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Article in *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine* · January 2016

Impact Factor: 3.05 · DOI: 10.5664/jcsm.5704

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REVIEW ARTICLES

Medium Increased Risk for Central Sleep Apnea but Not Obstructive Sleep Apnea in Long-Term Opioid Users: A Systematic Review and Meta-Analysis

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Study Objective: Opioids are associated with higher risk for ataxic breathing and sleep apnea. We conducted a systematic literature review and meta-analysis to assess the influence of long-term opioid use on the apnea-hypopnea and central apnea indices (AHI and CAI, respectively).

Methods: A systematic review protocol (Cochrane Handbook guidelines) was developed for the search and analysis. We searched Embase, Medline, ACP Journal Club, and Cochrane Database up to November 2014 for three topics: (1) narcotics, (2) sleep apnea, and (3) apnea-hypopnea index. The outcome of interest was the variation in AHI and CAI in opioid users versus non-users. Two reviewers performed the data search and extraction, and disagreements were resolved by discussion. Results were combined by standardized mean difference using a random effect model, and heterogeneity was tested by χ^2 and presented as I^2 statistics.

Results: Seven studies met the inclusion criteria, for a total of 803 patients with obstructive sleep apnea (OSA). We compared 2 outcomes: AHI (320 opioid users and 483 non-users) and 790 patients with CAI (315 opioid users and 475 non-users). The absolute effect size for opioid use was a small increased in apnea measured by AHI = 0.25 (95% CI: 0.02–0.49) and a medium for CAI = 0.45 (95% CI: 0.27–0.63). Effect consistency across studies was calculated, showing moderate heterogeneity at $I^2 = 59%$ and 29% for AHI and CAI, respectively.

Conclusions: The meta-analysis results suggest that long-term opioid use in OSA patients has a medium effect on central sleep apnea.

Keywords: opioid, narcotic, sleep apnea, central sleep apnea, apnea-hypopnea index, systematic review, meta-analysis

Citation: Filiatrault ML, Chauny JM, Daoust R, Roy MP, Denis R, Lavigne G. Medium increased risk for central sleep apnea but not obstructive sleep apnea in long-term opioid users: a systematic review and meta-analysis. *J Clin Sleep Med* 2016;12(4):XXX-XXX.

INTRODUCTION

Rationale

Almost 20% of the North American population reports chronic pain, and about 1/5 of these are chronic opioid users.^{1–3} Opioids (e.g., morphine, methadone, oxycodone, fentanyl) are frequently used in postoperative medicine, in addiction and chronic pain management.^{4–7} These drugs have been associated with higher risk of sleep apnea, particularly central sleep apnea (CSA), and they tend to contribute to hypoxemia during wakefulness and sleep, and to suppress breathing.^{4,5,7–13} Discrepancies in findings due to different research methodologies and study designs preclude comparison between studies and consequently, the calculation of a risk-to-benefit ratio for opioid prescriptions.^{4,8,9,14–19} Given this inconsistency in the scientific literature, it is not surprising that neither the American nor the Canadian guidelines for the safe and effective use of chronic opioid therapy in chronic non-cancer pain provide a clear answer to clinicians on whether or not opioid use aggravates sleep disordered breathing (SDB) symptoms.^{20,21}

No systematic review or meta-analysis of optimal diagnostic data on opioid-induced sleep apnea has been published to date.¹⁴ There is an urgent need to fill the gap in best practice guidelines

in order to improve pain management and assist clinicians in making informed decisions about prescribing opioids.

In this article, the term “opioid” refers to any substance, either natural (i.e., opium) or synthetic (e.g., morphine, methadone) that produces morphine-like effects.²²

Objectives

In order to assess the impact of long-term opioid use on sleep breathing disorders, and more precisely the risk of aggravated sleep apnea, we conducted a meta-analysis of studies that examined the effects of long-term opioid use on the apnea-hypopnea index (AHI) and the central apneas index (CAI).

METHODS

We conducted the analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²³

Eligibility Criteria

The inclusion and exclusion criteria (Table 1) were developed according to the population, intervention, comparison and

Table 1—Inclusion and exclusion criteria.**Inclusion criteria**

- Article must have been published in English or French.
- Article must have been published in the last 30 years (in-process and non-indexed citations included).
- Article must be relevant to the PICO question (refer to Table 2).
- Article must have enrolled adult males or females (≥ 18 y).
- Article must describe a study that included 2 distinct groups: a control group (medication-free) and a case group (long-term opioid users).
- Study must include precise measures of the central apnea index (CAI) for both the case and control groups assessed by in-laboratory polysomnography (PSG), home testing with portable monitors (PM), or any other validated screening device for sleep-disordered breathing (e.g., portable ventilation effort recorder) in accordance with the recommendations of the American Academy of Sleep Medicine.

