alone, 27% nonopioid CNSAMs alone, and 16% used a combination of these medications. In adjusted analyses, opioids-only users had a nearly twofold increase in CSA odds, whereas those who used a combination of opioids and nonopioid CNSAMs had fivefold higher odds of CSA relative to the reference group. In contrast, the use of nonopioid CNSAMs alone had protective associations with CSA.

Conclusions: This report showed increased odds of CSA, particularly among patients with sleep complaints who were prescribed opioids in combination with nonopioid CNSAMs compared with those who did not use any of these medications.

Keywords: opioids; nonopioid central nervous system active medications; central sleep apnea.

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Opioids are associated with central sleep apnea; nonopioid central nervous system active medication may negatively affect respiration and could drive the development of central sleep apnea. This study examined the relationships between opioids, nonopioid central nervous system active medications, and their combination with central sleep apnea.

Study Impact: When used in combination, opioids and nonopioid central nervous system active medications are associated with a higher odds of central sleep apnea. The co-prescription of these medications is common and warrants attention to the potential associations between these combinations and increased odds of central sleep apnea.

INTRODUCTION

Central sleep apnea (CSA) is the repetitive cessation or decrease of airflow and ventilatory effort during sleep lasting ≥ 10 seconds. CSA occurs because of temporary failure in the generation of breathing rhythm by the pontomedullary pacemaker. The estimated prevalence of CSA in the general population is approximately 1%.[1] Associations with advanced age, male sex, congestive heart failure, atrial fibrillation, strokes, and other medical conditions have frequently been observed.[2,3] The diagnostic criteria of CSA include the presence of at least one of the following sleep disturbances: sleepiness, frequent awakenings, snoring, and witness of apneas. Furthermore, objective confirmation of CSA on polysomnogram (PSG) is defined by ≥ 5 central apneas or hypopneas per hour of sleep or central apnea index (CAI). Central respiratory events must constitute > 50% of the total apneas and hypopneas noted observed during baseline PSG recording.[4]

Medication use is another risk factor for CSA. Opioids have a well-established association with respiratory depression, and mechanisms include binding to the mu-opioid receptors in structures responsible for generating the respiratory rhythm located in the brainstem.[5,6] This interaction causes a decreased respiratory rate, lower tidal volume, and a reduction in respiratory controller responsiveness to carbon dioxide and hypoxia.[7,8] Opioids are associated with a mixed pattern of sleep-disordered breathing, although central apneas generally predominate.[9–11] In individuals without prior evidence of sleep-disordered

breathing, administration of opioids can precipitate central sleep apnea.[12]

Drugs like myorelaxants, antidepressants, H1 antihistamines, benzodiazepines, and nonbenzodiazepine hypnotics act on the central nervous system and are thought potentially to induce sleep-disordered breathing.[13,14] These medications are often coadministered with opioids in patients with acute or chronic pain and presumably may act in association to promote CSA[15]; however, this relationship is not well understood. Without knowledge regarding the risk of central sleep-disordered breathing related to this common pattern of combination of medications, prescribing practices remain unguided. Therefore, the objective of this study was to identify the contribution of nonopioid central nervous system active medications (CNSAMs) to CSA, whether used in isolation or coadministered with opioids.

METHODS

Data source

This retrospective case-control study used a sample of adult participants (defined as 18 years or older) who underwent a baseline PSG at the University of Michigan Sleep Disorders Center from 12/2013 to 11/2018.

Identification of cases and controls

We identified all patients who underwent an in-lab baseline PSG for different sleep complaints within the study time frame. Of a total of 10,606 patients, 212 CSA cases were identified. From a list of 10,394 patients without CSA, we randomly selected 300 unmatched controls, such that of every approximately 30 patients included in the list, one control was selected. Prevalent use of opioids or nonopioid CNSAMs in the population, in addition to statistical and cost efficiency have guided the selection of 300 controls, reflecting nearly a 1:1.5 ratio of controls to cases.

Data collection

All data were deidentified and Health Insurance Portability and Accountability Act compliant and approved by the University of Michigan Institutional Review Board.

We conducted electronic health record review on cases (n = 212) and controls (n = 300) and extracted information about their age, sex, body mass index, and medication use at the time PSG was performed.

The University of Michigan conducts sleep studies with monitoring of electroencephalogram (frontal, central, and occipital leads), electro-oculogram, submentalis, and bilateral anterior tibialis electromyogram, oronasal thermocouple, nasal pressure, electrocardiogram, thoracic and abdominal inductance plethysmography, snore sensor, and pulse oximetry. Data are collected and digitally stored in accordance with *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*.[16] From the Nexus PSG database, we determined the patients' demographics, body mass index, and CAI.

