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Review Article

The Association of Obstructive Sleep Apnea and Pain Outcomes in Adults: A Systematic Review

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Abstract

Objective. The specific link between obstructive sleep apnea (OSA) and pain is unknown, but it has been hypothesized that OSA patients are hyperalgesic because of fragmented sleep and hypoxemia that enhance sensitivity to pain, promote inflammation, and increase spontaneous pain. We conducted a systematic review of the literature assessing whether OSA is a risk factor for subjective pain intensity and experimental pain tolerance and threshold. **Design/Participants**. A search of published studies in English in MEDLINE, PubMed, Embase, and the Cochrane Database of Systematic Reviews from database inception through May 2017 was performed. Search terms included "sleep apnea," "continuous positive airway pressure," "CPAP," "pain," and "chronic pain." **Methods**. We included any study that reported an association between OSA or polysomnogram assessments with pain outcomes or reported the effect of CPAP on pain outcomes. Controlled studies, cohort studies, and case–control studies were included. **Results**. We identified 448 studies from PubMed and 959 studies from Embase, giving a combined 1,333 studies after removing duplicates. After detailed selection, 28 articles were reviewed in full and 12 met study inclusion criteria. Whereas several studies found an association between OSA and pain intensity or experimental pain, there was considerable variability among study outcomes. Delivery of CPAP may improve pain and decrease opioid use, although the exact nature of the relationship between pain and the various pathophysiologic components of OSA is unclear. **Conclusions**. This systematic review summarizes the current evidence for the association of OSA and pain outcomes. Further research is needed to identify the differential effects of nocturnal hypoxemia and fragmented sleep on pain intensity. Clinicians might consider screening patients with chronic pain for OSA.

Key words: Opioids; Pain; Obstructive Sleep Apnea; Hypoxemia

Introduction

Obstructive sleep apnea (OSA) is a prevalent condition of complete or partial upper airway obstruction during sleep. Overall, 10–17% of men and 3–9% of women in the United States have moderate to severe OSA [1], which when untreated can lead to adverse cardiovascular and metabolic events, decreased quality of life, and motor vehicle accidents. OSA, defined as episodes of respiratory airflow cessation caused by upper airway obstruction during sleep, is generally categorized by sleep fragmentation and nocturnal recurrent hypoxemia [2]. Risk factors associated with OSA include male sex, older age, postmenopausal status, obesity, craniofacial abnormalities, smoking, post-traumatic stress disorder, and

central nervous system depressant use (opioids, alcohol, and benzodiazepines) [3].

Pain is frequently reported by patients with OSA [4,5]. In addition, OSA is associated with the development and progression of many painful conditions, such as headaches, temporomandibular disorders, and fibromyalgia [6]. It is thought that this association is bidirectional [7], as pain and opioid use have been shown to be associated with sleep-disordered breathing and/or arousals [8,9].

The specific link between OSA and pain is not fully understood, but it has been hypothesized that OSA patients are hyperalgesic because of disrupted sleep [10], which enhances sensitivity to pain, promotes inflammation, and increases spontaneous pain [2,11]. However, the pathophysiologic disturbances of OSA consist not only of sleep disruption, but also of frequent night time hypoxemia. Mechanistically, hypoxemia can directly impact reactive oxygen species formation, which sensitizes pain receptors [12] and increases inflammatory mediators that contribute to neuronal pain sensitivity [13,14].

It is important to further analyze the association of OSA and pain due to the potential therapeutic implications this entails; treating the sleep apnea (e.g., continuous positive airway pressure [CPAP]) may potentially improve pain intensity, decrease the need for opioid analgesics, and help predict a patient's opioid sensitivity in acute care settings. Therefore, we conducted a systematic literature review to assess if OSA is an independent risk factor for pain intensity and pain tolerance and threshold to examine the pathophysiologic components of OSA that might be associated with worse pain outcomes and to examine the effects of CPAP on pain outcomes among patients with OSA.

Methods

Search Strategy

A systematic search of published studies in English in MEDLINE, PubMed, Embase, and the Cochrane Database of Systematic Reviews from database inception through May 2017 was performed. Search terms included "sleep apnea," "continuous positive airway pressure," "CPAP," "pain," "chronic pain," and combinations of these terms. Additional articles were identified by examining bibliographies of manuscripts.

