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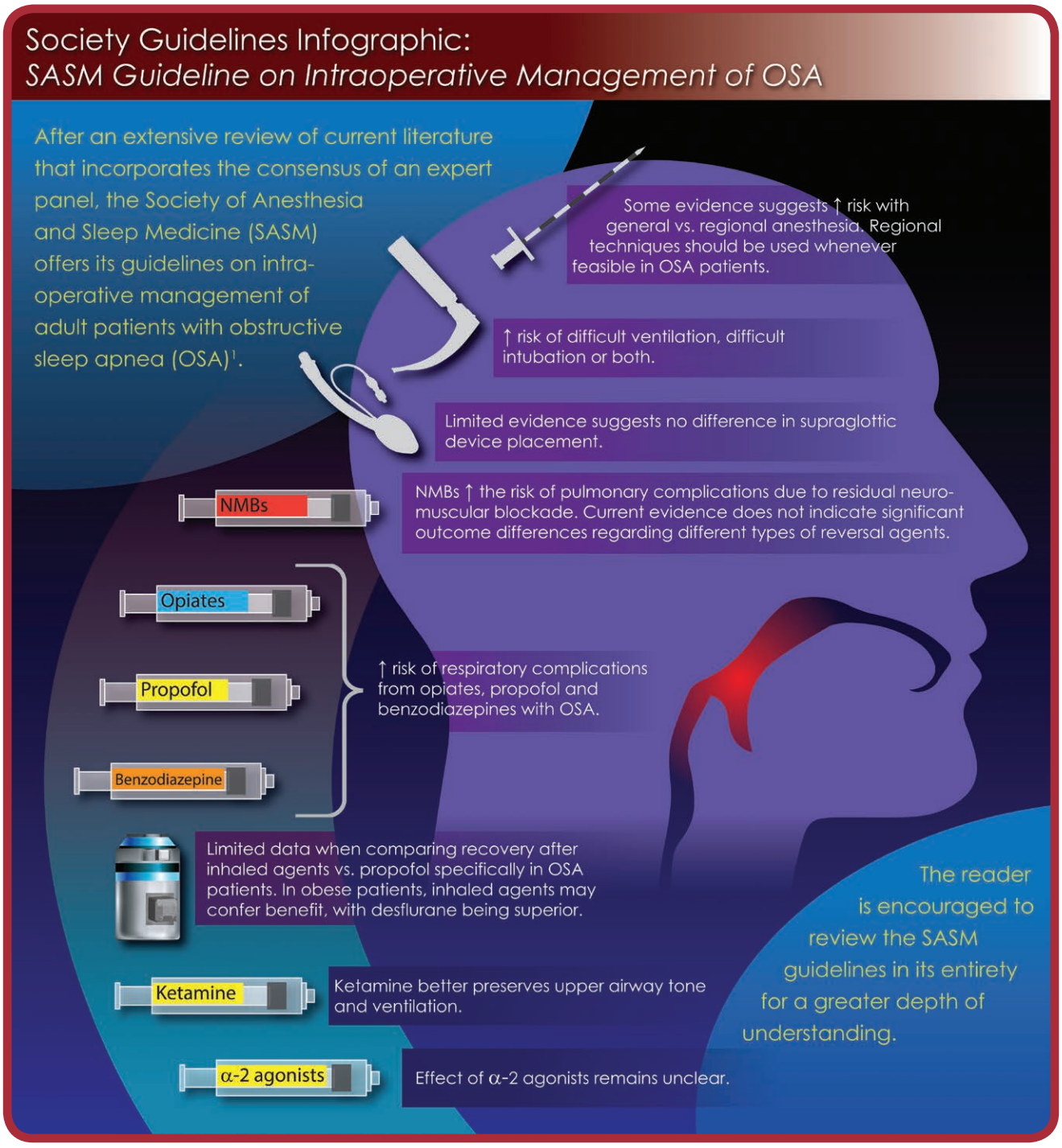


This infographic summarizes the consensus guideline for intraoperative management of patients with obstructive sleep apnea developed by a panel of experts on behalf of the Society of Anesthesia and Sleep Medicine. There continues to be a paucity of data with respect to outcomes derived from specific anesthetic drugs and/or techniques in patients with sleep apnea. As such, this guideline is meant to serve as a recommendation for management based on interpretation of available evidence as of this publication. The reader is strongly encouraged to review analysis of the society of the literature for a contextual perspective of this evidence.

The Infographic is composed by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine (n-nathan@northwestern.edu). Illustration by Naveen Nathan, MD.



IARS International Anesthesia Research Society

The author declares no conflicts of interest.

**REFERENCE**

1. Memtsoudis SG, Cozowicz C, Nagappa M, et al. Society of Anesthesia and Sleep Medicine guideline on intraoperative management of adult patients with obstructive sleep apnea. *Anesth Analg*. 2018;127:967–987.

# Opioids for Acute Pain Management in Patients With Obstructive Sleep Apnea: A Systematic Review

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The intrinsic nature of opioids to suppress respiratory function is of particular concern among patients with obstructive sleep apnea (OSA). The association of OSA with increased perioperative risk has raised the question of whether patients with OSA are at higher risk for opioid-induced respiratory depression (OIRD) compared to the general population. The aims of this systematic review were to summarize current evidence with respect to perioperative OIRD, changes in sleep-disordered breathing, and alterations in pain and opioid sensitivity in patients with OSA. A systematic literature search of studies published between 1946 and October 2017 was performed utilizing the following databases: Medline, ePub Ahead of Print/Medline In-process, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, PubMed—NOT-Medline and ClinicalTrials.Gov. Of 4321 initial studies, 40 met the inclusion criteria. The Oxford level of evidence was assessed. Overall, high-quality evidence on the comparative impact of acute opioid analgesia in OSA versus non-OSA patients is lacking. The current body of evidence is burdened by significant limitations including risk of bias and large heterogeneity among studies with regard to OSA severity, perioperative settings, outcome definitions, and the presence or absence of various perioperative drivers. These factors complicate an accurate interpretation and robust analysis of the true complication risk. Nevertheless, there is some consistency among studies with regard to a detrimental effect of opioids in the presence of OSA. Notably, the initial 24 hours after opioid administration appear to be most critical with regard to life-threatening OIRD. Further, OSA-related increased pain perception and enhanced opioid sensitivity could predispose patients with OSA to a higher risk for OIRD without overdosing. While high-quality evidence is needed, retrospective analyses indicate that critical, life-threatening OIRD may be preventable with a more cautious approach to opioid use, including adequate monitoring. (Anesth Analg 2018;127:988–1001)

While opioids are essential parts of acute pain management, their intrinsic nature of suppressing the respiratory system demands caution.[1] Traditionally, this issue has been of special concern in obstructive sleep apnea (OSA), which is marked by recurring episodes of hypopnea and apnea. In this context, opioids may potentially predispose affected patients to increased risk for opioid-induced respiratory depression (OIRD). The concern that OSA is a perioperative risk factor[2–4] has spurred the development of perioperative guidelines proposing measures to restrict opioid use in this patient population.[5,6] Robust scientific evidence, however, to directly demonstrate the merit of this concern and guide safe opioid practice in OSA is largely lacking.[7] Potential implications of perioperative opioid analgesia in OSA have mostly been studied in observational studies with the primary focus on respiratory outcomes.