Exclusion criteria

- Case report, case series, systematic review or review, meta-analysis, or expert opinion.
- Study presenting preliminary data.
- Study not providing precise outcome measures (e.g., CAI ≥ 5 , no mean or standard deviation available).
- Study including opioid antagonist (e.g., naloxone) or anesthetic drug use.
- For duplicate studies in searched databases, only the most complete studies will be included.

Table 2—PICO question.**PICO Question**

In adult (≥ 18 y.) males or females with long-term opioid use compared to no treatment (clean subjects), what is the effect on both the apnea-hypopnea index (AHI) and the central apnea index (CAI) for both groups assessed by in-laboratory polysomnography (PSG), home testing with portable monitors (PM), or any other validated screening device for sleep-disordered breathing (e.g., portable ventilation effort recorder) in accordance with the recommendations of the American Academy of Sleep Medicine?

P: Adult males or females (≥ 18 y.)

I: Long-term opioid use

C: No treatment (clean subjects)

O: Effect on the AHI and CAI

outcomes (PICO) model (**Table 2**). In summary, the apnea-hypopnea breathing index was compared between adult patients who were long-term opioid users or non-users.

Data Sources

A total of six bibliographic databases were searched (EMBASE, MEDLINE, ACP Journal Club, Cochrane Central Register of Controlled Trials – CENTRAL, Cochrane Database of Systematic Reviews – CDSR, and Database of Abstracts of Reviews of Effects – DARE) using Medical Subject Headings (MeSH) vocabulary and keywords up to November 26, 2014). We also examined the reference lists of retrieved articles, relevant reviews, systematic reviews, and meta-analyses. The search was performed by one reviewer (M-L.F.) and verified by a certified librarian. Authors ($n = 2$) mentioned in relevant conference abstracts were contacted by email, but neither responded. One author of a recent review was contacted, but the data were unavailable because the article was accepted for publication but not yet published. One author of an included study clarified some of our questions. An AutoAlert (OvidSP) was posted on the research platforms to identify relevant studies published after the study was underway.

Search

The three following keywords (MeSH for MEDLINE, Emtree for EMBASE, keywords for Cochrane) were grouped and limited to English or French language and published within the last 30 years: (1) narcotics, (2) sleep apnea, and (3) apnea-hypopnea index. Details on the online search strategy for each database are presented in **Appendix 1A to 1C** (see supplemental material for appendices).

Study Selection

Figure 1 depicts the study selection process. A total of seven studies were included in the meta-analysis: five nested case-control studies, one prospective case-control study, and one cross-sectional study that assessed the relationship between long-term opioid use and central sleep apneas as a main or secondary outcome. Two reviewers (M-L.F. & M-P.R.) performed the final screening independently, and one mediator (J-M.C.) was designated for cases of disagreement. The team discussed whether the studies met the inclusion and exclusion criteria, as presented in **Table 1**, and complied with the PICO question, as presented in **Table 2**. In cases of disagreement, the mediator reviewed the article and the conflict was resolved by discussion.

Data Collection and Items

Two reviewers independently extracted data on outcomes and characteristics of the study participants (opioid users and non-users separately) onto standardized forms. Data included the apnea-hypopnea index (AHI) and central apnea index (CAI) (mean and standard deviation) for opioid users and non-users (presented as forest plots, **Figures 2 and 3**). Both indices were reported as events per hour. Study and participant characteristics are presented in **Tables 3A and 3B**: first author, publication date, study design, population size, mean age, sex, BMI, reason for opioid use, opioids used, dosage, and comorbid conditions. The reviewers then met to agree on the extracted data.

Risk of Bias in Individual Studies

Two independent reviewers assessed the risk of study bias in the included studies using modified Study Quality Assessment

Tools for case-control and observational cohort and cross-sectional studies by the National Heart, Lung and Blood Institute, as presented in **Appendix 3A** and **3B**.²⁴ Results were summarized in a modified Cochrane version of a risk of bias summary figure, presented in **Appendices 3C** and **3D**.²⁵ The gathered data are discussed below.

Summary Measures and Synthesis of Results

Results were combined using standardized mean difference with a random effect model, and heterogeneity was tested with the χ^2 test and presented as I^2 statistics. The absolute effect of long-term opioid use on the AHI and CAI was quantified by estimating the standardized mean difference (SMD) of the means and standard deviations (SD) of both indices between opioid users and non-users. We estimated the effect size and 95% confidence intervals (CI) by pooling extracted data using RevMan 5.3 Public Beta software. Results are presented as forest plots in **Figures 2** and **3**.

