Study Title: Opioid Physiology and Individual Outcomes with Supplemental O_2 (OPIO2)

Protocol Number: 814959

National Clinical Trial (NCT) Identified Number:

Principal Investigator: Jeremy Orr, MD; Associate Professor; Division of Pulmonary, Critical Care, Sleep Medicine, and Physiology

Funded by: R01 HL179220

Version Number: v.2.0

July 28, 2026

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

Table of Contents

1 PROTOCOL SUMMARY 1
1.1 Synopsis 1
1.2 Schema 2
1.3 Schedule of Activities (SoA) 3
2 INTRODUCTION 4
2.1 Study Rationale 4
2.2 Background 5
2.3 Risk/Benefit Assessment 7
2.3.1 Known Potential Risks 7
2.3.2 Known Potential Benefits 8
2.3.3 Assessment of Potential Risks and Benefits 8
3 OBJECTIVES AND ENDPOINTS 9
4 STUDY DESIGN 9
4.1 Overall Design 10
4.2 Scientific Rationale for Study Design 12
4.3 Justification for Dose 12
4.4 End of Study Definition 13
5 STUDY POPULATION 13
5.1 Inclusion Criteria ..... **Error! Bookmark not defined.**
5.2 Exclusion Criteria 14
5.3 Lifestyle Considerations 15
5.4 Screen Failures 15
6 STUDY INTERVENTION 16
6.1 Study Intervention(s) Administration 16
6.1.1 Study Intervention Description 16
6.1.2 Dosing and Administration 17
6.2 Preparation/Handling/Storage/Accountability 18
6.2.1 Acquisition and accountability 18
6.2.2 Formulation, Appearance, Packaging, and Labeling 18
6.2.3 Product Storage and Stability 18
6.2.4 Preparation 18
6.3 Measures to Minimize Bias: Randomization and Blinding 18
6.4 Study Intervention Compliance 19
6.5 Concomitant Therapy 19
6.5.1 Rescue Medicine 20
7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 20
7.1 Discontinuation of Study Intervention 20
7.2 Participant Discontinuation/Withdrawal from the Study 20
7.3 Lost to Follow-Up 21
8 STUDY ASSESSMENTS AND PROCEDURES 21

8.1 Efficacy Assessments 21
8.2 Safety and Other Assessments 26
8.3 Adverse Events and Serious Adverse Events 27
8.3.1 Definition of Adverse Events (AE) 27
8.3.2 Definition of Serious Adverse Events (SAE) 27
8.3.3 Classification of an Adverse Event 28
8.3.4 Time Period and Frequency for Event Assessment and Follow-Up 29
8.3.5 Adverse Event Reporting 29
8.3.6 Serious Adverse Event Reporting 29
8.3.7 Reporting Events to Participants 31
8.3.8 Events of Special Interest 31
8.3.9 Reporting of Pregnancy 31
8.4 Unanticipated Problems 31
8.4.1 Definition of Unanticipated Problems (UP) 32
8.4.2 Unanticipated Problem Reporting 32
8.4.3 Reporting Unanticipated Problems to Participants 32
9 STATISTICAL CONSIDERATIONS 32
9.1 Statistical Hypotheses 32
9.2 Sample Size Determination 33
9.3 Populations for Analyses 34
9.4 Statistical Analyses 34
9.4.1 General Approach 34
9.4.2 Analysis of the Primary Efficacy Endpoint(s) 34
9.4.3 Analysis of the Secondary Endpoint(s) 35
9.4.4 Safety Analyses 35
9.4.5 Baseline Descriptive Statistics 36
9.4.6 Planned Interim Analyses 36
9.4.7 Sub-Group Analyses 36
9.4.8 Tabulation of Individual participant Data 36
9.4.9 Exploratory Analyses 36
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 37
10.1 Regulatory, Ethical, and Study Oversight Considerations 37
10.1.1 Study Discontinuation and Closure 37
10.1.2 Confidentiality and Privacy 38
10.1.3 Future Use of Stored Specimens and Data 39
10.1.4 Informed Consent ..... **Error! Bookmark not defined.**
10.1.5 Key Roles and Study Governance 40
10.1.6 Safety Oversight 41
10.1.7 Conflicts of Interest ..... **Error! Bookmark not defined.**
10.1.8 Clinical Monitoring 41
10.1.9 Data Handling and Record Keeping 41