The aim of this systematic review was to summarize current evidence with respect to perioperative outcomes among patients with OSA receiving acute opioid analgesia. This review was prepared as part of the Society of Anesthesia and Sleep Medicine taskforce for the Guideline on the Intraoperative Management of Adult Patients With Obstructive Sleep Apnea.

## METHODS

### Search Strategy

This review was planned and performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The systematic search was conducted to identify prospective and retrospective studies addressing the impact of acute opioid analgesia in the context of OSA (Figure). With the assistance of research librarians, the following databases were systematically searched for relevant studies (1946 to October 2017): Medline, ePub Ahead of Print/Medline In-process, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, PubMed-NOT-Medline, and ClinicalTrials.Gov.

Excerpt of utilized MESH key words: "obstructive sleep apnea" or "syndrome," "sleep disordered breathing," "obesity hypoventilation syndrome," "apnea," "hypopnea,"

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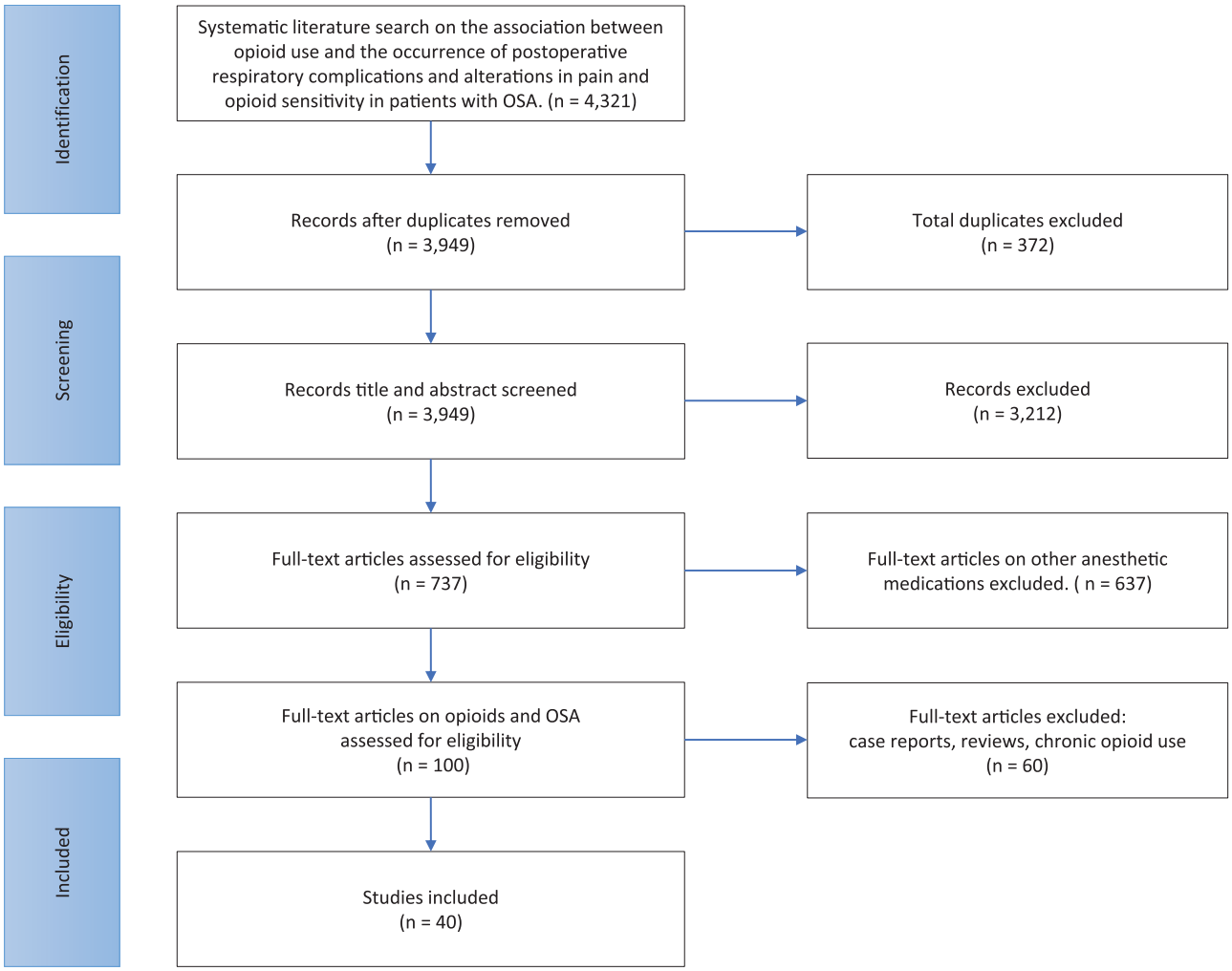


**Figure.** Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram. OSA indicates obstructive sleep apnea.

"postoperative period," "complications or outcome," "risk," "morbidity," "mortality or death," "anesthesia," "anesthetics," "opioid," "drug effects," "adverse effects," "adverse drug reactions," "abnormalities drug induced," "adverse drug events," "alfentanil," "buprenorphine," "butorphanol," "codeine," "fentanyl," "hydromorphone," "meperidine," "morphine," "oxycodone," "remifentanil," "sufentanil," "tramadol." Full search strategy is presented in Supplemental Digital Content, Appendix 1, http://links.lww.com/AA/C444.

Inclusion criteria are randomized controlled trials, prospective and retrospective observational studies reporting data on postoperative outcomes. Studies reporting outcomes in patients with OSA receiving short-term (perioperative or experimental opioid analgesia), rather than chronic opioid utilization. Within studies, OSA was identified by polysomnography (PSG), screening tools, medical history, chart diagnosis, International Classification of Disease (ICD)-9 codes from administrative and billing records, and clinical assessment.

Exclusion criteria are non-English language, nonhuman studies, studies not pertinent to patients with OSA or not reporting outcomes, studies addressing chronic opioid use, descriptive reviews, and case reports.

## Study Selection

Articles obtained from the search were reviewed and assessed by 2 authors independently (C.C., S.G.M.). Titles and abstracts were assessed according to inclusion and exclusion criteria by using the Covidence platform.[8] Subsequently, relevant studies selected for full-text review were analyzed and data were extracted. For completeness of all relevant references, a citation search was conducted manually from relevant articles. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart is presented in the Figure. Disagreements were resolved by consensus among the authors.