Risk of Publication Bias

We conducted funnel plots of standard error and difference in means, as presented in **Appendix 2A** and **2B**, to assess for potential publication bias, as described below.²⁶

RESULTS

Study Selection

A total of 196 potential studies were reviewed, of which 189 did not meet the inclusion criteria (flowchart, **Figure 1**) and were rejected. Seven studies met the inclusion criteria, for a total of 803 patients with AHI (320 opioid users, 483 non-users) and 790 patients with CAI (315 opioid users, 475 opioid non-users).

Study Characteristics

Tables 3A and **3B** present the characteristics of the studies included in the meta-analysis.^{8,14–19}

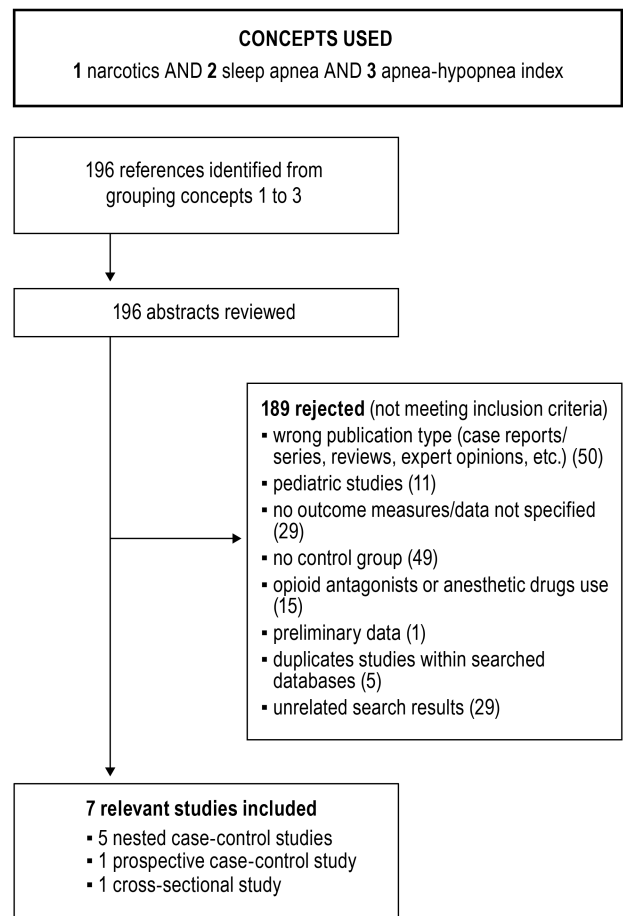
Risk of Within-Study Bias

Appendices 3C and **3D** summarizes the within-study bias. Studies were evaluated on eight criteria for case-control studies, as presented in **Appendix 3C**: research question, study population, groups recruited from the same population, inclusion and exclusion criteria pre-specified and applied uniformly, case and control definitions, exposure assessed prior to outcome measurement, exposure measures, and assessment and statistical analyses.

Studies were also evaluated on eight criteria for observational cohort/cross-sectional studies, as presented in **Appendix 3D**: research question, study population, groups recruited from the same population and uniform eligibility criteria, exposure assessed prior to outcome measurement, sufficient timeframe to see an effect, exposure measures and assessment, follow-up rate, and statistical analyses.

The labels low risk, high risk, and unclear in **Appendix C** and **D** refer to the following responses to the eight criteria in **Appendix A** and **B**: yes, no, and cannot determine/not applicable/not reported, respectively.

Figure 1—Flowchart of articles identified and evaluated during the study selection process.



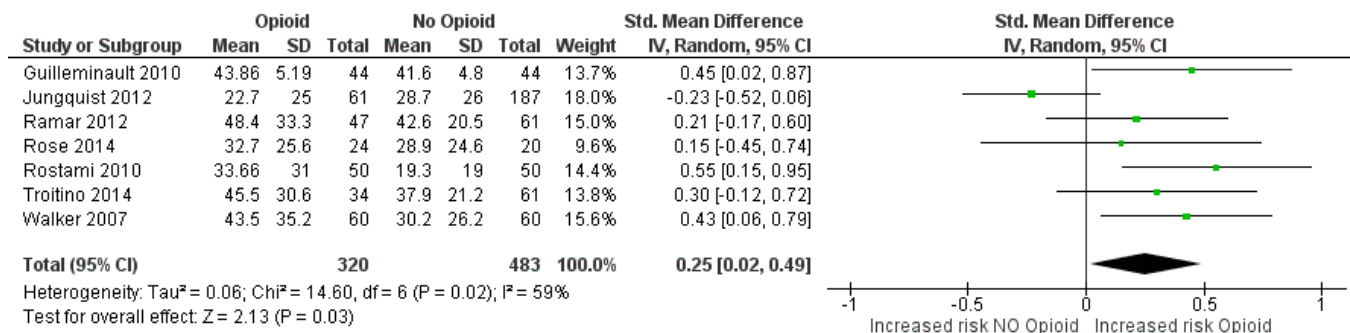
The flowchart presents the key concepts used to search the articles, the number of articles retrieved by the search, the number of abstracts reviewed and rejected, and the relevant studies included in the systematic review and meta-analysis.