Selecting Abstracts for Full Text Review

Two co-authors (CS, LB) used inclusion criteria to assess abstracts. Abstracts included by either reviewer underwent full-text review. To be included in this review, studies had to be in English, include only adults, have 10 or more participants, report a quantitative association between OSA diagnosis and pain, and include a comparison group with no OSA. Studies were also included of OSA patients that compared the effects of CPAP on pain.

Data Extraction and Quality Assessment

Two co-authors (AC, MC) extracted data from published reports into evidence tables; additional co-authors read over evidence tables (CS, LB). For included studies, data were extracted on study populations, interventions, comparators, outcomes, quality, and applicability. Two co-authors independently rated quality using key criteria described in the Newcastle-Ottawa Quality Assessment Scale for case–control, randomized clinical trial (RCT), and cohort studies [15] and assigned a numerical score out of a possible nine points (Kappa score = 0.77). Disagreements were adjudicated by obtaining a third co-author's (CG) opinion.

Results

The electronic literature search identified 448 studies from PubMed and 959 studies from Embase, giving a combined 1,407 studies. There were 74 duplicates initially found between the two databases, leaving a new total of 1,333 abstracts. One additional article was identified from examining bibliographies of included manuscripts. Of these, 28 were reviewed in full and 12 met study inclusion criteria (Figure 1).

The prevalence of OSA was high in the majority of the studies (Table 1). We identified one RCT, three case–control, and eight cohort studies. Tables 1 and 2 outline the characteristics and quality assessment of each study. The majority of the studies were of low risk of bias. There were three studies (Group 1) that examined OSA and experimental pain threshold or pain tolerance (heat or pressure), four studies (Group 2) that examined OSA and a subjective pain assessment (intensity and/or frequency), and five studies (Group 3) that examined the effects of CPAP on pain outcomes (Table 3).

Two of the three studies in Group 1 found a significant association of OSA—or one of its constituent pathophysiologic components, such as nocturnal arterial oxygen saturation (SaO2), apnea–hypopnea index (AHI), or respiratory disturbance index (RDI)—with experimental pain tolerance [16,17]. However, Smith et al. [18] found that OSA was associated with increased pain tolerance.

In Group 2, the results were mixed. Two of the studies that measured self-reported pain intensity found that hypoxemia was associated with increased pain intensity [16,19]. Doufas et al. [16] took volunteers at risk for OSA, of which 72% turned out to have OSA after polysomnogram, and showed that nocturnal hypoxemia and the serum hypoxemia marker (IGFBP-1), but not sleep fragmentation, were associated with increased potency of the opioid remifentanil [2]. Roberts et al. [19] found that the risk of sleep apnea (as examined by the Berlin Questionnaire, not actual polysomnography) did not correlate significantly with current pain, although poor sleep duration (more than sleep quality) increased pain intensity. Sand et al. [20] found no correlation between