10.1.10 Protocol Deviations 42
10.2 Additional Considerations 42
10.3 Abbreviations 43
10.4 Protocol Amendment History 45
11 REFERENCES 46

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:

Opioid Physiology and Individual Outcomes with Supplemental O_2 (OPIO2)

Study Description:

This study is a Phase II, single-center, randomized, double-blind, sham-controlled, cross-over trial designed to evaluate the effects of nocturnal supplemental oxygen on ventilatory stability and sleep-disordered breathing in adults with chronic opioid use. Participants will receive both oxygen and sham air in a randomized sequence, separated by a washout period, allowing each participant to serve as their own control.

Objectives:

Primary Objective: To determine whether nocturnal supplemental oxygen improves ventilatory stability in adults with chronic opioid use and sleep-disordered breathing.
Secondary Objectives: To evaluate the effect of supplemental oxygen on apnea–hypopnea severity, as well as to assess changes in respiratory pattern variability and arousal threshold, oxygenation, and nocturnal hypercapnia. The study will also evaluate neurobehavioral performance using psychomotor vigilance testing and assess patient-reported sleep quality and related symptoms.

Endpoints:

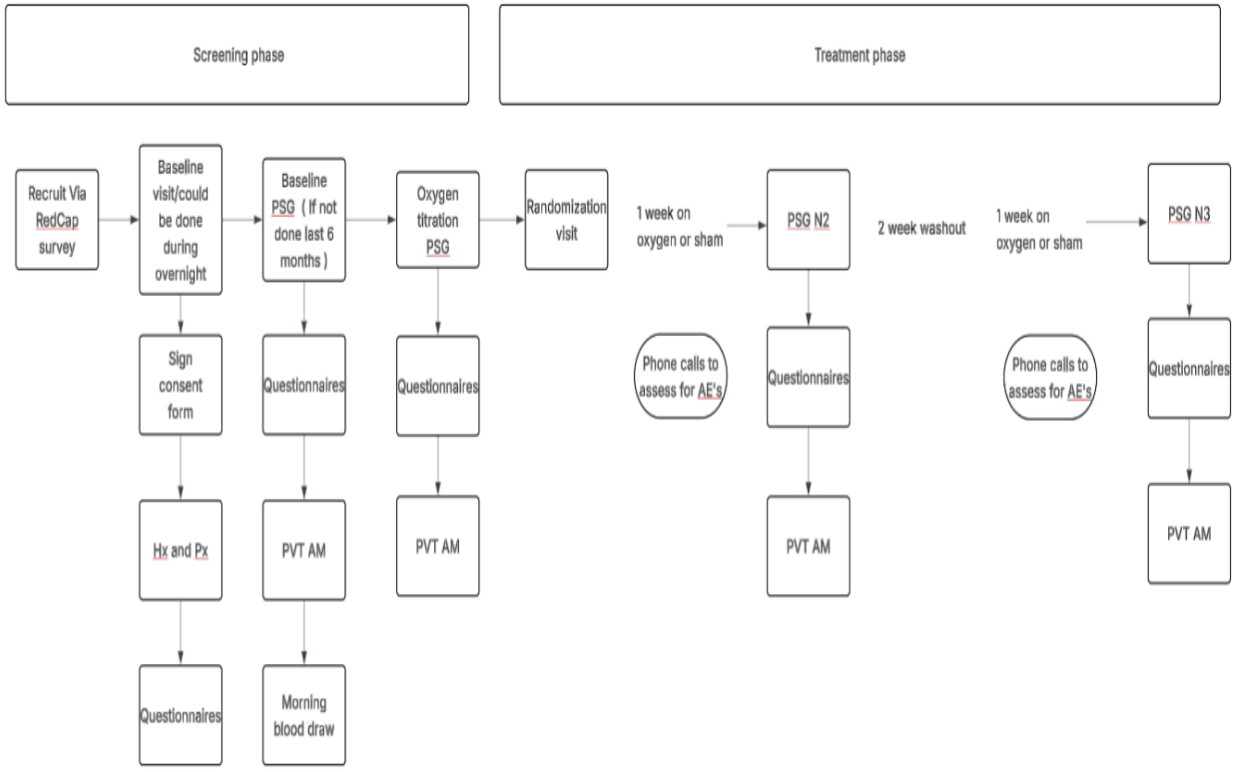
Primary Endpoint: Flow-based apnea–hypopnea index (AHIflow), which is not dependent on oxygen desaturation and is therefore appropriate during oxygen therapy.
Secondary Endpoints: Loop gain (a marker of ventilatory instability), respiratory pattern variability metrics, arousal threshold, time spent with SpO_2 <90%, transcutaneous carbon dioxide ($TcCO_2$) levels, standard polysomnography outcomes (including AHI), psychomotor vigilance test (PVT) outcomes, and patient-reported outcome measures evaluating perceived sleep quality and related symptoms.

