Chronic Opioid Use and Central Sleep Apnea, Where Are We Now and Where To Go? A State of the Art Review

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Opioids are commonly used for pain management, perioperative procedures, and addiction treatment. There is a current opioid epidemic in North America that is paralleled by a marked increase in related deaths. Since 2000, chronic opioid users have been recognized to have significant central sleep apnea (CSA). After heart failure–related Cheyne-Stokes breathing (CSB), opioid-induced CSA is now the second most commonly seen CSA. It occurs in around 24% of chronic opioid users, typically after opioids have been used for more than 2 months, and usually corresponds in magnitude to opioid dose/plasma concentration. Opioid-induced CSA events often mix with episodes of ataxic breathing.

The pathophysiology of opioid-induced CSA is based on dysfunction in respiratory rhythm generation and ventilatory chemoreflexes. Opioids have a paradoxical effect on different brain regions, which result in irregular respiratory rhythm. Regarding ventilatory chemoreflexes, chronic opioid use induces hypoxia that appears to stimulate an augmented hypoxic ventilatory response (high loop gain) and cause a narrow CO₂ reserve, a combination that promotes respiratory instability.

To date, no direct evidence has shown any major clinical consequence from CSA in chronic opioid users. A line of evidence suggested increased morbidity and mortality in overall chronic opioid users. CSA in chronic opioid users is likely to be a compensatory mechanism to avoid opioid injury and is potentially beneficial. The current treatments of CSA in chronic opioid users mainly focus on continuous positive airway pressure (CPAP) and adaptive servo-ventilation (ASV) or adding oxygen. ASV is more effective in reducing CSA events than CPAP. However, a recent ASV trial suggested an increased all-cause and cardiovascular mortality with the removal of CSA/CSB in cardiac failure patients. A major reason could be counteracting of a compensatory mechanism. No similar trial has been conducted for chronic opioid-related CSA. Future studies should focus on (1) investigating the phenotypes and genotypes of opioid-induced CSA that may have different clinical outcomes; (2) determining if CSA in chronic opioid users is beneficial or detrimental; and (3) assessing clinical consequences on different treatment options on opioid-induced CSA. (Anesth Analg 2021;132:1244–53)

GLOSSARY

ABDO RES = abdominal movement; AHI = apnea/hypopnea index; ASV = adaptive servo-ventilation; BPAP = bilevel PAP; CAI = central apnea index; CHF = congestive heart failure; CI = confidence interval; CPAP = continuous positive airway pressure; CSA = central sleep apnea; CSB = Cheyne-Stokes breathing; ECG = electrocardiogram; EEG = electroencephalogram; EMG = electromyography; EOG = electrooculography; HCVR = hypercapnic ventilatory response; HR = hazard ratio; HVR = hypoxic ventilatory response; ICU = intensive care unit; ICSD = International Classification of Sleep Disorders; LOC = Left outer canthus; MI = myocardial infarction; MME = morphine milligram equivalent; MMT = methadone maintenance treatment; NASAL PR = nasal pressure; OSA = obstructive sleep apnea; PAP = positive airway pressure; PB = periodic breathing; PSG = polysomnographic; RCT = randomized controlled trial; REM = rapid eye movement; ROC = right outer canthus; RTN/pFRG = retro-trapezoid and parafacial respiratory group; Sao₂ = arterial oxygen saturation; SE = standard error; SERVE-HF = Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure; Spo₂ = oxygen saturation; THERM = thermistor; THOR RES = thoracic movements; VHA = Veterans Health Administration.
third of American adults used a prescription opiate, and prescription opioid overdose deaths have more than quadrupled between 1999 and 2015.1,2 There is also a dose-related increase in the risk of overdose hospitalization or death.3,4 Opioid-related deaths are mostly caused by respiratory arrest and often occur during sleep where ventilation is primarily regulated by autonomic neurochemical control.5,6 Since 2000, chronic opioid users have been reported to have central sleep apnea (CSA) in polysomnographic (PSG) sleep studies.7–11 In the 2005 edition of International Classification of Sleep Disorders (ICSD), “Central Sleep Apnea due to Drug and Substance” was officially recognized.12 Opioid-related CSA is one of the 2 most commonly seen CSA, besides heart failure-related CSA/Cheyne-Stokes breathing (CSB), but was less studied.13 In 2015 and 2016, 2 systematic reviews on chronic opioid use and CSA confirmed that 24% of chronic opioid users had CSA that was dose-related11; while these patients have substantial risk for CSA, a similar risk was not found for obstructive sleep apnea (OSA).14 There were subsequent large-scale multicenter studies15–17 as well as mechanistic studies that may help to better understand the correlates and consequences of opioid-related sleep-disordered breathing and its potential phenotypes and genotypes. The aim of the present state of the art review is to synthesize the current understanding of CSA in chronic opioid users and identify the gaps in current knowledge and future research priorities. Thus, we provide a catalyst for health care professionals to collaborate and conduct clinical trials to elucidate this perplexing sleep-disordered breathing in chronic opioid users.