## Data Extraction

Data extracted included study ID, study year, study type, method of OSA identification, exposure definition, diagnosis of outcome (eg, perioperative outcomes and complications), patient characteristics, as well as the type of surgery and intervention. To assess the overall quality of evidence, the original intent was to utilize the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach including quantitative and qualitative analysis.[9] However, given the large heterogeneity of studies and lack of high-quality trials, quantitative meta-analysis and a

comprehensive conventional GRADE analysis were not feasible. Nevertheless, the risk of bias for every study in relation to the outcome of interest was assessed, and the Oxford level of evidence was reported.[10] Methods of OSA identification within studies are presented in Tables 1 and 2.

## POSTOPERATIVE RESPIRATORY COMPLICATIONS

OIRD is a serious concern, particularly in patients with OSA. In this context, Esclamado et al[14] were among the first to suggest an opioid dose-dependent increase in postoperative, particularly respiratory, complications in OSA (Table 1). In a retrospective analysis of PSG-tested patients undergoing surgery for OSA, patients with postoperative complications, had significantly lower nocturnal nadir oxyhemoglobin saturations ($SpO_2$ 66% vs 79%) and higher apnea/hypopnea indices (AHI of 75 vs 57 events per hour of sleep) preoperatively and had received greater amounts of opioids intraoperatively. These data, therefore, indicated that greater OSA severity and increased intraoperative opioid use may present drivers of respiratory complications.[14]

Blake et al[12] suggested a potentially greater detrimental impact of opioids in patients with OSA, which was established by body mass index, medical history, upper airway, and physical examination,[51] compared to controls. Patients at OSA risk experienced significantly more postoperative obstructive apneas and hypopneas, more severe hypoxemia, and a higher percentage of sleep duration at $SpO_2$ levels <90%.[12]

While perioperative morphine dose predicted central apneas regardless of OSA status, patients at OSA risk experienced hypoxemia of significantly greater severity, predominantly due to obstructive respiratory events.

An association between oxyhemoglobin desaturation and opioid use was also reported by Bolden et al[13] in unadjusted data. Odds for postoperative hypoxia were increased by >10-fold in patients with OSA identified by PSG and medical history when using intravenous or oral opioids compared to patients not treated with opioids ($P < .001$, respectively). Although opioids depress respiration in the general population and with common postoperative hypoxemia,[52] it is worth noting that desaturation in this analysis was not reliably prevented by continuous positive airway pressure (CPAP) therapy.[13]

In contrast, Khanna et al[17] found that OSA determined by STOP-BANG did not predict hypoxemia during recovery from noncardiac surgery. Although in the obese population with a high OSA prevalence, the occurrence of postoperative oxyhemoglobin desaturation and other respiratory complications after opioid consumption is common, studies focusing on obesity could not establish OSA as an independent driver of postoperative hypoxemia in this setting.[11,25,53] While these reports may be affected by the wide use of CPAP treatment, possibly diminishing increased respiratory risk,[53] comorbidities associated with OSA, such as obesity and diabetes, are potential confounders when it comes to the occurrence of postoperative complications.[54]

A recent large-scale population-based analysis of >107,000 ICD-9 code-identified patients with OSA undergoing orthopedic surgery showed that increased perioperative opioid prescription was associated with greater odds for gastrointestinal complications, prolonged length of stay, and increased cost, while no effect for myocardial infarction, thromboembolic complications, or renal failure was observed.[20] In patients with increased opioid dose, however, reduced odds for pulmonary complications were observed, which was potentially indicative of higher use of preventive measures and surveillance in patients with OSA receiving higher opioid levels.[20] More insight was provided in a separate analysis by the same investigators, presenting findings in the general surgical population of the same dataset.[55] When comparing the occurrence of respiratory and other types of postoperative complications between patients with and without OSA, the incidence of pulmonary (2.49% vs 1.83%), cardiac (2.81% vs 0.23%), gastrointestinal (0.45% vs 0.33%), renal (3.47% vs 1.83%), and thromboembolic (0.41% vs 0.33%) complications was significantly higher in patients with OSA versus those without OSA at similar opioid dose levels.[17,53] In sum, these data indicate a higher perioperative complication risk in OSA, while the higher prevalence of respiratory complications at baseline may not per se further increase within conventional opioid dose limits. The contribution of other factors besides sheer opioid dosage, such as OSA severity and opioid sensitivity, is also indicated in studies reporting that a significant amount of life-threatening or fatal events occurs at relatively low opioid consumption.[18,21,23]

In this context, a number of retrospective observational analyses have studied the occurrence of life-threatening anesthesia-related respiratory events in association with perioperative opioid analgesia and the presence of OSA. OSA is typically identified by patient records and ICD-9 codes in these studies.

Using naloxone as a surrogate marker for severe OIRD, 2 matched control studies by Weingarten et al[24,26] demonstrated that the postoperative requirement for naloxone was significantly associated with OSA and higher opioid use. This finding was supported by Etches,[15] who showed that in patient-controlled analgesia (PCA) with morphine, postoperative severe respiratory depression with rescue naloxone requirement occurred in 0.5% of cases, while OSA was reported as a driver. Melamed et al[19] also found that severe postoperative respiratory failure with ICU requirement after elective orthopedic surgery was associated with higher intraoperative opioid utilization and established OSA as an independent risk factor after multivariable analysis.

Ramachandran et al[21] demonstrated that the odds for life-threatening respiratory failure during postoperative parenteral opioid analgesia, including unresponsiveness, hypoxic or apneic conditions requiring naloxone, endotracheal intubation, or cardiopulmonary resuscitation, were increased by >15-fold in patients with OSA, while a similar complications risk was also observed in patients with postoperative acute renal failure. Moreover, OSA was a prevalent factor among fatalities during concurrent opioid therapy. Among cases of critical respiratory complications, the utilized opioid dose was low, while a tendency for higher pain scores was found. These observations may support the notion of increased opioid sensitivity in OSA,[1,44] possibly lowering the threshold for OIRD in a subset of patients. Ramachandran et al[22] recently corroborated their previous findings in a new analysis by showing that high OSA risk, assessed by the Perioperative Sleep Apnea Prediction (PSAP) score, was significantly associated with the requirement for postoperative endotracheal intubation.