Of 48 possible responses, bias assessment for the six case-control studies revealed 40, 5, and 3 low risks, high risks, and unclear risks, respectively. Of 8 possible responses, bias assessment for Junquist et al. (cross-sectional study) revealed 5, 2, and 0 low risks, high risks, and unclear risks, respectively.

Results on Individual Studies

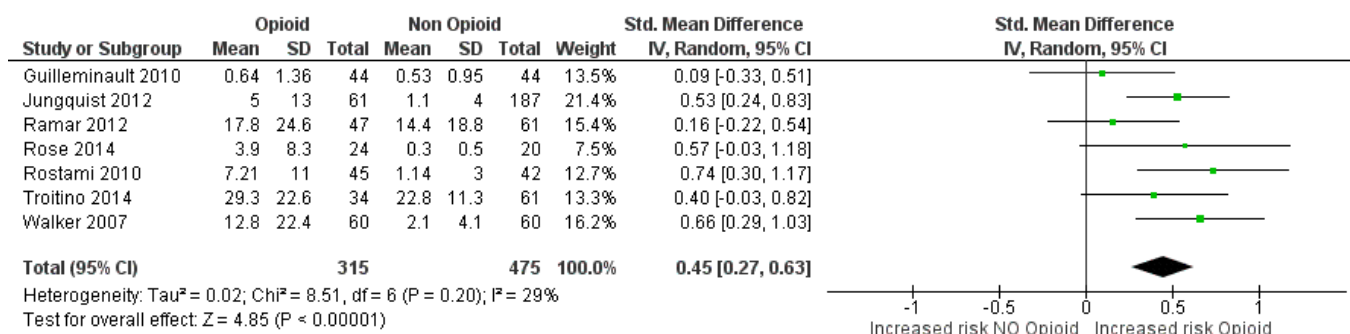
Figures 2 and **3** present the sleep apnea syndrome outcome measures, including the AHI and CAI per hour of sleep for opioid users and non-users in the studies. Data are presented as mean \pm SD, with the following mean range for AHI and CAI: AHI 22.7 to 48.4 for users and 19.3 to 42.6 for non-users; CAI 0.64 to 29.3 for users and 0.3 to 22.8 for non-users. **Figures 2** and **3** present the forest plot for each study, including the standardized mean difference and 95% CI for the AHI and CAI, respectively. SMD for the seven studies ranged from -0.23 to 0.55 for the AHI and 0.09 to 0.74 for the CAI. Three studies demonstrated a significant impact on the AHI (SMD: 0.45 ;

Figure 2—Forest plot for mean difference in apnea-hypopnea index (AHI) and corresponding 95% CI.



Forest plot for mean difference in AHI using a random effect model. Includes means, standard deviations, and sample size for opioid users and non-users. Corresponding weights, standard mean difference, and corresponding 95% confidence intervals are presented for each study included in the meta-analysis. Chi², chi-square test; df, degrees of freedom IV, inverse variance; SD, standard deviation. Mid-point diamond represents the overall effect of the treatment.

Figure 3—Forest plot for mean difference in central apnea index (CAI) and corresponding 95% CI.



Forest plots for mean difference in CAI using a random effect model. Includes means, standard deviations, and sample size for opioid users and non-users. Corresponding weights, standard mean difference, and corresponding 95% confidence intervals are presented for each study included in the meta-analysis. Chi², chi-square test; df, degrees of freedom IV, inverse variance; SD, standard deviation. Mid-point diamond represents the overall effect of the treatment.