DEFINITION OF OPIOID-INDUCED CSA

CSA indicates a cessation of airflow without respiratory effort—defined during PSG studies as a pause of breathing for >10 seconds in nasal flow, chest, and abdomen movement channels18 (Figure 1). In the third edition of ICSD, diagnosis criteria of an abnormal opioid-induced CSA is required to have a PSG of (1) 5 or more central apneas and/or central hypopneas per hour of sleep; (2) the number of CSA and/or central hypopneas is >50% of the total number of apneas and hypopneas; and (3) absence of CSB.9 Also, the patient is taking an opioid and the disorder occurs as a consequence of the opioid (not better explained by another current sleep disorder). A CSA syndrome diagnosis also needs to have one or more of the following 5 clinical symptoms: (1) sleepiness; (2) difficulty initiating or maintaining sleep, frequent awakenings, or nonrestorative sleep; (3) awakening short of breath; (4) snoring; and (5) witnessed apneas.9

There are 2 practical issues with the ICSD third edition criteria. First, it is difficult to clearly distinguish central hypopneas from obstructive hypopneas in PSG studies. In most of the clinical PSG laboratories, all hypopneas are simply regarded as obstructive in nature, which resulted in an overestimate in opioid-related OSA and underestimate in CSA.13 Second, there is no evidence to support that the 5 clinical symptoms listed above are consequences of opioid-induced CSA.13 Chronic opioid users may have increased daytime sleepiness, but CSA index is not a predictor of the sleepiness.19 The snoring and witnessed apnea symptoms are more likely to be consequences of OSA rather than CSA.

PREVALENCE OF CSA IN CHRONIC OPIOID USERS

CSA is typically seen after opioids have been used for at least 2 months.18,20 Chronic opioid therapy is usually defined as the use of opioids on most days for at least 3 months.21 In a recent review that included 8 studies and 560 chronic opioid users, the overall prevalence of CSA was 24%.11 Five of the 8 studies reported a positive correlation between either oral opioid dose or plasma concentration with central apnea index (CAI).11 Similarly, a meta-analysis review summarized 9 studies with 3791 chronic opioid users for pain management.22 CSA prevalence was 33% for sleep clinic and 20% for pain clinic in the pain group on opioids.22 In a recent prospective multicenter study (Op-Safe study) with 332 participants from chronic pain clinics, 20% had CSA.16 In a large retrospective population study of 6002 US veterans who were diagnosed with CSA, chronic prescription opioid use had an increased odds ratio of 1.99 (95% confidence interval [CI], 1.87–2.13) for CSA.17 In another meta-analysis review that included 7 studies and 803 patients, the absolute effect size for opioid use was a small increase in overall apnea hypopnea index (AHI) = 0.25 (95% CI, 0.02–0.49), and a medium for CAI = 0.45 (95% CI, 0.27–0.63), suggesting chronic opioid use has a moderate increased risk for CSA but not OSA.14 Again, we have to emphasize that the real prevalence of CSA in chronic opioid users could be larger given the central hypopnea misclassification issue we described in the last section.