Medication use

Information on medication use on the date of performing the PSG was abstracted from Nexus PSG database and electronic health record. Current medication use reported by the patients in the Nexus database was matched with information on active prescriptions in their electronic health record. Medication use was stratified into the following groups: opioids only, nonopioid CNSAMs only, opioids and nonopioid CNSAMs combined, and reference group (those who did not use either opioids or nonopioid CNSAMs). The category of opioid medications included naturally occurring (ie, morphine and codeine), semisynthetic (ie, oxycodone and buprenorphine) or synthetic drugs (ie, fentanyl, methadone, and tramadol). The nonopioid CNSAMs included myorelaxants, antidepressants (selective serotonin reuptake inhibitors, selective noradrenergic reuptake inhibitors, bupropion, and trazodone), H1 antihistamines, benzodiazepines, and nonbenzodiazepine hypnotics.

Central sleep apnea

In accordance with the *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*, respiratory events were scored when an at least 10-second reduction of airflow amplitude of at least 30% (hypopneas) or 90% (apneas) are observed during a PSG.[16]

Respiratory events may be obstructive, central, or mixed according to the presence or absence of respiratory effort. The sum of these events divided by the total hours of sleep provides the apnea-hypopnea index. An apnea-hypopnea index ≥ 5 events per hour confirms a diagnosis of sleep-disordered breathing. Central sleep apnea was defined when the CAI was ≥ 5 events per hour and central respiratory event constituted more than 50% of the total apneas and hypopneas scored during PSG.[4]

Statistical analyses

We used descriptive statistics procedures to examine demographic and health characteristics for all patients in the sample. Proportions or means of age, sex, and body mass index were computed for patients stratified by CSA diagnosis. Medication use was classified into four groups: opioids only, nonopioid CNSAMs only, opioids and nonopioid CNSAMs in combination, and a reference group, including those who did not use any of these medications.

Bivariate logistic models were constructed to examine the associations of medication use with CSA diagnosis. We also conducted secondary analysis with CAI as a continuous variable. In the adjusted logistic and linear models, demographically relevant variables associated with CSA diagnosis or CAI ($P < .05$ in bivariate analyses) were included to account for potential confounding. To evaluate the impact of combined medication use on CSA in relation to the use of opioids only, we compared the odds of using co-prescribed nonopioid CNSAMs in a population of opioids users. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Among a sample of 512 patients who sought sleep evaluation, the average (standard deviation) age was 50 years (14), 58% were men, and 41% carried a diagnosis of CSA (**Table 1**).

Table 1—Demographic and health characteristics of 512 patients evaluated for sleep disturbances with and without central sleep apnea 2013–2018.

Characteristic	Total Sample	CSA Patients	Controls	*P* Value[a]
Sample size, n (%)	512 (100)	212 (41)	300 (59)	
Age, y, mean (SD)	50 (14)	55 (13)	47 (14)	< .01
Sex, n (%)				< .01
Female	216 (42)	56 (26)	160 (53)	
Male	296 (58)	156 (74)	140 (47)	
BMI, kg/m^2, mean (SD)	33 (7)	32 (7)	33 (8)	.28
Heart failure, n (%)	31 (6)	21 (10)	10 (3)	< .01
Atrial fibrillation, n (%)	60 (12)	32 (15)	28 (9)	.04
Coronary artery disease, n (%)	49 (9)	32 (15)	17 (6)	< .01
Stroke, n (%)	24 (5)	17 (8)	7 (2)	< .01
Diabetes, n (%)	89 (17)	39 (18)	50 (17)	.61
COPD, n (%)	25 (5)	12 (6)	13 (4)	.49
Asthma, n (%)	55 (11)	18 (8)	37 (12)	.16

[a]*P* value is based on Wald test; BMI = body mass index, COPD = chronic obstructive pulmonary disease, CSA = central sleep apnea, SD = standard deviation.

Of these patients, 6% used opioids only, 27% used nonopioid CNSAMs only, and 16% used a combination of opioids and nonopioid CNSAMs. About half of these patients did not use either opioids or nonopioid CNSAMs. A detailed list of the medications included in this study is provided in **Table 2**. Patients with CSA were older and more likely to be men than controls. Mean CAI was higher in patients who used a combination of opioids and nonopioid CNS active medications compared with other groups **(Figure 1)**.