95% CI: 0.02, 0.87], [SMD: 0.55; 95% CI: 0.15, 0.95], [SMD: 0.43; 95% CI: 0.06, 0.79]),^{8,18,27} Three other studies demonstrated a significant impact on the CAI ([SMD: 0.53; 95% CI: 0.24, 0.83], [SMD: 0.74; 95% CI: 0.30, 1.17], [SMD: 0.66; 95% CI: 0.29, 1.03]).^{8,18,19}

Synthesis of Results

The pooled estimate of the change in means and the corresponding 95% CI for the AHI and CAI from each study were small at 0.25 (95% CI: 0.02, 0.49) and medium 0.45 (95% CI: 0.27, 0.63) respectively. Data are presented in **Figures 2 and 3**.

The consistency of effects across studies was assessed using the I² test. With an I² index of 59% (p = 0.02) for the AHI and 29% (p = 0.20) for the CAI, the data indicate heterogeneity for the AHI and homogeneity for the CAI, respectively.

Risk of Publication Biases

Appendix 2B presents the AHI data, which show a slightly asymmetrical funnel shape, indicating a small risk of publication bias. **Appendix 2B** presents the data on the CAI, which show a more symmetrical shape, indicating no publication bias.

DISCUSSION

Summary of Evidence

The pooled estimate indicated a significant but modest impact of long-term opioid use on both the apnea-hypopnea and central apnea indices in patients with OSA. However, the risk associated with long-term opioid use was medium for the central apnea index.

Seven studies assessed the impact of long-term opioid use on the apnea-hypopnea and central apnea indices. Except for one study (opium addiction), the reason for opioid use was chronic pain management.¹⁸ Overall, increased opioid use, evidenced by an increase in both diagnostic indexes, and particularly the central apnea index, appears to generate significant risks of aggravated sleep apnea. Our findings concur with a recent study by Rose and collaborators, where 46% of chronic opioid users had severe sleep apnea and 71% had moderate sleep apnea.¹⁴ In addition, 17% of chronic opioid users had a CAI ≥ 5.¹⁴ However, in the study by Javaheri et al., 80% of chronic opioid users had CSA (CAI ≥ 5/h of sleep).²⁸ These differences could be explained by other factors, including variations in opioid type, dosage, and use duration, as well as pain type, individual sensitivity to opioids, and concomitant medications used.²⁹ Both

Table 3A—Overview of the 7 included studies and characteristics of opioid non-users.

First Author, Year	Study Design	n	Age (SD)	Sex (M/F)	BMI (SD)	Comorbid Conditions
Guilleminault, 2010	Nested case-control study	44	43.4 (9.6)	22/22	26.4 (2.0)	SAS (100%)
Jungquist, 2012	Cross-sectional study	187	50.7 (12)	84/103	34.9 (8.0)	SAS (100%), CV, **systems (pulmonary (including smoking), neuromuscular, Dp.)
Ramar, 2012	Nested case-control study	61	70.9 (9.4)	54/7	30.8 (5.8)	SAS (100%), SCHF (75%)
Rose, 2014	Nested case-control study	20	52.9 (9.8)	11/9	34.9 (8.4)	SAS (100%)
Rostami, 2010	Prospective case-control study	50	52.8 (11)	50/0	30.0 (5)	OSA (100%), HTN, DM, obesity, HC
Troitino, 2014	Nested case-control study	61	62.0 (14.7)	*All: 93/2	31.8 (4.9)	SAS-CSA (idiopathic) (100%)DM (28%), HTN (67%), CAD (31%), Dp (29%), Alcoholism (11%)
Walker, 2007	Nested case-control study	60	52.9 (13.0)	20/40	32.5 (7.6)	SAS (100%), HTN (58.3%), AR (21.6%), GERD (46.6%), HT (33.3%), Dp (71.6%), DM (20%)

AR, arrhythmias; CV, cardiovascular; Dp, depression; GERD, gastroesophageal reflux disease; HC, hypercholesterolemia; HT, hypothyroidism; OSA, obstructive sleep apnea; SAS, sleep apnea syndrome; SCHF, systolic congestive heart failure. *Includes controls and cases. **Reported as number of systems affected by comorbid diagnoses.

opioid users and non-users had a mean body mass index (BMI) classified as obese type 1 and were from 50 to 60 years old on average. However, these differences cannot be explained by BMI or age. Diagnostic measures also varied widely across the seven studies, as discussed below in the limitations section.