DOES OPIOID INTAKE INCREASE OSA?

Another direct ramification from the confusion of central or obstructive hypopnea is the question of whether opioids can increase OSA? The findings are controversial. While some studies found that chronic opioid use increases both CSA and OSA,10,21,23 other studies found it only increases the risk of CSA.7,9,14 While it is not possible to check if the hypopneas were obstructive or central origin in every study, there are indirect approaches to validate the type of sleep apnea. A predominant OSA usually has increased apnea/hypopnea index (AHI) during rapid eye movement (REM) sleep (with further reduced upper airway muscle tone), while predominant CSA usually has decreased AHI during REM (with dampened ventilatory chemosensitivity/loop gain).9,10 The other more compelling
evidence is that the latest randomized controlled trial (RCT) investigating the effect of morphine on key upper airway physiology in OSA patients found oral morphine 40 mg blunted ventilatory control but did not impair upper airway measures, including upper airway collapsibility, pharyngeal muscle responsiveness, or arousal threshold. 24 We therefore believe that OSA is predominantly unchanged or marginally increased by opioids. 22,25

**ATAXIC BREATHING (BIOT’S RESPIRATION)**

Opioid-induced CSA events often mix with episodes of ataxic breathing. 6 Ataxic breathing is a pattern of breathing with irregular variations in respiration cycle time and tidal volume. 6,10 A long pause of breathing >10 seconds could qualify a CSA, and some short pauses may look like subcriteria CSA (Figure 2). Ataxic breathing is very commonly seen in PSG studies in opioid users. A study showed that the

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**Figure 1.** Two examples of CSA found in methadone maintenance treatment patients. A, Example of PB type but without crescendo-decrescendo breathing typical of Cheyne-Stokes respiration. The PB cycle time is shorter than seen in Cheyne-Stokes respiration associated with CHF. B, Non-PB type of CSA. The time base is 30 s for the upper epoch and 5 min for the lower epoch for each example. Patients were in stage 2 sleep in both examples. This graph is reused with permission from Wang et al. 9 ABDO RES indicates abdominal movement; CHF, congestive heart failure; CSA, central sleep apnea; ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyography; EOG, electrooculography; LOC, left outer canthus; NASAL PR, nasal pressure; PB, periodic breathing; ROC, right outer canthus; SaO₂, arterial oxygen saturation; THERM, thermister; THOR RES, thoracic movements.
proportion of patients with ataxic breathing patterns was 92% in those with morphine milligram equivalent (MME) ≥200 mg, and 61% in MME <200 mg. Ataxic breathing is usually identified manually through eyeballing PSG epoch by epoch. Recent technology has been developed to quantify and standardize the measurement of ataxic breathing as a sensitive respiratory depression marker using semiautomatic analysis. Variability measures of interbreath interval (coefficient of variation and standard deviation) cross-correlated with both CAI and opioid plasma concentration. These 2 variables could be considered as clinical markers for opioid-induced breathing irregularity (ataxic breathing).

PATHOPHYSIOLOGY OF OPIOID-INDUCED CSA AND ATAXIC BREATHING

The fundamental drive to respiration is generated in the brainstem and modulated by inputs from conscious input (cortex), and central (brainstem) and peripheral (carotid and aortic bodies) chemoreceptors. During sleep, there is a lack of conscious input, so the pathogenesis of opioid-induced CSA can be explained mainly from 2 aspects: respiratory rhythm generation and chemoreceptors.