Adjusted logistic regression for age and sex suggested a nearly twofold increase in CSA odds in opioids-only users, (1.96, 95% confidence interval [CI] 0.88, 4.37) and a protective effect among individuals prescribed nonopioid CNSAMs without opioids (0.76, 95% CI 0.47, 1.24) compared with the reference group. A statistically significant fivefold increase in CSA odds was associated with using a combination of opioids and nonopioid CNSAMs (5.20, 95% CI 2.86, 9.46) compared with the reference group **(Table 3)**. Similarly, linear regression results suggest that patients who used both opioids and nonopioid CNSAMs had a CAI that was, on average, 18 events per hour higher than those who used opioids only (95% CI 12.4, 23.9) **(Table 4)**.

Within opioid users, the odds ratio of CSA in those who also used nonopioid CNSAMs was 2.65 (95% CI 1.06, 6.63) compared with those with opioid use only.

DISCUSSION

In this case-control study of adults who underwent baseline PSG, we report a fivefold increased odds of CSA among patients using a combination of opioids and nonopioid CNSAMs compared with those who did not use those medications. Conversely, users of nonopioid CNSAMs in isolation (without opioids) had lower odds of CSA, although they were not statistically significant. With opioid users, the additional use of nonopioid CNSAMs increased CSA odds by 2.7-fold.

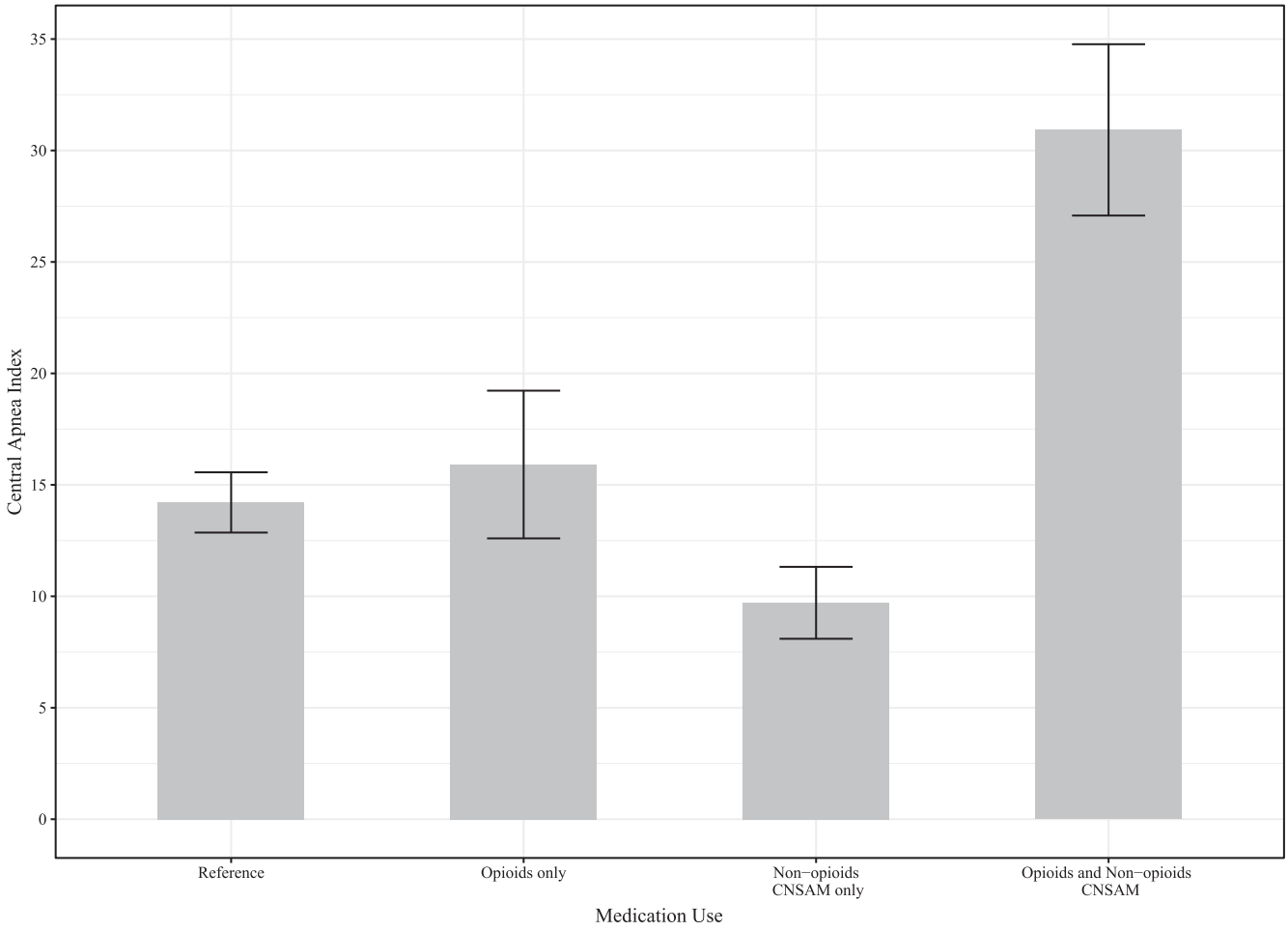
The capacity of opioids to increase the risk of CSA is well known; however, the relationship between nonopioid CNSAMs and sleep-disordered breathing remains less clear.[5–10,12,13] Our findings that opioids combined with nonopioid CNSAMs, but not opioids alone, significantly increased the odds of CSA and, in a population restricted to opioid users, co-prescribed nonopioid CNSAMs nearly tripled the odds of CSA, collectively suggest the possibility of synergy between these classes of medication.