**Table 1. Outcome Studies**

| Study | Study Design | Population | OSA Assessment | Procedure | Outcomes | Conclusion | Effect | Oxford LOE |
|---|---|---|---|---|---|---|---|---|
| Postoperative respiratory complications | | | | | | | | |
| Ahmad et al (2008)[11] | Prospective/ observational | OSA/ non-OSA N = 40 | PSG | Bariatric surgery, morphine PCA | 24-h postoperative oxygen saturation | OSA did not increase the risk for postoperative hypoxemia | Opioid effect not detrimental | 3 |
| Blake et al (2008)[12] | Prospective/ observational | OSA/ non-OSA N = 63 | History, BMI, upper airway examination | Surgery, postoperative analgesia | Respiratory obstructive events and oxygen desaturation | Prediction of central apneas by cumulative opioid dose; OSA risk factor for obstructive events and desaturation | Opioid effect detrimental—dose gradient | 3 |
| Bolden et al (2007)[13] | Observational/ letter | OSA N = 438 | PSG, clinical history | Various surgeries, opioid analgesia | Oxygen desaturation | Opioid use associated with postoperative desaturation | Opioid effect detrimental | 3 |
| Esclamado et al (1989)[14] | Retrospective | OSA N = 136 | PSG | OSA surgery | Pulmonary complications, death | Opioid use associated with complications. OSA severity associated with complications | Opioid effect detrimental—dose gradient | 4 |
| Etches et al (1994)[15] | Retrospective | OSA/ non-OSA N = 8/1600 | Database/charts | PCA | Factors associated with severe respiratory depression | OSA risk factor for respiratory depression in PCA | Opioid effect detrimental | 4 |
| Fouladpour et al (2016)[16] | Retrospective | OSA N = 24 | Patient records in legal databases | Various surgeries | Perioperative complications leading to lawsuit | Respiratory arrest and difficulties in airway management were most common complications; opioids played a role in 38% of the cases | Opioid effect detrimental | 4 |
| Khanna et al (2016)[17] | Prospective/ observational | 630 | STOP-BANG questionnaire | Noncardiac surgery | Oxygen desaturation | STOP-BANG score not associated with hypoxemia | - | 4 |
| Lee et al (2015)[18] | Retrospective | OSA/ non-OSA N = 92 | Patient records | Anesthesia—acute pain management | Acute claims of opioid-induced respiratory depression | 25% of national cases of opioid-induced respiratory depression claims identified with OSA | Opioid effect detrimental in OSA | 4 |
| Melamed et al (2016)[19] | Retrospective: case-control | OSA/ non-OSA N = 204 | Patient records | Orthopedic surgery | Respiratory decompensation requiring ICU | OSA and higher opioid use independently associated with respiratory complications | Opioid effect detrimental—dose gradient | 4 |
| Mörwald et al (2017)[20] | Retrospective | OSA N = 107,610 | Patient records/ ICD-9 codes | THA, TKA | Postoperative complications | Higher opioid dose associated with increase in gastrointestinal complications, LOS, and cost | Opioid effect detrimental—dose gradient | 3 |
| Ramachandran et al (2011)[21] | Retrospective | OSA/ non-OSA N = 32 | Patient records | Various surgeries, PCA | Critical respiratory events | OSA driver of critical respiratory events in PCA | Opioid effect detrimental | 4 |
| Ramachandran et al (2017)[22] | Retrospective | OSA N = 108,479 | PSAP score | Various surgeries | Postoperative intubation | OSA and high morphine dose driver of early postoperative. respiratory complications | Opioid effect detrimental—dose gradient | 4 |
| Subramani et al (2017)[23] | Retrospective Case series | OSA N = 60 | Patient records | Various surgeries | Death, near-death events, critical respiratory events | Opioids among perioperative risk factors for death and near-death events in patients with OSA | Opioid detrimental effect | 4 |
| Weingarten et al (2015)[24] | Retrospective Case control | OSA/non-OSA N = 134 | Patient records | Naloxone | Opioid-induced respiratory depression | OSA driver of respiratory depression requiring naloxone | Opioid effect detrimental—dose gradient | 4 |

(*Continued*)

**Table 1. Continued**

| Study | Study Design | Population | OSA Assessment | Procedure | Outcomes | Conclusion | Effect | Oxford LOE |
|---|---|---|---|---|---|---|---|---|
| Weingarten et al (2015)[25] | Retrospective Case control | OSA/ non-OSA N = 781 | Patient records, PSG, overnight oximetry, Flemons criteria | Bariatric surgery, postoperative analgesia | Respiratory complications, anesthesia recovery time | OSA not identified as risk factor for respiratory complications and prolonged anesthesia recovery | Opioid effect detrimental—but OSA not identified as an independent risk factor during CPAP | 3 |
| Weingarten et al (2016)[26] | Retrospective Case control | OSA/ non-OSA N = 413 | Patient records | Naloxone | Drivers of naloxone requirement | OSA driver of respiratory depression requiring naloxone | Opioid effect detrimental—dose gradient | 4 |
| Sleep architecture, sleep-disordered breathing, and ventilatory chemoreflexes | | | | | | | | |
| Bernards et al (2009)[27] | RCT | OSA N = 19 | PSG | No surgery Experimental | PSG parameter, oxygen desaturation | Remifentanil increased central apneas | Opioid effect detrimental | 2 |
| Chung et al (2014)[28] | Prospective/ observational | OSA/ non-OSA N = 376 | PSG | Various surgeries, PSG | PSG parameters | Cumulative 72-h opioid dose associated with severity of postoperative AHI | Opioid effect detrimental—dose gradient | 3 |
| Wang et al (2013)[29] | Prospective/ observational | OSA N = 10 | PSG | PSG, single-dose oral morphine | Ventilation, PSG parameters | OSA single dose may paradoxically improve OSA through modulating chemoreflexes | Opioid effect positive | 3 |
| Neuraxial opioid administration in OSA | | | | | | | | |
| Ladha et al (2017)[30] | Prospective observational | OSA/ non-OSA N = 721 | Berlin Questionnaire | Intrathecal morphine Cesarean delivery | Blood oxygen desaturation | OSA increased odds for blood oxygen desaturation | OSA a risk factor for hypoxemia after intrathecal morphine | 3 |
| Orlov et al (2013)[31] | Systematic review including references[73–77] | OSA N = 121 | PSG, clinical history, questionnaires | Neuraxial opioid administration | Cardiorespiratory complications | Incidence of major cardiorespiratory complications 4.1% after neuraxial opioid use | Opioid effect detrimental, true incidence not quantifiable | 4 |
| Thompson et al (2017)[32] | Retrospective observational | OSA/ non-OSA THA/TKA N = 990 | Patient records, STOP-BANG | Intrathecal morphine administration | Pulmonary complications, LOS | Adverse events were not associated with OSA status in intrathecal morphine administration | Intrathecal morphine showed no increased risk for complications in OSA | 3 |
| Zotou et al (2014)[33] | RCT | OSA/ non-OSA N = 48 | PSG, clinical assessment | Morphine loading in levobupivacaine PCEA with morphine Bariatric surgery | Pain, opioid and levobupivacaine consumption, blood oxygen saturation, ambulation, and return of bowel function | Morphine loading associated with no improvement of pain, no reduction in analgesic requirement, longer return to bowel function and delayed ambulation | No beneficial effect of morphine loading | 2 |
| Opioid dose reduction in OSA | | | | | | | | |
| Abdelmageed et al (2011)[34] | RCT | OSA N = 39 | PSG | UPPP | Opioid consumption, pain complications | Dexmedetomidine reduced opioid consumption by more than 50%—this in turn significantly reduced the incidence of respiratory obstruction in OSA | Opioid effect detrimental—dose gradient | 2 |
| Blake et al (2009)[35] | RCT | OSA N = 62 | BMI and clinical symptoms History and physical examinations | Elective surgery | Respiratory complications | Central apneas and adverse respiratory events per hour related to postoperative morphine dose in OSA | Opioid effect detrimental—dose gradient | 2 |