Opioid Effect on Respiratory Rhythm Generation

The most sensitive aspect of opioids on respiration is on rhythm generation. Changes in respiratory rhythm can be observed at lower opioid doses than changes in tidal volume. Respiratory rhythm is controlled by pons and medulla in the brainstem. A small area in the ventrolateral medulla called pre-Bötzinger complex is the major generator of respiratory rhythm. It couples with the nearby retro-trapezoid and parafacial respiratory group (RTN/pFRG) to form respiratory oscillations. The pre-Bötzinger complex is active during inspiration and it is inhibited by opioids slowing down the inspiratory drive. In contrast, the RTN/pFRG is active during expiration but is not sensitive to opioids. This paradoxical effect on different brain regions is a major mechanism for the irregular respiratory rhythm observed during opioid administration. In addition, those rhythm-generating centers in the medulla are modulated by influences from the pons, which include the Kölliker-Fuse nucleus, the parabrachial complex, and the locus coeruleus. Opioids effect on Kölliker-Fuse nucleus and the parabrachial complex can also contribute to an irregular respiration. Kölliker-Fuse nucleus is known to control the transition from inspiration to expiration, and opioids can prolong the duration of inspiration. During sleep, clinical studies showed that both acute and chronic opioid use can cause longer and more irregular breath intervals.

Opioids Effect on Ventilatory Chemoreflexes

Ventilatory chemoreflexes in chronic opioid users are not well studied. Central ventilatory chemoreceptors are based in the brainstem, providing tonic drive to the respiratory motor output by sensing changes in pH/Pco₂. Peripheral chemoreceptors are essentially based at the carotid body and are the main sensors.

Figure 2. Examples of ataxic breathing (A) compared with normal breathing pattern (B). Irregular variations in respiration cycle can be seen in (A). The graph is reused with permission from Walker et al. The 11-s pause in the middle could qualify a CSA event. CSA indicates central sleep apnea; SpO₂, oxygen saturation.
for hypoxia.40 There are 2 important factors critical to the breathing instability and CSA: a sensitive apneic threshold and heightened ventilatory chemosensitivity (high loop gain).13 Relevant concept is illustrated in Figure 3. CSA patients generally have a narrower CO2 reserve (PCO2 difference between the eupneic and apneic threshold).51,42 Meanwhile, to form cyclic CSA events, a high chemosensitivity (loop gain/controller gain) is needed to create a ventilatory overshoot (hyperventilation) with resultant hypocapnia to reach the apneic threshold and form a cluster-type breathing pattern.13,43,44 Acute opioid use can reduce both ventilatory responses to hypercapnia and hypoxia and blunt ventilatory chemosensitivities (controller gain).5 Hence cluster-type CSA is not commonly seen with acute opioid use, despite prolonged breathing cycles and increased breathing irregularity.27 Chronic opioid use has a different ventilatory control pattern.45,46 Methadone maintenance treatment patients (>2 months) were found to have blunted hypercapnic ventilatory response, but significantly higher (nearly doubled) hypoxic ventilatory response compared to the matched control subjects9,45 (Figure 4). This augmented hypoxic ventilatory response could be a compensatory response from the long-term stimulation of hypoxia.9,45 Also, hypoxia can reduce CO2 reserve and make it more susceptible to apnea and breathing instability.41,47 This mechanism is somewhat similar to hypoxia at high altitude leading to high hypoxic ventilatory response (controller gain), reduced CO2 reserve, and cyclical CSA.9,44,45

However, although the augmented hypoxic ventilatory response could be a major mechanism for CSA in chronic opioid users, it may not be applicable to all cases. There could be different phenotypes as causative mechanisms.9,42,45 For example, in Figure 1, on inspection of Figure 1A, the breathing pattern is consistent with high chemosensitivity–induced periodic breathing (PB) CSA. The breathing pattern in Figure 1B is consistent with a sensitive apneic threshold (narrow CO2 reserve) subtype of CSA. Just 1 breath was enough to cross the apneic threshold and cause a CSA episode; high chemosensitivity (loop gain) may not be necessary for this instance. For those patients with severely blunted hypercapnic ventilatory response (impaired central drive), they are prone to develop hypercapnic CSA, an extreme form that could be similar to congenital central hypoventilation syndrome (Ondine’s curse).48