These findings may also represent unmeasured confounders such as opioid potency and frequency of use. The daily morphine dose equivalent is thought to be the most important factor predicting opioid-related CSA.[15,17,18] Because we did not distinguish between opioid formulations or identify dose in our study, we cannot eliminate the possibility that individuals who are co-prescribed nonopioid CNSAMs along with opioids are more likely to consume higher daily morphine dose equivalents than those prescribed opioids in isolation. Similarly, co-prescribed opioids and nonopioid CNSAMs may indicate nightly, chronic opioid use as opposed to as needed, intermittent dosing. This is supported by a US survey of opioid users that found that 31% regular opioid users (≥ 5 days per week

Table 2—List of observed medications among 512 patients evaluated for sleep disturbances 2013–2018.

Opioids	Hydrocodone, tramadol, oxycodone, buprenorphine, morphine, methadone, fentanyl, codeine, oxymorphone, and hydromorphone	
Central nervous system active medications	Myorelaxants	Cyclobenzaprine, baclofen, and methocarbamol
	Antidepressants	Citalopram, escitalopram, fluoxetine, sertraline, paroxetine, duloxetine, venlafaxine, bupropion, trazodone.
	H1 antihistamines	Diphenhydramine, hydroxyzine, meclizine, promethazine
	Benzodiazepines	Alprazolam, clonazepam, diazepam, lorazepam, temazepam
	Nonbenzodiazepines hypnotics	Zolpidem, zaleplon, eszopiclone

Figure 1—Mean central apnea index and standard deviation by medication use.



Reference group includes those who do not use opioids or nonopioid medication. CNSAM = central nervous system active medications.

Table 3—Associations of medication use and central sleep apnea among 512 patients evaluated for sleep disturbances 2013–2018.

Medication Use	n	Unadjusted Odds Ratio (95% CI)	*P* Value	Adjusted[a] Odds Ratio (95% CI)	*P* Value
Reference	262	Ref		Ref	
Opioids only	33	1.94 (.94, 4.03)	.07	1.96 (0.88, 4.37)	.09
Nonopioids CNSAM only	136	0.65 (.42, 1.02)	.06	0.76 (0.47, 1.24)	.27
Opioids and nonopioids CNSAM	81	3.43 (2.02, 5.82)	< .01	5.20 (2.86, 9.46)	< .01

[a]Adjusted for age and sex; CI = confidence interval, CNSAM = central nervous system active medications.

Table 4—Association between medication use and central apnea index among 512 patients evaluated for sleep disturbances 2013–2018.

Medication Use	n	Unadjusted Beta (95% CI)	*P* Value	Adjusted[a] Beta (95% CI)	*P* Value
Reference	262	Ref		Ref	
Opioids only	33	1.7 (−6.8, 10.2)	.70	1.2 (−7.1, 9.5)	.78
Nonopioids CNSAM only	136	−4.5 (−9.4, 0.4)	.07	−3.1 (−7.9, 1.7)	.21
Opioids and nonopioids CNSAM	81	16.7 (10.9, 22.6)	< .01	18.1 (12.4, 23.9)	< .01

[a]Adjusted by age and sex; CI = confidence interval; CNSAM = central nervous system active medications.

for ≥ 4 weeks) also took antidepressants.[19] Additionally, in an investigation of previously opioid-naïve individuals, mood, anxiety, other mental disorders, hypnotic use, and musculoskeletal relaxant use were all predictors of prolonged opioid use.[20] Therefore, the concurrent use of nonopioid CNSAMs potentially modifies opioid use patterns and may increase the likelihood of higher-potency opioid use and administration on the sleep study night; however, because prescription status but not actual patient use was assessed, we cannot confirm this possibility.