(*Continued*)

**Table 1. Continued**

| Study | Study Design | Population | OSA Assessment | Procedure | Outcomes | Conclusion | Effect | Oxford LOE |
|---|---|---|---|---|---|---|---|---|
| Lee et al (2007)[36] | RCT | OSA N = 90 | PSG | UPPP | Complications, pain, postoperative discomfort, patient satisfaction | IV ketorolac reduced pain and was more effective in increasing patient comfort; Ketorolac was noninferior compared to mefenamic/meperidine | Opioid effect not detrimental | 2 |
| Pain management after uvulopalatopharyngoplasty in OSA | | | | | | | | |
| Huang et al (2009)[37] | RCT | OSA N = 12 | PSG | UPPP | Complications, pain, clinical global impression in severity and improvement | Transnasal butorphanol is safe and alleviates wound pain after UPPP | Positive effect of nasal butorphanol | 2 |
| Madani et al (2000)[38] | Prospective/ observational | OSA N = 20 | UPPP clinical | UPPP | Safety, pain | Pain reduction, number of oral medications reduced with butorphanol | Positive opioid effect | 3 |
| Yang et al (2015)[39] | RCT | OSA N = 260 | PSG | UPPP | Pain scores, Bruggmann comfort scale, postoperative cognitive dysfunction | Preemptive intranasal butorphanol safe and effective, reduction of pain, postoperative cognitive dysfunction and use of postoperative analgesics | Positive effect of nasal butorphanol | 2 |

Abbreviations: BMI, body mass index; ICD, international classification of disease; IV, intravenous; LOE, level of evidence; LOS, length of stay; OSA, obstructive sleep apnea; PCA, patient-controlled analgesia; PCEA, patient-controlled epidural analgesia; PSAP, perioperative sleep apnea prediction score; PSG, polysomnography; RCT, randomized controlled trial; STOP-BANG, snoring, tiredness, observed apnea, blood pressure, body mass index, age, neck circumference and gender; THA, total hip arthroplasty; TKA, total knee arthroplasty; UPPP, uvulopalatopharyngoplasty.

Focusing specifically on postoperative death or near-death events in patients with OSA, Subramani et al[23] recently analyzed 60 case reports.[23] Besides factors including undiagnosed or untreated OSA and lack of monitoring, opioids and sedatives were among the risk factors for postoperative death or near-death events in OSA. Furthermore, consistent with Ramachandran et al,[21] the majority of affected patients had consumed typical or less than typical doses of opioids, suggesting increased opioid sensitivity as a possible mechanism.[1,7]

A closed claims analysis by Lee et al[18] identified 92 cases of postoperative OIRD in the National Anesthesia Closed Claims Project database. Consistent with previous studies, most complications occurred within 24 hours postoperatively,[19,21] the majority resulting in severe brain damage or death, while 97% of the cases were deemed preventable. Of all identified OIRD claims, 25% were related to OSA. PCA and neuraxial analgesia were the most common modes of opioid analgesia, while no claims were associated with peripheral nerve blocks or catheters. About 50% of the cases received opioids by using >1 modality. Thus, nearly 50% had a continuous background opioid infusion in addition to PCA, while excessive opioid dosages were administered in only a minority of cases (16%).[18] Perioperative respiratory complications directly related to OSA are also increasingly recognized in the legal arena, as shown by Fouladpour et al[16] in cases of adverse postoperative outcome that resulted in lawsuits. More than half of the cases occurred in an unmonitored setting, and in 38% of cases opioids played a role. These cases were most likely to be associated with death as the outcome.[16]

In summary, these studies support the heightened level of concern regarding perioperative opioid consumption in patients with OSA (Table 1). Evidence indicates a particularly increased risk within the first 24 hours of opioid utilization, while notably, life-threatening OIRD may not only occur in excessive or high opioid utilization. This finding suggests a potential impact of other additional contributors, such as OSA severity and possibly altered opioid sensitivity and pain perception.[1] In the absence of high-quality randomized evidence to robustly verify this notion, adequate postoperative monitoring in OSA during opioid therapy initiation could possibly prevent life-threatening OIRD.

## POSTOPERATIVE SLEEP ARCHITECTURE AND SLEEP-DISORDERED BREATHING

Patients with OSA are known to postoperatively experience a significant deterioration in sleep architecture and sleep-disordered breathing, which is sustained for about 7 days and reaches its peak severity on postoperative night 3.[43] These postoperative changes reflected in decreased sleep efficiency and increased AHI can also occur in the general population but at a lower incidence and with blunted severity.[43] The exact underlying pathophysiology has not been established so far[56,57]; however, potential drivers may include postoperative rebound of nocturnal rapid eye movement sleep (REM), OSA severity, and perioperative complications.[56]

Given the postoperative risk resulting from deteriorations in sleep architecture and sleep-related breathing, Chung et al[28] investigated possible causes by enrolling 376

**Table 2. Pain Perception and Opioid Sensitivity in OSA**

| Study | Study Design | Population | Procedure | Outcomes | Conclusion | Effect | Oxford LOE |
|---|---|---|---|---|---|---|---|
| Brown et al (2006)[40] | Prospective blinded | OSA Pediatric N = 22 | Adenotonsillectomy | Arterial oxygen saturation, morphine dose | Arterial oxygen saturation <85% associated with half the total morphine dose required postoperatively | Hypoxemia associated with increased analgesic sensitivity to morphine | 3 |
| Brown et al (2004)[41] | Retrospective | OSA Pediatric N = 46 | Adenotonsillectomy | Arterial oxygen saturation, morphine dose | Age and preoperative blood oxygen saturation individually or in combination exhibited a significant correlation to the morphine dose required for analgesia | Hypoxemia reduced morphine requirement | 3 |
| Brown et al (2003)[42] | Retrospective | OSA/ non-OSA N = 54 | Urgent adenotonsillectomy | Respiratory complications, arterial oxygen saturation levels | Severe OSA and preoperative saturation nadir <80% is a risk factor for respiratory complications | Preoperative hypoxemia increased perioperative risk | 3 |
| Chung et al (2014)[43] | Prospective | N = 58 | Various surgeries | Arterial oxygen saturation | Postoperatively, sleep architecture disturbed, AHI increased | No association between hypoxemia and opioid analgesic effect | 3 |
| Doufas et al (2013)[44] | Prospective | OSA/ non-OSA N = 48 | Pain test | Heat and cold pain thresholds and tolerances, hypoxia marker, proinflammatory mediators<br>PSG descriptors | Nocturnal hypoxemia, serum hypoxia marker, and proinflammatory mediators associated with enhanced opioid potency.<br>Serum hypoxia marker associated with hypoalgesia | Opioid effect increased hypoalgesia | 3 |
| Doufas et al (2013)[45] | Retrospective | OSA N = 634 | PSG | Pain, blood oxygen saturation, genotype data | Minimum nocturnal saturation of 75%, approximately doubled the odds for pain | Hypoxia associated with increased pain | 3 |
| Khalid et al (2011)[46] | Prospective | Severe OSA N = 12 | PSG and heat stimulus | AHI, sleep continuity, finger withdrawal latency | CPAP treatment reduces pain sensitivity in OSA | Pain perception increased | 3 |
| Sadhasivam et al (2012)[47] | Prospective | OSA/non-OSA Pediatric N = 194 | Adenotonsillectomy | Postoperative pain, postoperative opioid requirement | African American children experienced more pain measured by postoperative opioid requirement | Unequal perioperative pain and opioid-related adverse effects by race | 3 |
| Sanders et al (2006)[48] | Prospective | OSA/non-OSA Pediatric N = 82 | Adenotonsillectomy | Postoperative complications | Higher respiratory disturbance index in OSA associated with higher morphine use | Altered analgesic sensitivity | 3 |
| Smith et al (2009)[49] | Prospective | OSA/non-OSA N = 35 | PSG | Pain | Sleep-disordered breathing associated to hypoalgesia | Pain perception decreased | 3 |
| Turan et al (2015)[50] | Retrospective | OSA/non-OSA N = 218 | Bariatric surgery | Arterial oxygen saturation, opioid consumption | Time spent in hypoxemia inversely associated with opioid consumption | Opioid sensitivity increased with hypoxemia | 3 |