PHENOTYPES, GENOTYPES, AND RISK FACTORS OF OPIOID-INDUCED CSA

Different phenotypes of opioid-induced CSA based on their pathogeneses may lead to different clinical consequences and treatment strategies. Awake ventilatory chemoreflex testing could be a useful tool to identify different ventilatory control phenotypes.9,49–51 It is a brief daytime test to assess ventilatory response

![Figure 3. Conceptual illustration of ventilatory chemosensitivity and CO2 reserve. The oblique line A represents a breathing response during sleep. Apneic threshold represents that after previous breath, PCO2 dropped to a certain point where breathing pulsed (ventilation = 0 L/min). Then after a gradual increase in PCO2 where ventilatory drive crossed the metabolic hyperbola (curved horizontal line), ventilation is reinitiated (eupneic threshold). CO2 reserve is the PCO2 difference between the 2 thresholds. The slope of the response line A is calculated as the ventilatory chemosensitivity (ventilatory response to CO2), which also generally indicates the level of loop gain/controller gain. A higher chemosensitivity (a steeper slope) usually corresponds to a narrower CO2 reserve.](image-url)
to hypercapnia and hypoxia, with the outcomes of ventilatory chemosensitivities and ventilatory response thresholds (Figure 5). We have demonstrated that some chronic opioid users have heightened hypoxic ventilatory response, which may contribute to ventilatory overshoot and PB type of CSA (Figure 1A). Also, there could be a sensitive CO₂ apneic threshold (narrow CO₂ reserve) type that is prone to cross the apneic threshold and stops breathing (Figure 1B). There are also chronic opioid users with a blunted hypercapnic ventilatory response, which may lead to hypercapnic/hypoventilation CSA. A recent study showed that baseline ventilatory CO₂ response threshold may predict individual response to acute morphine use in OSA patients; this technique may also apply to future chronic opioid studies. Moreover, loop gain techniques might also be useful to phenotype CSA in chronic opioid users.

There is also a genetic component to individual responses to opioids in sleep and breathing. ABCB1 and OPRM1 are 2 key genes involving opioid pharmacokinetics and pharmacodynamics, respectively. Genetic polymorphisms related to ABCB1 and OPRM1 may cause differential sleep symptoms measured by sleep questionnaires in cancer and noncancer pain sufferers using opioids and in methadone maintenance treatment patients. A recent RCT demonstrated that OPRM1 variants have different responses to acute morphine in hypercapnic ventilatory response and oxygen desaturation during sleep in 60 OSA patients. In addition, a multicenter study found that cancer patients receiving morphine with a variant on the HTR3B gene were 3 times more likely to have more intense breathlessness. Despite never tested, ABCB1, OPRM1, and HTR3B are the 3 candidate genes potentially to have genetic variances on CSA related to chronic opioid use.

Regarding risk factors, the most convincing evidence comes from the prospective multicenter Op-Safe study. Significant predictive factors for CAI ≥5 are MME and daytime oxygen saturation (SpO₂). For each 10 mg MME increase, the odds of CAI ≥5 increased by 3%, and for each 1% drop in SpO₂, the odds increased by 45%. This finding is logical considering the mechanism of opioid-induced hypoxia stimulating a heightened hypoxic ventilatory response and therefore increased cyclic CSA events. The concomitant drug effects of opioids with other drugs (mainly benzodiazepines and antidepressants) are very complex. One study showed that antidepressants worsen CSA in chronic opioid users while other studies showed no effect. There was also a recent report showing concomitant benzodiazepine reduces the magnitude of overall AHI in chronic opioid users. Those concomitant effects may be variable across different drug types and the phenotypes and genotypes of CSA, and related to interactions of loop gain/chemosensitivity, apneic threshold, arousal threshold, and time course of interaction.