Study Population:

Adults aged 18–75 years with chronic opioid use (≥3 months) and sleep-disordered breathing (AHI ≥5 events/hr).

Phase:	Phase II
Description of Sites/Facilities Enrolling Participants:	Participants will be enrolled through UC San Diego clinical practices and all study procedures will be conducted at the UC San Diego Sleep Research Laboratory and the Altman Clinical and Translational Research Institute (ACTRI).
Description of Study Intervention:	Nocturnal supplemental oxygen versus sham air delivered via nasal cannula in a randomized cross-over design.
Study Duration:	Up to 5 Years
Participant Duration:	Approximately 6–10 weeks per participant.

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening/ Baseline visit	Oxygen Titration visit	Randomization day visit	Oxygen or Sham (Home x 1 week)	End of Period 1 PSG Visit	Washout (2 weeks)	Oxygen or sham (Home x 1 week)	End of Period 2 PSG Visit
Inclusion/exclusion review	x	x[1]	x[1]					
Informed consent	x							
Demographics	x							
Medical and sleep history	x	x	x		x			x
Concomitant medications review	x	x	x		x			x
Physical examination	x							
Vital signs (BP, HR, RR, SpO_2)	x	x	x		x			x

Height / weight / BMI	x	x	x		x			x
Questionnaires / study testing	x				x			x
PSG with $TcCO_2$ monitoring	x[2]	x			x[3]			x[3]
Supplemental oxygen titration during PSG		x						
Randomization			x					
Morning blood draw	x							
Study device training / home-use instructions			x					
At home treatment				x			x	
Under mattress cardiorespiratory sensor home monitoring				x		x		x
Compliance / adherence review/Adverse event review	x	x	x	x[4]	x	x	x[4]	x

1- TcCO2 > 55 for >10min will be excluded
2- If not done in the last 6 months
3- With supplemental oxygen or sham oxygen, depending on treatment phase
4- Call 24 hours after initial set up and then one other time during treatment phase

2 INTRODUCTION

2.1 STUDY RATIONALE

Sleep-disordered breathing (SDB) is highly prevalent among individuals receiving chronic opioid therapy and is characterized by instability in ventilatory control, including central sleep apnea and periodic breathing. Opioids alter respiratory control by depressing ventilatory drive and increasing the sensitivity of the respiratory control system, resulting in abnormal breathing patterns during sleep.

Supplemental oxygen has been shown to stabilize ventilatory control by reducing chemosensitivity and dampening fluctuations in respiratory drive. In prior physiologic studies, oxygen therapy has been associated with reductions in central apnea events and improvements in breathing stability during sleep.

Despite these findings, the role of supplemental oxygen as a targeted therapy for opioid-associated sleep-disordered breathing (SDB) has not been well defined in a controlled clinical setting. In particular, the effects of oxygen on apnea–hypopnea index based on airflow (AHIflow), ventilatory control stability (e.g., loop gain), and gas exchange (including transcutaneous carbon dioxide [$TcCO_2$]) require further investigation.