Abbreviations: AHI, apnea/hypopnea indices; CPAP, continuous positive airway pressure; LOE, level of evidence; OSA, obstructive sleep apnea; PSG, polysomnography.

elective surgery patients to undergo pre- and postoperative PSG.[43] Results revealed a modest but significant association between cumulative 72-hour opioid dose and the severity of postoperative AHI. Moreover, increased postoperative central apnea index was associated with general versus regional anesthesia and male sex, suggesting an impact of general anesthesia drugs. The finding of an opioid dose-dependent impact on postoperative AHI is consistent with Blake et al,[12] who found that opioid dose predicted postoperative central apneas in patients with and without OSA. OSA-related postoperative exacerbation of sleep-disordered breathing may therefore present a detrimental risk, potentially augmented by opioid effects in a dose-dependent manner.[28]

Based on the concern of opioid-related worsening of sleep-related respiratory insufficiency in OSA, Bernards et al[27] conducted a nonsurgical, randomized placebo-controlled study among 19 PSG-confirmed patients with OSA. Patients received an additional sleep study during randomization to either saline or remifentanil infusion. Similar to Chung et al,[28] significant changes in sleep architecture as a result of opioid use were revealed. Remifentanil markedly increased stage 1 sleep, decreased REM sleep, increased arousals from sleep, and decreased sleep efficiency. Moreover, remifentanil conferred an increase in the incidence of central apneas, while reducing the number of OSAs, probably through reduced REM sleep. Moreover, arterial oxyhemoglobin saturation was also significantly lower in OSA patients with remifentanil infusion.

Overall, because OSA was worsened during remifentanil infusion, results indicated that the primary risk may perhaps arise from central rather than obstructive apnea, which may render ineffective attempts to eliminate OIRD using CPAP therapy.[27] Notably, about 15% of CPAP-naïve patients with OSA develop central apneas (complex apnea) with the initiation of CPAP treatment.[27,58] Despite the small sample size, Bernards et al[27] provide largely lacking high-quality evidence on the impact of opioids in OSA.[27,59]

Wang et al[29] presented contrasting findings among 10 mild to moderate patients with OSA undergoing PSG before and after experimental administration of a single oral dose of 30 mg controlled- release morphine. Morphine plasma concentrations, although highly variable among subjects, were positively associated with $CO_2$ ventilatory recruitment threshold (ie, the level of $CO_2$ required to reinstate rhythmic breathing after hyperventilation-induced hypocapnia, when rebreathing of $CO_2$ is initiated) and, paradoxically, negatively associated with the fraction of sleep time spent at $SpO_2$ <90% (ie, morphine administration, in this context, decreased hypoxemia during sleep), compared to baseline. These results would suggest that, rather than worsening sleep-disordered breathing, a single oral dose of morphine could paradoxically improve oxygenation through modulating chemoreflexes in OSA. However, these findings are limited by the factors of large (30-fold) interindividual variability in morphine plasma concentrations, small sample size, limited OSA severity, and use of oral, controlled-release morphine (Table 1).[60]

## PAIN PERCEPTION AND OPIOID ANALGESIC POTENCY IN OSA

Inherent features of OSA, including recurrent hypoxia and chronic sleep fragmentation, have been suggested to interact with pain processing and sensitivity to opioid analgesia.[7,40,61] Both chronic recurrent hypoxia and sleep disruption appear to enhance sensitivity to pain, while hypoxia may also potentiate opioid analgesic effects (Table 2).[1]

### Recurrent Hypoxia

The idea of changes in pain and opioid sensitivity was originally sparked in pediatric patients with OSA. In 2 independent analyses, Brown et al[40,41] found that children with preoperative recurrent hypoxemia (nocturnal nadir $SpO_2$ <85%) required half the dose of morphine postoperatively compared to children who were less or not hypoxemic ($SpO_2$ ≥85%). This finding was consistent in children living at high altitudes under chronic sustained hypoxia.[62] Based on earlier animal experiments, these observations were attributed to upregulation of central opioid receptors triggered by recurrent hypoxia,[63,64] while 2 other pediatric prospective studies could not confirm these findings.[47,48] Sadhasivam et al[47] suggested that African American versus Caucasian children with OSA presented with more pain requiring a higher dose of morphine for postoperative analgesia, while Sanders et al[48] also reported higher postoperative morphine use in children with OSA.

In adult patients with OSA, Doufas et al[44] applied an experimental pain paradigm and found that nocturnal hypoxemia potentiated the analgesic effect of a μ-opioid agonist. Furthermore, lower nocturnal nadir $SpO_2$ and insulin-like growth factor binding protein-1, a serum marker of hypoxia,[65] predicted increased sensitivity to opioid analgesia, while the augmented potency of opioid analgesic effect was also predicted by serum levels of proinflammatory mediators.[44] This finding suggests the involvement of inflammatory activity,[44,66] which appears particularly important given that OSA represents a chronic inflammatory condition with intermittent hypoxia as a causal protagonist. Moreover, inflammatory mediators associated with these processes, such as interleukin-6, interleukin-1, and tumor necrosis factor-α, have been shown to confer both hyperalgesia[67] and increased analgesic opioid potency.[44] Although apparently contradictory at the surface, evidence suggests that these developments are not mutually exclusive.[1,50]

In a large retrospective analysis of prospectively collected data (Cleveland Family Study), Doufas et al[45] demonstrated that intermittent hypoxia was significantly associated with increased pain in patients with OSA; these findings were independent of sleep fragmentation and systemic inflammation, as measured by PSG and serum cytokines.[45] More specifically, a decrease in the nocturnal nadir $SpO_2$ from 92% to 75% approximately doubled the odds for reporting pain in patients with OSA, rendering recurrent hypoxemia a potential risk marker for enhanced pain behavior. However, Turan et al[50] showed that opioid consumption after bariatric surgery was significantly reduced in OSA patients with longer sleeping periods and nocturnal intermittent hypoxia.[50]

### Chronic Sleep Fragmentation

Next to hypoxia, chronic sleep fragmentation has been implicated in enhancing pain behavior, as shown in patients with insomnia due to temporomandibular joint disorder and patients with primary insomnia who demonstrated

hyperalgesia.[49,68] In contrast, patients with OSA with temporomandibular joint disorder presented with hypoalgesia to experimental pain.[49] Evidence from burn patients also supports an interaction between insomnia and pain, demonstrating that in hospitalized patients, insomnia symptoms and poor sleep quality were linked to higher pain intensity during the day.[69,70] Consistent with these findings, Khalid et al[46] showed that CPAP treatment, which improved ventilation and sleep continuity, reduced pain sensitivity in patients with OSA.