Conversely, patients who were prescribed nonopioid CNSAMs had a lower odds of CSA compared with the reference group in line with the well-described increased arousal threshold and greater respiratory stability observed with certain hypnotic medications, such as zolpidem and triazolam, when used in the context of CSA.[21]

Biological mechanisms

Opioid medications contribute to CSA through respiratory instability caused by reduced hypercarbic ventilatory drive and increased hypoxemic ventilatory drive.[22] The mu-opioid receptors depress respiration through the brainstem respiratory centers.[23] Several potential mechanisms suggest how nonopioid medications, in conjunction with opioids increase the risk of CSA. These include drug-drug interactions, which alter drug pharmacokinetics (absorption, distribution, metabolism, or elimination of another), pharmacodynamics (a change in the sensitivity of a target tissue or organ to the effects of a second drug), or a synergistic effect.[22,24,25]

The potential for pharmacokinetic and pharmacodynamic interaction is predominately through the cytochrome P450 (CYP) superfamily (subtypes CYP2D6 and CYP3A4/5) enzymes. The metabolism of opioids is often through conversion to active metabolites.[22] For example, codeine's analgesic properties are due to its conversion via CYP2D6 to morphine, which has a 200-fold higher affinity for mu-opioid receptors than codeine. Bupropion and many selective serotonin reuptake inhibitors are CYP2D6 inhibitors. This can cause an increase in the prodrug and a decrease in the metabolite. How the metabolism of different prodrugs and metabolites influence the development of CSA is not clear, but concurrent use of CYP inhibitors can change the bioavailability and activity of opioids and metabolites.

Mechanistically nonopioid CNSAMs influence respirations and CSA. Antidepressants may depress the hypercarbic ventilatory drive and interact with opioids.[10,26,27] Benzodiazepines have a synergistic hypnotic and ventilatory depressant effect.[25] The ventilatory depressant effect is thought not to be through mu-opioid receptors.[28] Baclofen, a muscle relaxant, can decrease the respiratory drive in rats; a recent case series found an association with baclofen and CSA among humans,[14] likely related to changes in central and peripheral ventilatory control. Antihistamines are thought to have the potential of a synergistic relationship with opioids, but an exact mechanism is not known.[29] Ultimately, if a synergistic association of opioids, nonopioid CNSAMs, and CSA is confirmed, further research is needed to better elucidate the biologic mechanisms.

Strengths and limitations

This study is one of the largest to date to examine the impact of opioids and nonopioid CNSAMs on CSA.[10,18,30] The sample size of 512, including 212 cases and 300 controls, provided sufficient statistical power (> .80) to detect the effect of opioids and nonopioid CNSAM on CSA, as confirmed by formal post hoc power calculations. Further, current reports highlight the role of opioids in incident CSA, whereas few data investigated the influence of nonopioid CNSAMs or their interaction with opioids in relation to CSA. This study has some limitations, however. First, medication data were abstracted from medical charts at the time PSG was performed and may not represent the actual intake or dose of the medication. Second, most patients were prescribed opioids in combination with nonopioid CNSAMs, whereas only a few took opioids alone; however, this pattern of medication use aligns with current medical practice. Additionally, nonopioid CNSAMs are a broad group of medications that could have different pharmacologic interactions with opioids. Finally, this was a retrospective investigation of a clinical population; therefore, these findings do not represent the relationship between CSA and opioids and nonopioid CNSAMs in general, but only among patients who presented with sleep-related symptoms or other indications that precipitated both the ordering (and completion) of a sleep study. This may result in evaluation of a group of patients with inherent differences from individuals who take opioids and/or nonopiod CNSAMs but are free of sleep-related symptoms. Further, as the relationship between CSA and opioid medications is well known, but the contribution of nonopioid CNSAM to CSA is poorly understood, providers may have had a higher index of suspicion for central sleep disordered breathing in individuals on opioid medications. Such referral bias may have enriched the prevalence of opioid use among CSA patients. Therefore, the generalizability of the findings to broader and nonclinical populations is limited. Nonetheless, these findings could spark future clinical investigations to uncover the mechanistic relationships between opioids and nonopioid CNSAMs in relation to CSA.

CONCLUSIONS

This report showed increased odds of CSA, particularly among patients with sleep complaints who were prescribed opioids in combination with nonopioid CNSAMs compared with the reference group. Despite the observational design of this study, clinicians should be aware of the potential association between the combination of these medications and increased CSA odds.

ABBREVIATIONS

CAI, central apnea index
CI, confidence interval
CNSAMs, central nervous system active medications
CSA, central sleep apnea
PSG, polysomnography

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DISCLOSURE STATEMENT

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