2.2 BACKGROUND

This study will focus on patients using long term opioids, rather than acute opioids.

For this study, chronic opioid use refers to adults receiving prescribed opioid medications for chronic pain or opioid use disorder (OUD) under medical supervision for at least 3 months. Eligible participants must be receiving a daily opioid dose equivalent to at least 20 mg of oral morphine (morphine equivalent daily dose [MEqD]). Recreational or illicit opioid use is not the focus of this study, and individuals using non-prescribed opioids are excluded.

Given substantial differences in respiratory physiology between acute and chronic use (owing to tolerance and other changes), the proposed work differs from prior work examining oxygen use in the post-operative setting, which consists of acute opioid administration. Nonetheless given the potential for mixed physiological changes with oxygen, we include a robust strategy for risk mitigation and monitoring. Of note, recent studies using supplemental oxygen in patients with sleep apnea (e.g. HEART-BEAT, LOFT-HF) have not identified major safety concerns, and supplemental oxygen is considered an option for central sleep apnea based on recent guidelines. In addition, our lab has a long history of research employing supplemental oxygen for sleep apnea, including studies showing that supplemental oxygen may improve sleep apnea particularly in patients with ventilatory instability, a physiological pattern seen in patients who use opioids.

The opioid epidemic is an ever-accelerating public health issue in the USA (Figure 1) (1-4). Increases in opioid use were noted in the 1990s, driven by several political, social, and demographic factors (5-11). Despite being labeled as a public health emergency in 2017, opioid-related deaths have continued to increase, with most recent data finding over 81,000 deaths in 2023 (12). While a substantial proportion of deaths are related to illicit synthetic opioids, adverse effects of prescription opioid use play an important direct and indirect role in driving the ongoing crisis. Even under medical supervision, opioid use is associated with an increased risk of death (13) potentially via increased arrhythmia and sudden death (14), cardiovascular disease (15-19), respiratory infections (20), and therapeutic misadventures (13).

Opioids are – and will remain – a mainstay in modern medical care. In the setting of chronic pain, opioids remain a CDC guideline-supported intervention for refractory pain (21). A

commonly cited Cochrane meta-analysis found that while escalating opioid doses were not associated with better pain control, the effectiveness of sustained therapy has not been disproven (22). Other metanalyses have found modest improvements in pain and physical functioning with opioids compared to non-opioid pharmacotherapy (23). Clinical practice has reflected that carefully adjusted long-term opioids might be warranted for some individuals; the incidence of new prescriptions and average dose of opioid per prescription dose has decreased (Figure 1), while the average duration of opioid use has increased (24, 25). In terms of opioid use disorder (OUD), medications for OUD (e.g. methadone, buprenorphine) have been shown to substantially reduce relapse and death but are nonetheless opioids (26). In the setting of palliative care (particularly oncology), opioids are often used long term for pain and dyspnea, i.e., not just at immediate end-of-life. With increasing therapeutic options for advanced cancer leading to improved survival, maintaining pain control without compromising outcomes is imperative. Overall, there is a need for safe prescribing, monitoring, and therapeutics to mitigate adverse impacts related to opioids.

Adults receiving long-term prescribed opioid therapy for chronic pain or medications for opioid use disorder under medical supervisionhave an increased risk of sleep disordered breathing (SDB). Although estimates vary, data suggest up to 50% of patient using opioids have evidence of central sleep apnea (CSA) (27-32) with a dose-dependent but highly variable relationship to opioids. OSA is also a very common disease with major health impact (33-44). In those with OSA, opioids contribute to central apneas and worsened hypoxemia (45-47), and are a well-established risk factor for failure of first-line continuous positive airway pressure (CPAP) treatment due to emergent and persistent respiratory events (48-51). Overall, opioids appear to contribute to the severity and complexity of SDB (46, 52-63).