The International Classification of Sleep Disorders (ICSD) has identified six types of central sleep apnea syndrome (CSAS).³⁰ Those are characterized by SDB that is correlated with absent or decreasing breathing effort combined with symptoms such as excessive daytime sleepiness and recurrent nocturnal awakenings.³⁰ Untreated SDB is associated with serious health problems such as obesity as well as cardiovascular, metabolic, and neurocognitive diseases.^{31,32} The present meta-analysis focuses on CSA due to chronic drug or substance use.³⁰

This meta-analysis is particularly relevant for healthcare providers because the prevalence of opioid-induced sleep apnea is growing rapidly.³³ The exact mechanisms of CSAS due to opioid use remain unclear.³⁰ The appropriate treatment is also unclear, but the emerging evidence suggests that treatment with adaptive servoventilation (ASV) is beneficial.^{16,28,34,35} Nonetheless, a recent systematic review found conflicting results on this treatment.⁶ Given the suboptimal compliance to positive airway pressure (PAP) treatment, it is urgent to provide guidance to physicians.³⁶ Moreover, according to recent articles, not only are opioid medications increasingly prescribed for chronic pain management, rates of other opioid use disorders (e.g., abuse, overdose, and dependence) are rising as well.^{37,38} The effectiveness of long-term opioid therapy remains unclear, and the benefits and harms must be weighed.³⁸

Clinical Relevance

From a clinical perspective, these data suggest that chronic opioid use might increase the risk of sleep-disordered breathing in patients with OSA, with a medium effect on the CAI.

Clearly, in the decision to maintain the use of opioids for a patient with SDB, the risks and benefits must be taken into account. It appears implicit that in the presence of SDB, the use of a breathing device is probably safer.⁷ Since most studies analyzed in the present meta-analysis are from patients with OSA as a comorbid condition, it is to be determined if the same effect can be observed in opioid users without SDB.

Both obstructive and central sleep apnea have been associated with higher risks of mortality and adverse cardiovascular events.³⁹ In fact, sleep apnea may increase the mortality risk by conferring greater risk of arrhythmias, myocardial ischemia/infarction, and stroke.³⁹ In another very recent study, a greater risk of higher cardiovascular event rate was observed in an older population under opioids.⁴⁰ The more frequent presence of sleep apnea and oxygen desaturation observed in opioid users could explain the opioid-associated cardiovascular morbidity.⁴⁰

Moreover, as mentioned above, our data indicated a more profound effect on the CAI than the AHI. Mogri and collaborators reported no significant correlation between the AHI and the amount of daily ingested opioids.⁴¹ These authors suggested that the AHI might not be the best metric for estimating the severity of opioid-associated SDB, unlike routine OSA. Finally, chronic opioid users had a high prevalence of sleep apnea and nocturnal hypoxemia.⁴¹ It remains to be determined in future studies whether hypoxemia and/or opioid-associated sleep apnea are predictive markers of sudden death in this population.⁴¹

Limitations

This study has certain limitations. All the included studies were observational studies, and none were randomized control trials (RCTs). Therefore, potential confounding factors may have affected our results. Five of the seven studies were nested case-control studies, and the two others were a prospective

Table 3B—Overview of the 7 included studies and characteristics of opioid users.

First Author, Year	Study Design	n	Age (SD)	Sex (M/F)	BMI (SD)	Rationale for Opioids Use	Opioids Used	Opioid Dosage	Comorbid Conditions
Guilleminault, 2010	Nested case-control study	44	45.9 (7.1)	22/22	25.6 (1.9)	Chronic pain	morphine, oxycodone, methadone, hydromorphone, fentanyl	morphine: n/a, fentanyl: 25–50 mcg TID, oxycodone: 15–30 mg/day, hydromorphone: 4–6 mg/day, methadone: 60–90 mg/day	SAS (100%)
Jungquist, 2012	Cross-sectional study	61	50.4 (11)	22/39	32.8 (7)	Chronic pain	methadone, oxycodone, morphine, fentanyl, hydrocodone, propoxyphene, hydromorphone	N/A	SAS (100%), CV, **systems (pulmonary (including smoking), neuromuscular, Dp.)
Ramar, 2012	Nested case-control study	47	59.1 (14.2)	23/24	33.9 (8.0)	Chronic pain	N/A	N/A	SAS-CAS or CompSAS (100%)
Rose, 2014	Nested case-control study	24	52.4 (9.4)	12/12	34.9 (9.4)	Chronic pain	morphine, oxycodone, methadone	MEQ: 141 mg/24h	SAS (100%)
Rostami, 2010	Nested case-control study	50	52.8 (10)	50/0	29.99 (5)	Opium addiction	opium	N/A	OSA(100%), HTN, DM, HC, Obesity
Troitino, 2014	Nested case-control study	61	60.8 (8.9)	*All: 93/2	31.2 (3.6)	Chronic pain	hydrocodone, fentanyl, oxycodone, morphine, methadone, buprenorphine, tramadol	MEQ: 168 mg/24h	SAS-CSA (opioid-related) (100%), DM (35%), HTN (68%), CAD (26%), Dp (44%), Alcoholism (12%)
Walker, 2007	Nested case-control study	60	52.7 (13.1)	20/40	31.8 (7.7)	Chronic pain	hydrocodone, methadone, oxycodone, morphine, fentanyl, propoxyphene	MEQ: 143.9 mg/24h	SAS (100%), HTN (53.3%), AR (28.3%), GERD (46.7%), HT (36.6%), Dp(86.7%), DM(28.3%)