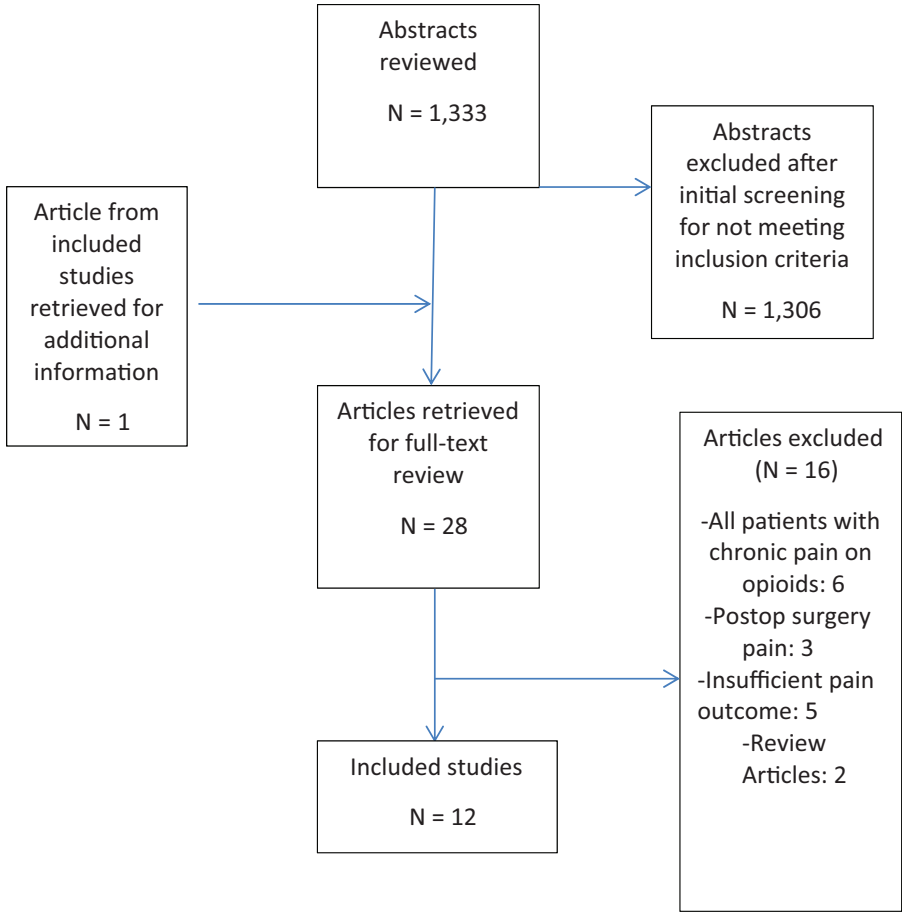

Figure 1. Study flow diagram.

OSA severity and pain frequency in a cohort of patients with headache. Turan et al. [21] examined a cohort of patients admitted for bariatric surgery, of which 88% had OSA, and demonstrated that nocturnal hypoxemia in the preoperative polysomnogram, rather than AHI, enhanced sensitivity to opioids postoperatively, although it did not affect subjective pain intensity measures.

The majority (four out of five) of the Group 3 studies examining the effect of CPAP treatment demonstrated an improvement in pain outcomes. In a pre/post cohort with OSA by Khalid et al. [10], CPAP treatment improved pain tolerance. In a randomized blinded crossover trial of geriatric patients with OSA by Onen et al. [22], pain tolerance was improved by high-CPAP settings but not low-CPAP settings. In a different population of opioid-treated veterans with chronic pain and psychiatric comorbidities, Jaoude et al. [23] found that CPAP nonadherence (as opposed to adherence) was positively associated with pain intensity; however, adherence to CPAP among the CPAP-adherent patients did not decrease pain intensity during follow-up after 12 months. In two studies focusing on the response of headache to CPAP, investigators found that treatment with CPAP markedly improved headache intensity and frequency [24,25]. Kallweit et al. [24] found that even though patients with migraines had no difference in AHI when compared with those without migraines, implementation of CPAP lead to marked reduction in migraine frequency that was larger than that of prophylactic pharmacotherapy. Goksan et al. [25] found that severity of morning headache varied proportionally to AHI, and implementation of CPAP lead to a 92% reduction in morning headache by one month of treatment.

Discussion

There are increasing rates of OSA and chronic pain, and this systematic review summarizes the current evidence for the association of OSA and pain outcomes. Overall, there is an association of OSA and increased pain intensity or decreased pain tolerance. Doufas et al. [2] hypothesized that the two pathophysiologic components of OSA—namely nocturnal hypoxemia and fragmented sleep—may exert opposite effects on pain sensing, so that whichever one predominates leads to hyper- or hypoalgesia accordingly. Most of the included studies do not adjust for differential effects of nocturnal hypoxemia and fragmented sleep. The balance between these two factors can be influenced significantly by the specific study population, including the severity of apnea, the presence of