**CLINICAL CONSEQUENCES OF OPIOID-INDUCED CSA**

There is no direct evidence showing any major clinical consequence from CSA in chronic opioid users. In the multicenter Op-Safe study, compared to patients with CAI <5, those CSA patients with CAI >5 had no significant difference in occurrence of cardiovascular diseases, hypertension, and diabetes, despite with almost 3 times the opioid dose/MME. Similarly, in the largest cohort (Veterans Health Administration [VHA] cohort) of 6002 CSA patients, all-cause CSA
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(including CSB) was associated with 1.5 times higher odds of cardiac hospital admission. However, while chronic opioid users had 1.17 times increased odds of cardiac hospital admission, those users with CSA (interaction) did not.17

In contrast, there is a line of evidence showing increased cardiac risks and mortalities in overall chronic opioid users.62–65 One study compared a chronic opioid user cohort of 148,657 patients with a matched cohort of general population in coronary heart disease outcomes.62 Chronic opioid users showed 2.7 times the rate of myocardial infarction (MI), and 2.4 times the rate of MI or coronary revascularization.62 A similar study investigated 1.7 million opioid users in UK General Practice Research Database, and found a 1.28-fold risk of MI in current opioid users.64 Another retrospective cohort study compared 22,912 new episodes of drug therapy for chronic noncancer pain for both long-acting opioids and control medications.65 Overall hazard ratio (HR) for total mortality was 1.64 for chronic opioid users with a risk difference of 68.5 excess deaths per 10,000 person-years. The stratified analysis showed that during the first 30 days, the overall HR of mortality was 4.16; between 30 and 180 days, overall HR was 1.56; and for more than 180 days, the risk of death did not differ between opioids and control medications (overall HR = 1.03).65 Although the above studies convincingly demonstrated increased morbidity and mortality in chronic opioid users, they did not test breathing during sleep. Therefore, we do not know what role does CSA play in the increased clinical consequences in chronic opioid users.

Another potential consequence of CSA in chronic opioid users is daytime sleepiness and reduced daytime neurocognitive functioning.19 A study of 50 methadone maintenance treatment patients found that they had increased daytime sleep propensity and reduced daytime function.19 However, multiple regression analysis showed that the severity of CSA did not contribute to either of the problems.19 Those neurocognitive impairments are more likely due to the sedative effect of opioids and depression.18,19 There are other speculations that CSA may cause clinical consequences through increasing arousals or intermittent hypoxia, but the clinical consequences are rather speculative and not evidence-based.66,67

Judging from pathophysiology, chronic opioid-related CSA is mainly a ventilatory control phenomenon with an increased hypoxic ventilatory response/chemosensitivity/loop gain as a long-term stimulation from opioid’s central depressant effect. It is a compensatory feedback response to keep blood gas homeostasis and likely to be beneficial rather than detrimental. Similarly, it is increasingly recognized that CSB in heart failure patients is a compensatory mechanism, which could be more beneficial than injurious.66 Certainly future well-controlled studies are needed to clarify whether CSA is preventing or causing excess morbidity and mortality in chronic opioid users. One practical issue in CSA consequence study is that opioid dose/MME must be controlled for, as the severity of CSA corresponds to opioid dose/plasma concentration.9,11 For example, in Op-Safe study, CAI ≥5 group had significantly lower Spo2 nadir (82.8% vs 87%; P < .001) compared to the CAI <5 group.16 That may not necessarily mean that CSA caused significant oxygen desaturation, as CAI ≥5 group had a nearly tripled opioid dose. Without CSA, Spo2 nadir could be even lower.16

Figure 5. An example of awake ventilatory chemoreflex test setting. It is also called “ventilatory response to hypercapnia and hypoxia test,” or “ventilatory response to CO2 and O2.” Detail testing method has been described in references 49, 50, 52.
Given the previous discussions, we believe that opioid-related injuries could be more prevalent in patients who did not develop a compensatory mechanism of cyclic CSA with high loop gain. They could have a combination of certain phenotype and genotype, for example, obesity hypoventilation syndrome or Ondine’s curse patients with hypercapnic CSA, with reduced ventilatory chemosensitivity/loop gain and blunted arousal response to hypoxia. They would be unlikely to have a high CSA index, given the reduced chemosensitivity/loop gain and associated prolonged hypventilation event. Again, future specifically designed phenotyping/genotyping studies are needed to investigate these hypotheses.