It is increasingly appreciated that SDB impacts patient-oriented outcomes in the setting of opioid use. Sleep complaints are extremely common in patients with chronic pain and negatively impact quality of life (64-68). While several issues might contribute to sleep disturbance in such patients, SDB can impact subjective sleep quality but often is not clinically recognized. Also, sleep disorders appear to play a role in pain sensitivity (64, 65, 69-71), which may limit opioid effectiveness and contribute to ongoing use. Although the data are variable, at least some studies indicate that SDB leads to increased levels of pain, while CPAP therapy leads to reduced responses to pain (72, 73). Thus, there is potential for a vicious cycle whereby SDB may worsen pain, while pain may lead to worsened SDB via opioid use (74). Other lines of evidence support the potential importance of SDB in those using opioids: 1) Sleep disorders are associated with mood disturbance (75-78), which in turn is associated with long term opioid use (79). 2) Sleep disorders are associated with poor quality of life (80-83) and impaired daytime function (84-86). 3) Patients with untreated SDB may have decreased memory and alertness (i.e. vigilance) and thus may be at risk of opioid mismanagement (87). 4) Finally, opioids may lead to chronic respiratory failure, which untreated portends poor outcomes in other groups of patients (88-91), perhaps via risk for respiratory decompensation (92) or pulmonary hypertension (93). Overall, one could argue that treatment of SDB may lead to improvements in health via several mechanisms (94-96). The need for research regarding management of SDB in the setting of opioid use was highlighted by a recent American Academy of Sleep Medicine position statement (97).

In general, continuous positive airway pressure (CPAP) is the first-line treatment for SDB. The major effect of CPAP is in stabilizing the upper airway (98) although decreased hypoxemia and

blunted changes in CO_2 can contribute to stability of respiratory control (98-105). In otherwise healthy individuals, these effects often lead to resolution of OSA in but may lead to improvements in CSA as well, best studied in heart failure (106). On the other hand, CPAP may unmask central apneas via alleviation of restricted ventilation from upper airway obstruction (107-114). Observational studies implicate opioid use as a strong risk factor for development and persistence of CSA during use of CPAP, termed treatment-emergent CSA (50, 51). Overall, CPAP has been observed to have variable effects in opioid related SDB (115-118).

Given these limitations on CPAP efficacy, along with challenges with long term adherence with similar devices (e.g., BIPAP), targeted strategies are needed to address SDB related to opioid use (119). While complete elimination of opioids may serve to reverse the complexity of SDB (120, 121), in practice this goal can be difficult to achieve. Indeed, population studies suggest despite some reductions in opioid initiation, mean duration of opioid use appears to be increasing (25). More realistic goals include opioid dose reduction, which is supported by CDC recommendations (21). However, randomized trials of slow dose reduction have shown successful reduction of opioid doses over a 6-month timeframe but been variable in terms of individual-level short-term symptomatic benefit (122-124). Similarly, there are currently no published studies that have examined the effect of dose reduction on SDB; the effects of dose reduction on SDB and attendant outcomes are likely to differ based on the extent to which opioid-induced ventilatory instability is driving SDB.

Addressing sleep hypoxemia might represent a well-targeted approach for those using opioids, particularly given that opioids appear to predispose to excessive hypoxemia relative to controls (47, 125, 126). Sleep hypoxemia (both sustained and intermittent) is linked with several adverse health outcomes including cardiovascular, neurocognitive, and mortality (127, 128). Moreover, hypoxemia may have a “feed forward” effect on SDB via neuroplastic effects on hypoxic ventilatory responses (129), increasing loop gain and arousal (130). Supplemental oxygen has been used in the setting of CSA due to heart failure as well as in OSA (131, 132). In these contexts, the responses to supplemental oxygen are dependent on the underlying SDB physiology, with the strongest evidence for improved responses in the setting of high loop gain and effects mediated by a reduction in loop gain (133-135). Supplemental oxygen can improve outcomes such as blood pressure, particularly in the setting of high loop gain (136). On the other hand, studies of oxygen in patients with severe obstructive lung disease have noted increases in respiratory event length and (137-139) oxygen use with acute opioid administration might worsen reductions in respiratory drive (140); whether those using chronic opioids have similar responses remains unknown.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

- Discomfort or sleep disruption from overnight polysomnography or other physiologic testing.
- Morning drowsiness or impaired vigilance after overnight research procedures.