Table 1. Characteristics of included studies

Author Year	No.	Country	Age, Mean or Range, y	Setting	Pain Type	Study Type	Patient Selection	Prevalence of OSA, %
Doufas 2013 [2]	634	USA	16–89	Sleep study	4 types of pain	Cohort	Cleveland Family Cohort participants	28
Jaoude 2016 [23]	226	USA	60	VA sleep center	Current general pain	Nested case–control	Retrospective chart review	100
Roberts 2016 [19]	101	Australia	15–83	Pain clinic	Current general pain	Cohort	Informed consent recruitment	42
Sand 2003 [20]	324	Norway	15–73	Sleep center	Headache, neck pain	Cohort	Consecutive	40
Turan 2015 [21]	218	USA	47	Bariatric surgery	Postoperative pain	Cohort	Retrospective chart review	88
Doufas 2013 [16]	43	USA	19–54	Sleep study	Hot & cold pain threshold & tolerance	Cohort	Consented volunteers at risk for OSA	72
Khalid 2011 [10]	12	USA	18–66	Sleep center	Hot pain tolerance	Cohort	Informed consent recruitment	100
Onen 2010 [22]	11	France	>70	Sleep center	Electric pain tolerance	RCT	Informed consent recruitment	100
Smith 2009 [18]	53	USA	34	Pain clinic TMD pts	Pressure and heat pain thresholds	Cohort	Informed consent recruitment	28
Terzi 2015 [17]	62	Turkey	18–45	Sleep center	Tender point threshold, pressure pain threshold	Case–control	Randomly selected females	50
Kallweit 2011 [24]	107	Switzerland	NA	Inpatient sleep center	Migraine frequency	Cohort	Consecutive	100
Goksan 2009 [25]	462	Turkey	50.9	Sleep center	Morning headache	Case–control	Consecutive	100

CPAP = continuous positive airway pressure; RCT = randomized clinical trial; TMD = temporomandibular joint disorder; VA = Veteran Affairs.

Table 2. Study quality assessment using the Newcastle-Ottawa Quality Assessment Scale

Author Year	Selection	Comparability	Outcome	NOS Score	Comment
Doufas 2013 [2]	***	**	**	7/9	Self-reported pain outcomes
Jaoude 2016 [23]	****	**	**	8/9	The opioid-treated group was primarily analyzed
Roberts 2016 [19]	*	**	**	5/9	Based in a pain clinic and used a screening questionnaire for OSA
Sand 2003 [20]	***		**	5/9	Focused on patients with headache
Turan 2015 [21]	*	**	**	5/9	All patients undergoing bariatric surgery
Doufas 2013 [16]	***	**	***	8/9	Patients with chronic pain excluded
Khalid 2011 [10]	****	**	***	9/9	Patients referred to a sleep clinic
Onen 2010 [22]	****	**	***	9/9	Patients with chronic pain excluded
Smith 2009 [18]	*	*	**	4/9	Patients with TMD recruited from pain clinic
Terzi 2015 [17]	**	*	**	5/9	All women and patients with OSA not on CPAP
Kallweit, 2011 [24]	***	**	**	7/9	Migraine headaches improved with CPAP
Goksan 2009 [25]	****	*	**	7/9	Morning headache improved with CPAP

CR = chart review; NOS = Newcastle Ottawa Scale; TMD = temporomandibular joint disorder.
*Asterisk indicates that item achieves one point on the NOS.

sedative meds that could prevent arousal, or the presence of psychiatric comorbidities that may further fragment sleep. To complicate things, sleep fragmentation variables, such as arousal index, have been shown to have high interobserver variability [26]. The main study that specifically measured and accounted for the differential effect of nocturnal hypoxemia and sleep fragmentation was by Doufas et al. [2]; it showed that nocturnal hypoxemia was independently hyperalgesic. The pathophysiologic basis of this conclusion relies on inflammatory pathways induced by hypoxemia [27].

The cohort of Smith et al. [18] consisted of patients with temporomandibular joint disorder (TMD) and found that OSA was hypoalgesic and increased pain tolerance. In this cohort, patients were mostly female and had an average BMI of 26.4 kg/m^2, which is atypical for the classic OSA patient. It may be that TMD is associated with a different pathophysiologic mechanism of OSA. Furthermore, the vast majority of the OSA patients in this study had mild OSA (RDI 5–14.9), and there was no sleep architecture or sleep continuity disturbance [18].