AR, arrhythmias; CAD, coronary artery disease; CSA, central sleep apnea; CV, cardiovascular; DM, diabetes mellitus; Dp, depression; GERD, gastroesophageal reflux disease; HC, hypercholesterolemia; HTN, hypertension; HT, hypothyroidism; MEQ, morphine equivalence; N/A, not available; OSA, obstructive sleep apnea; SAS, sleep apnea syndrome; TID, three times a day. *Includes controls and cases. **Reported as number of systems affected by comorbid diagnoses.

case-control and a cross-sectional study. Five studies were from the United States (Guilleminault, Jungquist, Ramar, Troitino, Walker), one was from Australia (Rose), and the remaining study was from Iran (Rostami).

The results on the effects of long-term opioid use on both the AHI and CAI could have been affected by clinical heterogeneity related to patient characteristics in terms of age, sex, BMI, and comorbidities. However, it is worth mentioning that the majority of OSA patients, both opioid users and non-users, were from 50 to 60 years old on average. The total ratio of males to females was consistent for both opioid users and non-users. All patients had a BMI classified as overweight or obese,

with the majority classified as obese type I (BMI: 30.0–34.9).⁴² All patients had sleep apnea syndrome at baseline. Unsurprisingly, in the studies that provided details on comorbid conditions, most patients suffered from coronary heart disease. The study settings were sleep clinics at either academic hospitals or research centers. Outcome data were gathered by in-laboratory polysomnography (PSG) in six studies and home testing with portable monitors (PM) in one study (Rose), in accordance with recommendations by the American Academy of Sleep Medicine.⁴³

Potential confounders for the results on opioid users would include opioid type, use period, administration route, use

duration, and dosage. For example, short- versus long-acting opioids have different action onset times and durations of analgesic activity.⁴⁴ The opioid use period ranged from over one month to 15 years across studies, and data were unavailable in one study.¹⁸ Moreover, data on concomitant medications and opioid use on the day of sleep assessment were missing in most cases. One study clearly indicated that 14% of opioid users reported taking a dose on the day of diagnostic PSG (Jungquist), and another study confirmed opioid intake on the day of PSG (Guilleminault). We speculate that opioid use was also maintained in the 5 other studies included in the present analysis. Discontinuation of regular use of prescribed pain medications is not a common practice in clinical sleep studies.⁴⁵ Note that the reported dosage might also differ from the actual dosage ingested on the day of the PSG. In fact, chronic pain patients tend to adjust their day-to-day dosage based on pain intensity.⁴¹

Four of the studies selected for our analysis reported patient use of centrally acting medications such as antidepressants or benzodiazepines.^{8,14,15,19} Control for the use of illicit drugs and over-the-counter medications is challenging in research. Like centrally acting medications, these substances potentially contribute to SDB, interfere with sleep patterns, and can provoke drug interactions.^{14,15} The impact of concomitant medications was not assessed due to lack of information. Details on the administration route for long-term opioid use were missing, as well as opioid doses in some cases.^{16,18,19} CSA events appear to be positively correlated with the morphine-equivalent opioid dose (MED).¹⁹ Moreover, the wide interindividual variability in sensitivity to opioids could be attributed to environmental and genetic factors (i.e., genes encoding metabolic enzymes, opioid transporters, opioid system signal transduction mediators, or genes involved in opioid pharmacokinetics and pharmacodynamics).^{29,46}

In the bias assessment for case-control studies, most criteria showed low risk bias. The most problematic criterion was “Groups recruited from the same population,” with one article graded as high risk (Rose) and two articles graded as unclear risk (Rostami, Walker).

For the assessment of bias in Jungquist (cross-sectional study), the criteria “Exposure assessed prior to outcome measurement” and “Sufficient timeframe to see an effect” were graded as high risk.

A slightly higher possibility of publication bias was found for AHI than CAI data, as presented in **Appendix 2A** and **2B**.