**CLINICAL TREATMENTS OF OPIOID-INDUCED CSA**

Current major treatment options are as follows: (1) positive airway pressure (PAP) therapies including continuous PAP (CPAP), bilevel PAP (BPAP), and PAP via adaptive servo-ventilation (ASV), (2) oxygen therapy or PAP therapy with adding oxygen, (3) reducing opioids dose or replacing opioids with drugs with less toxicity. Among those therapies, PAP treatments are considered as the most effective therapies. Given opioids’ potent respiratory depression effect, PAP therapy can ameliorate hypoxia, hypercapnia, reduce ventilatory chemosensitivity/loop gain, and ventilatory overshoot, thus reducing cyclic respiratory events. However, residual respiratory events are often seen in fixed pressure CPAP. One study showed that CPAP + O₂ and BPAP + O₂ have better CSA reducing effect. ASV is potentially more superior in reducing CSA than CPAP and BPAP, as it was designed for CSA/CSB treatment through modulating respiratory rhythms. However, in the recent ASV trial (Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure [SERVE-HF]) tested on 1325 heart failure patients, despite ASV successfully eliminating CSA/CSB episodes, both all-cause and cardiovascular mortality were significantly increased. A major explanation is that CSA serves as a compensatory mechanism with protective effects as previously hypothesized. Nevertheless, SERVE-HF trial was tested on heart failure patients, we do not know if similar findings could apply to chronic opioid users, despite sharing a similar mechanism of augmented hypoxic ventilatory response/loop gain.

There are 2 issues regarding current clinical treatments of opioid-induced CSA. First, they are based on the premise that CSA in chronic opioid users is detrimental. While we know that chronic opioid use can have adverse clinical consequences, we do not have evidence that chronic opioid-induced CSA is detrimental in clinical outcomes. On the contrary, it is more likely to be a compensatory mechanism to avoid injury from opioids. Second, treatment success evaluation is based on reducing the number of CSA events rather than clinical consequences (such as cardiovascular and/or neurocognitive outcomes, quality of life, hospital/intensive care unit (ICU) admission, mortality risks, etc). This is an important distinction as the SERVE-HF trial demonstrated that a reduction of CSA events may be associated with worse clinical outcomes.

**SUMMARY AND FUTURE DIRECTIONS**

Since chronic opioid-related CSA was initially reported 20 years ago, it has been increasingly recognized and studied, particularly in the context of the current opioid epidemic and excess deaths in North America. It has become 1 of the 2 most common causes of CSA, but has been significantly less studied compared to heart failure–related CSA. Some key clinical questions remain to be answered. (1) Pathophysiology of opioid-induced CSA should be thoroughly investigated to better understand the phenotypes and genotypes, which could guide a targeted treatment solution. While CSA in chronic opioid users is generally safe and may serve as a compensatory mechanism, there is a possibility that certain phenotype/genotype of patients are particularly vulnerable and may associate with increased morbidity and mortality. (2) Well-controlled population study or multicenter pain/methadone clinic studies are needed to clarify any potential causative clinical consequences of opioid-induced CSA, that is, Is CSA in chronic opioid users beneficial or detrimental in clinical outcomes? (3) While SERVE-HF is designed for CSB in heart failure patients, similar RCT for opioid-induced CSA is needed to provide an unbiased assessment of current treatment options. Importantly, the key outcome measurements should be clinical consequences rather than CSA index. Finally, collaborations between respiratory and sleep researchers and pain researchers are crucially important to tackle these challenges.

**DISCLOSURES**

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REFERENCES