### Perioperative Implications

Ultimately, enhanced pain perception and augmented opioid potency modulated by intermittent hypoxia[7,45,66] could be critical in the perioperative care of patients with OSA, as suggested by numerous investigators, including Brown et al.[41,42,57] This group reported an association between preoperative hypoxemia severity and respiratory complications in pediatric patients with OSA.[42] Accordingly, adopting a precautionary line of practice, the American Society of Anesthesiologists (ASA) has encouraged adjusting opioid dosing in pediatric patients who demonstrate hypoxemia.[5]

Therefore, the apparently poor association between AHI and hypoxia severity[71] may indicate that AHI as a measure of OSA severity may not be optimal for the estimation of perioperative risk in adults,[6] possibly rendering $SpO_2$ a more accurate measure for perioperative risk stratification.[1]

In conclusion, evidence supporting changes in pain and opioid sensitivity[7,11,40,41,44,46,47,49,50,72] imply that opioid and analgesic requirements could be substantially lower in patients with OSA. Therefore, careful titration of opioid analgesia and postoperative monitoring tailored to the individual risk profile seems prudent. More research, however, is needed to robustly establish drivers of pain and opioid sensitivity in OSA.

## NEURAXIAL OPIOID ADMINISTRATION IN OSA

Evidence on the impact and safety of neuraxial opioid administration in patients with OSA is rather scarce and heterogeneous, while the differential role of either spinal or epidural opioid administration remains unstudied (Table 1).

In a systematic review including 5 studies, Orlov et al[31] estimated an incidence of 4.1% for cardiorespiratory complications in surgical patients with OSA undergoing neuraxial anesthesia with opioids. However, the authors emphasized significant limitations related to this estimate, based on heterogeneity, imprecision, and lack of information on concomitant medications.[31,73–77]

Only a few other studies have investigated the safety of neuraxial opioid administration in the context of OSA.[30,32,33] One randomized trial found that increased neuraxial opioid administration by intraoperative morphine loading did not improve postoperative analgesia but rather delayed ambulation and recovery in bariatric surgery.[33] Others showed that in parturients receiving intrathecal morphine for cesarean delivery, OSA diagnosis by Berlin questionnaire and obesity were independently associated with increased odds for a $SpO_2$ <90%.[30] In contrast, among patients with joint arthroplasty receiving a multimodal pain regimen, including neuraxial anesthesia, no correlation was found between OSA (identified by patient records and screening questionnaires) and pulmonary complications after intrathecal morphine analgesia, potentially indicating a benefit of multimodal analgesia.[32]

Overall, as suggested by the ASA, a potentially greater risk for neuraxial OIRD in patients with OSA should be considered, with special attention given to signs of adverse effects after opioid administration.[78] Preventive measures of OIRD after neuraxial opioid administration include careful decisions regarding opioid dose, type, and administration modality, such as single-injection neuraxial or continuous epidural opioids versus parenteral opioids, neuraxial fentanyl or sufentanil administration versus morphine, or continuous neuraxial opioids versus parenteral opioids. In any case, patients receiving neuraxial opioids should be continuously monitored for adequacy of ventilation (eg, respiratory rate, depth of respiration), oxygenation (eg, pulse oximetry when appropriate), and level of consciousness.[78]

## POSTOPERATIVE MONITORING TO PREVENT OIRD

Postoperative monitoring may allow for early detection of potentially dangerous or even fatal events. It may also enable risk stratification of patients with OSA in need of extended care.[79,80]

Besides the effect of opioids and sedatives on upper airway muscle tone and ventilation responsiveness, lack of monitoring has been found to be a risk factor or cause for critical life-threatening and fatal postoperative outcome in OSA.[18,21,23] Particularly, patients with OSA with a high arousal threshold appear to be susceptible to OIRD and respiratory arrest in an unmonitored environment.[23,81] Postoperative complications directly related to OSA are also increasingly recognized in the legal arena, with inadequate monitoring deemed causative in a significant proportion.[16,54,82]

Postoperative patients with confirmed or suspected OSA may, according to some reports, be admitted to a fully monitored care environment with continuous ventilatory and cardiac surveillance.[83,84] The ASA recommends continuous pulse oximetry monitoring and supplemental oxygen use after discharge from the recovery room in patients at increased risk of respiratory compromise from OSA until baseline oxygen saturation can be maintained at room air.[5,85] This can be facilitated in critical care units, in stepdown units, or on routine hospital wards by telemetry and observation.[5,86] The ASA guidelines also recommend nonsupine positioning during recovery and the consideration of CPAP or noninvasive positive pressure ventilation in severe airway obstruction.[5] Monitoring recommendations, however, are independent of CPAP use, given the uncertainty of compliance.[86] Other critical factors in the context of reducing the postoperative risk for OIRD include the avoidance of premature extubation[87] and repeated assessment of sedation levels.[18] While continuous monitoring in OSA is strongly supported,[13,84] population-based data indicate limited implementation of postoperative oximetry and supplemental oxygen therapy on a national level.[88] This could reflect the scarcity of institutional policies,[89,90] challenges in clinical feasibility, and resource availability, as well as lack of evidence on the efficacy of costly monitoring interventions. For instance, despite the conventional use of pulse oximetry, a significant body of evidence supports the use of capnography, measuring end-tidal carbon dioxide partial pressure as a more

accurate and sensitive indicator for respiratory depression.[84,91] Nevertheless, postoperative capnography use is relatively rare given the advanced training requirement for accurate interpretation in the absence of a secured airway.[82,92] New technologies, such as a recently presented impedance-based, noninvasive respiratory volume monitor with accurate real-time measurement of postoperative ventilation parameters could emerge as clinically feasible for OIRD prevention in OSA.[93] Overall, health care institutions aim to avoid patient harm with appropriate utilization of resources. While prevention of complications through monitoring may be less costly per patient compared to complication management, it should be noted that current preoperative OSA screening tools have high false-positive rates, potentially promoting the waste of resources as systems allocate funds to enhanced monitoring and treatment of patients truly at increased risk for OSA-related complications.[82] Moreover, poor specificity of monitoring alarms can lead to hazardous alarm fatigue, labor burden, and patient unrest.[82] Therefore, further research is critical to allow accurate risk stratification of suspected or verified patients with OSA at genuine postoperative risk and to provide evidence-based guidance on the optimal level and duration of individual monitoring requirements.[23,82,84] Nevertheless, the risk of postoperative opioid use[35] must be carefully weighed against the benefits of pain relief on an individual basis.[5,84,94]

## OPIOID DOSE REDUCTION IN OSA

Opioid effects in patients with OSA have also been indirectly demonstrated by studies reporting outcomes in patients randomized to opioid dose-reducing interventions (Table 1).