No linear dose–response relationship was identified between apnea index (AI; it excludes hypopneas) and oxygen desaturation index (ODI) and frequency of headache or neck pain among individuals admitted for polysomnography in the study of Sand et al. [20]. The

Table 3. Review results organized by study type and findings

Study	Exposure	Outcome	Results	Conclusion
Group 1: OSA or PSG variables associated with experimental pain				
Smith 2009 [18]	OSA (Y/N)	Pain threshold/tolerance	OSA increased pain tolerance	Negative
Doufas 2013 [16]	Nocturnal desaturation, hypoxemia marker (IGFBP-1) sleep fragmentation	Response of pain threshold values to opioid analgesia	Nocturnal hypoxemia and serum hypoxia marker (IGFBP-1) associated with increased potency to opioid analgesia	Positive
Terzi 2015 [17]	OSA (Y/N), nocturnal desaturation, AHI	Pressure pain tolerance using a dolorimeter	OSA decreased pain tolerance compared with no OSA	Positive
Group 2: OSA or PSG variables associated with pain				
Doufas 2013 [2]	Nocturnal desaturation (SaO2)	Numerical pain scales	Hypoxemia is independently associated with increased pain	Positive
Roberts 2016 [19]	OSA risk (Y/N), sleep duration and quality	Numerical pain scales	Sleep duration (more than sleep quality), weak independent association with pain	Positive
Sand 2003 [20]	AHI, ODI	Pain syndrome (headache or neck pain frequency)	No relationship between the severity of sleep apnea and headache or neck pain	Negative
Turan 2015 [21]	Nocturnal desaturation (SaO2), AHI	Opioid consumption, numerical pain scale	Preoperative nocturnal hypoxemia, rather than AHI, enhanced sensitivity to opioids postoperatively	Negative
Group 3: Effect of CPAP on pain outcomes				
Jaoude 2016 [23]	CPAP compliance	Numerical pain scales	Among opioid users, no correlation between CPAP compliance and pain	Negative
Khalid 2011 [10]	CPAP implementation	Pain threshold/tolerance	CPAP treatment improved tolerance to pain	Positive
Onen 2010 [22]	Low vs high CPAP settings	Pain threshold/tolerance	Pain tolerance was improved by high-CPAP (but not low-CPAP) settings	Positive
Kallweit 2011 [24]	CPAP for 1 y	Numerical pain scales, migraine frequency	Among patients with migraine, CPAP was effective in improving pain	Positive
Goksan 2009 [25]	CPAP for 1 mo	Presence of morning headache	Treatment with CPAP resulted in disappearance of morning headache in 92% of OSA patients at 1 mo	Positive

AHI = apnea hypopnea index; CPAP = continuous positive airway pressure; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; RDI = respiratory disturbance index; SaO2 = oxygen saturation in arterial blood.

authors found a weak trend toward "morning-type" headache and headache onset during the night in individuals with AI >5/h, but this did not reach statistical significance ($P = 0.08$ and 0.09, respectively). Although this study used different measures than others (i.e., AI instead of AHI, ODI instead of RDI), this was a mostly a negative study showing no association between OSA variables and pain frequency. Roberts et al. [19] also examined the relation between current pain (in numerical pain scale) and risk for OSA, sleep duration, sleep quality, and various psychiatric comorbidities and did multivariable analyses to adjust for confounding associations among all these variables. Although the study found an independent association mainly between pain and sleep duration, OSA in this study was actually defined as "risk for OSA" by using the Berlin Sleep Questionnaire, rather than actual polysomnographic confirmation and variables.

Studies of opioid sensitivity showed that nocturnal hypoxemia in OSA is associated with increased potency of opioids [16,21]. This finding has also been shown in children [28,29]. Although the association of nocturnal hypoxemia and increased potency of opioids can initially seem paradoxical—based on clinical studies of hypoxemia and pain such as by Doufas et al. [2] and Terzi and Yilmaz [17]—it makes sense if one considers the role of endogenous (mu) opioid receptors. It is possible that increased pain causes upregulation of the endogenous opioid receptors to try to counteract hypoxemia, and the increase in opioid receptors translates to increased opioid sensitivity. In animal models, recurrent hypoxemia was shown to increase mu-opioid receptor binding and subsequent sensitivity to exogenous fentanyl [30,31]. However, in one animal model study by Wu et al. [32], the hypoxemia-mediated increase in endogenous opioid receptors also led to increased sensitivity to endogenous opioids, thus increasing pain tolerance, instead of decreasing it as in prior clinical studies.