Although the search strategy was verified by a certified librarian, multiple search terms were used, and multiple databases were searched, it remains possible that not all relevant articles were retrieved. Six of the seven studies advocated intervention, indicating that long-term opioids have a deleterious effect on the AHI (**Figure 2**). The largest sample size study in our meta-analysis, Jungquist, demonstrated that chronic pain patients without opioid treatment (n = 187) had a higher AHI (28.7 [SD: 26]) than chronic pain patients with opioid treatment (n = 61) (AHI 22.7 [SD: 25]). Because the AHI is defined as the number of apneas and hypopneas per hour of sleep and takes into account obstructive, central, and mixed events, this discrepancy could be explained by the higher severity of obstructive sleep apnea syndrome (OSAS) in opioid non-users

(obstructive apnea index [OAI], pain/no opioids: 9.7 [SD: 14]; OAI pain/opioids: 4.4 [SD: 9]).⁴⁷ The statistically significant difference in average BMI between users and non-users (BMI pain/no opioids: 34.9 [SD: 8] kg/m²; BMI pain/opioids: 32.8 [SD: 7] kg/m²) could be an aggravating factor for OSAS severity.⁴⁸ In fact, Young and collaborators demonstrated that the odds ratio for SDB (defined as AHI ≥ 5) for a 1-SD increment in BMI was^{4,17,49}

Furthermore, it remains to be clarified whether patients who are long-term opioid users feel greater pain intensity. First, opioid non-users were prescribed antidepressants in 30% versus 18% of opioid users, with 13% and 10% for anticonvulsants, respectively. These drugs, which are used as adjuvant therapy to manage chronic noncancer pain, could also contribute to SDB and sleep architecture alterations.^{1,12,14,50} Second, as mentioned in Jungquist’s study, each 1 increment in pain intensity increases central apnea events by 0.288 and decreases obstructive apneic events by 0.599 per hour. Accordingly, it is unclear why pain/non-opioid users have higher average OAI than pain/opioid users.

All seven studies indicated a more pronounced deleterious effect on the CAI in OSA patients, as illustrated in **Figure 3**. In addition, Jungquist demonstrated that group membership (no pain, pain without opioid therapy, and pain with opioid therapy) was related to CSA and predicted an additional 6% of the variance besides risk factors in the CAI. No mean difference in central apnea was found between subjects with and without pain. However, long-term opioid use was significantly positively correlated with the mean CAI.

CONCLUSIONS

The findings of our meta-analysis suggest that long-term opioid use has a medium risk to increase CSA in OSA patients. However, the risk factors and mechanisms need to be further investigated in these SDB and non SDB patients using opioid over the long term. It would also be useful to verify the overall impact of long-term opioid use on sleep apnea diagnostic measures per category of morphine equivalent dose. In addition, the different phenotypes of breathing disturbances should be characterized, as suggested by Randerath and George.³³ A recent review by Correa et al. found a roughly 24% prevalence of central sleep apnea in chronic opioid users. This alarming situation underscores the need for further prospective studies on the perioperative risks and management in this particular population.⁵¹ Finally, given the significant lack of relevant data in 2014, the overall impact of opioid use for acute pain on sleep should be investigated using before-after study designs.

ABBREVIATIONS

AHI, apnea-hypopnea index
ASV, adaptive servoventilation
BMI, body mass index
CAI, central apnea index
CDSR, Cochrane Database of Systematic Reviews

CENTRAL, Cochrane Central Register of Controlled Trials
 CI, confidence interval
 CSA, central sleep apnea
 CSAS, central sleep apnea syndrome
 DARE, Database of Abstracts of Reviews of Effects
 ICD-10, International Classification of Diseases
 MED, morphine equivalent dose
 OAI, obstructive apnea index
 OSAS, obstructive sleep apnea syndrome
 PAP, positive airway pressure
 PICO, population intervention comparison outcome
 PM, portable monitors
 PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses
 PSG, polysomnography
 RCTs, randomized control trials
 SAS, sleep apnea syndrome
 SD, standard deviations
 SDB, sleep disordered breathing
 SMD, standardized mean difference

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ACKNOWLEDGMENTS

The authors thank Mr. Patrice Dupont, certified librarian, who participated in the research strategy process. We also thank Margaret McKyes, certified translator, who proofread and edited the final version of the article.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication May, 2015

Submitted in final revised form December, 2015

Accepted for publication December, 2015

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DISCLOSURE STATEMENT

This was not an industry supported study. This study was supported by the Canada Research Chair in Pain, Sleep and Trauma (GL) and grants from the Centre de recherche de l'Hôpital du Sacré-Coeur de Montréal and the Ronald Denis Foundation. The authors have indicated no financial conflicts of interest.