Abdelmageed et al[34] randomized 39 PSG-confirmed patients with OSA undergoing uvulopalatopharyngoplasty to dexmedetomidine versus placebo in addition to postoperative intravenous morphine titration and subsequent PCA. Patients with dexmedetomidine required 53% less morphine in the first 24 hours, expressed significantly lower pain scores, and experienced a longer time to first analgesic request. Concurrent with opioid dose reduction, dexmedetomidine use caused a significantly lower incidence of oxyhemoglobin desaturation and bradypnea. While supporting the use of dexmedetomidine,[95–97] these findings, in particular, indicate an opioid dose-dependent detrimental outcome on respiration in patients with OSA.[34]

An association between opioid use and impaired respiratory function was also demonstrated by Blake et al,[35] who randomized 62 clinically assessed patients with OSA to standard morphine PCA versus an opioid-sparing protocol, showing that postoperative morphine dose was significantly associated with central apnea respiratory events.

In the context of avoiding opioids for postoperative analgesia, Lee et al[36] showed that randomization to ketorolac versus oral mefenamic acid/intramuscular meperidine conferred noninferior postoperative wound pain alleviation and physical activity, as well as patient satisfaction in PSG-confirmed patients with OSA.[36]

## PAIN MANAGEMENT AFTER UVULOPALATOPHARYNGOPLASTY IN OSA

In the context of increasing perioperative safety in OSA, surgical interventions of uvulopalatopharyngoplasty, which are associated with significant postoperative pain, have proven suitable for the study of opioid effects in OSA. However, they are not without the caveat of dealing with an anatomically and functionally impaired airway inherent to the surgical intervention.[39,98]

Thus, butorphanol, a synthetic opioid-agonist-antagonist with 5-fold greater analgesic potency and a lower incidence of postoperative nausea and vomiting than morphine due to its antagonistic effect, has recently gained interest in uvulopalatopharyngoplasty.[99,100] Butorphanol can be administered intravenously, intramuscularly, or intranasally for moderate to severe pain, while it appears to lack OIRD due to its ceiling effect on respiration.[101]

Yang et al[39] recently found that in elderly PSG-verified patients with OSA randomized to 4 different modalities of preemptive opioid analgesia, including intranasal or intravenous butorphanol, intranasal fentanyl, and placebo (intravenous saline), all tested interventions decreased pain, opioid requirement, and postanesthesia care unit stay. Intranasal butorphanol, however, was superior to all other interventions with regard to reducing pain and opioid consumption and decreasing postoperative cognitive dysfunction. Reasons could include higher bioavailability of nasal butorphanol and potentially the impact of reduced opioid utilization on cognitive function.[102]

Advantages of intranasal butorphanol, compared to other conventional opioid analgesic modes, have also been suggested by others when studying patients with OSA undergoing uvulopalatopharyngoplasty (Table 1).[36–38,103]

## SUMMARY

This systematic review demonstrates the existence of a growing body of evidence addressing opioid effects in patients with OSA while supporting a heightened level of concern regarding the occurrence of OIRD and serious adverse outcome in the postoperative setting.

While there is a lack of high-quality randomized evidence on the effect of acute opioid analgesia in OSA,[29] the current body of evidence is largely based on relatively heterogeneous observational studies, including case-control analyses and case reports.[76,104] Given the nature of this health care matter, most studies are burdened by high risk of bias and heterogeneity due to the involvement of multiple unaccounted drugs, the presence of various perioperative potentially confounding interventions within a cohort (ie, CPAP), and differences in OSA assessment, severity, and related comorbidities. Inconsistencies are also prevalent between studies, based on differences in comparators and outcome definitions, while evidence involving direct comparisons between patients with and without OSA is generally rare. These factors reflect the complexities of study design and interpretation in this subject matter and impede robust conventional analysis to provide precise quantitative estimates of effect for important patient outcomes. Furthermore, the general tendency of underreporting of adverse events in the medical literature poses a significant limitation in observational analyses, bearing the risk for systematic underestimation or overestimation of true effects when trying to establish accurate risk estimates.[105–107]

Despite these limitations, a growing body of evidence consistently supports a detrimental impact of opioids in patients with OSA, thus raising the level of concern for the

occurrence of life-threatening OIRD in the perioperative setting even at the administration of typical or lower opioid dose levels.

The intrinsic ability of opioids to suppress central respiratory drive and induce a monotonous respiratory pattern clearly provides the grounds for concern for exaggerated respiratory compromise in OSA.[108] Although OSA implies vulnerability to the potent respiratory depressant effects of opioids, which are known to depress pharyngeal muscle activity and promote airway collapse leading up to airway obstruction, hypoxemia, and even death due to asphyxia,[40,78,109–111] the effect of opioids may be determined by underlying OSA phenotypes expressed in each particular patient (ie, airway muscle responsiveness, ventilatory control and chemoreflexes responsiveness, and arousal threshold).[112–114]

The initial 24 hours after opioid administration appear to be the most critical,[18,19,21] rendering patients most receptive to respiratory insufficiency during this period.[21,115] The postoperative period is marked by changes in sleep architecture, increased pain severity, and high analgesic requirement, resulting in worsening of sleep-disordered breathing. Opioids may play a significant role in the postoperative worsening of OSA.[27,28,109]

Other noteworthy implications relate to potential increase in pain perception due to chronic sleep fragmentation and enhanced opioid sensitivity possibly due to upregulation of opioid receptors by recurrent hypoxia.[41,64] Thus, changes in drug response may predispose patients with OSA to a higher risk of OIRD without overdosing.[78,116] Death from opioids often occurs during sleep when breathing is primarily regulated by autonomic neurochemical control.[117] Due to potential changes in pain and opioid sensitivity, the severity of OSA may be a factor of greater importance besides opioid dose.[22]

In conclusion, while more research is needed, retrospective analyses suggest that opioid-related serious adverse events may be largely preventable with a more cautious approach to opioid use. This includes the utilization of multimodal analgesia to reduce opioid requirement, caution, or avoidance of concurrent administration of sedatives and opioids by multiple pathways (eg, PCA plus background infusion). Moreover, adequate monitoring of ventilation, repeated assessment of sedation levels, and early response to emerging events present critical measures in the context of reducing postoperative risk in patients with OSA.[5,18,19]

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## DISCLOSURES

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