Despite the mixed picture of the effect of OSA on pain sensitivity, it seems that CPAP therapy for OSA improves pain intensity and tolerance. This was shown in a

thought-provoking study by Khalid et al. [10] in which a cohort of patients with severe OSA (AHI > 30/h) were given CPAP and their finger withdrawal latency (FWL; a measure for pain tolerance) significantly increased both soon after CPAP implementation and after six to eight weeks of CPAP use. Interestingly, even two days after CPAP discontinuation, the FWL of the patients decreased to their pretreatment baseline. Similar findings were also shown in the only randomized study, among the studies we identified, by Onen et al. [22]. Elderly patients with OSA (AHI > 20/h) and no dementia were randomized in a crossover fashion to low- or high-CPAP treatment. Although both low- and high-CPAP treatment reduced the AHI and improved oxygenation, only the high-CPAP treatment improved pain tolerance. Interestingly, the high-CPAP treatment improved AHI and improved oxygenation (especially mean SaO2) to a larger extent than low-CPAP treatment, and this may explain the findings. In a prospective cohort, Kallweit et al. [24] found that 10% of the cohort fulfilled the criteria for migraines, and when CPAP was implemented, there was a significant reduction in migraine frequency (larger than the reduction topiramate prophylaxis would provide), severity, days off work, and acute pain medication intake by 12 months. Similarly, Goksan et al. [25] noted that after one month of treatment, morning headache had disappeared in 92% of the CPAP-treated patients.

In contrast to the above findings, Jaoude et al. [23] examined veterans with OSA on or off opioid treatment but analyzed mainly the opioid-treated group. Among this opioid-treated group, CPAP-adherent patients had less subjective pain compared with CPAP-nonadherent patients, without any difference in opioid dose. However, at 12-month follow-up, the CPAP-compliant group did not have any additional decrease in subjective pain. Nevertheless, the opioid dose of the CPAP-compliant group did decrease considerably (from 40 to 30 mg/d of opioid equivalents, unclear statistical significance). The opioid dose of the CPAP-noncompliant group decreased by a lesser amount (from 30 to 25 mg/d of opioid equivalents with unclear statistical significance) at 12-month follow-up. Furthermore, the opioid-treated population that Jaoude et al. examined had a quite different phenotype than prior studies—more psychiatric comorbidities, more chronic-type pain (many other studies have excluded chronic pain patients)—and may have undergone other nonmeasured treatments for the pain before 12-month follow-up using the various multidisciplinary Veteran Affairs pain control resources (such as steroid injections, nerve blocks, physical therapy, etc.).

Limitations

Due to the variability of the study design, study cohorts, and study outcomes, we were not able to perform a meta-analysis of the above studies or quantitatively delineate the prevailing trend of the various studies, and instead performed a qualitative analysis. Furthermore, we restricted our analysis to studies of adult patients and specifically patients with OSA (rather than other sleep disorders, such as insomnia). Unfortunately, we were unable to isolate the effect of nocturnal hypoxemia vs sleep fragmentation on pain outcomes.

Conclusions

Overall, there is an association of OSA and increased pain intensity or decreased pain tolerance. The variability in results may be due to 1) the differential predominance of hypoxemia vs sleep fragmentation among the OSA phenotype of the patient cohort [2] and 2) the different cohort characteristics in terms of psychiatric comorbidities and presence and/or type of chronic pain and opioid use. Further research is needed to specifically examine the likely differential effect of OSA on pain intensity among the different subgroups. It is reasonable to consider screening for OSA in patients with chronic pain, both because of the frequency of sleep-disordered breathing in patients with chronic pain and also because preliminary evidence shows that treatment with CPAP may indeed improve pain.

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