- Blood-draw discomfort, bruising, or vasovagal symptoms.
- Questionnaire-related emotional distress from sensitive questions about sleep, pain, mood, or substance use.
- Identification of previously unrecognized sleep issues such as sleep apnea, arrhythmia, seizures, REM sleep without atonia.
- Identification of mental health issues including depression, suicidal ideation, or opioid misuse.
- Loss of confidentiality, despite use of coded data and secure institutional systems.
- Worsening pain, withdrawal symptoms, mood change including suicidality, functional decline, or other clinical destabilization during opioid dose adjustment.
- Reduced adherence or retention related to burden of safety monitoring or concern about pain worsening.
- Risks related to identification of sleep-disordered breathing through research testing rather than clinical care, with treatment occurring through usual clinical pathways rather than through the study.

2.3.2 KNOWN POTENTIAL BENEFITS

Potential benefits of participation are not guaranteed. Potential benefits to participants or others include:

- Identification of previously unrecognized sleep-disordered breathing or other clinically important findings requiring notification or referral.
- Possible short-term physiologic benefit from study interventions in some participants, including supplemental oxygen in Aim 2 or clinician-directed opioid dose adjustments in Aim 3.
- Improved understanding of sleep-disordered breathing, ventilatory instability, opioid-related respiratory physiology, and mechanisms that may inform future treatment strategies.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks associated with this study are considered minimal. There are no benefits expected for subjects participating this study outside that which the patient might receive by short-term treatment with supplemental oxygen (benefits are not known in this group). If SDB is discovered during the study, the subject will be counseled and referred for treatment. The information learned from the study may increase our understanding of the interaction between opioids and SDB, and therefore may benefit patients in the future. Because the risks to individual participants are minimal, we feel that they are reasonable when balanced against the potential benefits.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine whether nocturnal supplemental oxygen improves ventilatory stability in adults with chronic opioid use and sleep-disordered breathing (SDB).	Flow-based apnea–hypopnea index (AHIflow), which quantifies respiratory events using nasal airflow and does not rely on oxygen desaturation	(AHIflow) remains valid during supplemental oxygen use and is a sensitive measure of sleep physiology and treatment response.
Secondary		
To evaluate the effects of supplemental oxygen on sleep-disordered breathing (SDB) physiology, gas exchange, neurobehavioral performance, and patient-reported outcomes.	Loop gain, respiratory pattern variability, arousal threshold, time with SpO_2 <90%, $TcCO_2$, standard PSG metrics (AHI), psychomotor vigilance test (PVT), and patient-reported outcomes.	These endpoints assess both physiologic mechanisms and clinical outcomes, capturing the effects of oxygen on ventilatory control, gas exchange, and functional status.
Tertiary/Exploratory		
To explore factors associated with response to supplemental oxygen, including baseline physiology and sex-based differences.	Associations between baseline physiologic measures and changes in (AHIflow), ventilatory control, and functional outcomes.	These analyses may help identify factors associated with variability in response and provide insight into underlying physiologic and biologic mechanisms.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is designed to test the hypothesis that nocturnal supplemental oxygen improves ventilatory stability in adults with chronic opioid use and sleep-disordered breathing (SDB).

This is a Phase II, single-center, randomized, double-blind, sham-controlled, cross-over trial conducted at the University of California, San Diego. The study evaluates nocturnal supplemental oxygen compared with sham air in adults with chronic opioid use and SDB.

Potential participants may be recruited through IRB-approved flyers, secure MyChart messages, referrals from treating clinicians, or other IRB-approved recruitment methods. Recruitment will focus on individuals who self-identify as having opioid use disorder (OUD) or who are receiving long-term opioid therapy and express interest in learning more about the study. Individuals identified through review of the electronic medical record (EPIC) may be considered for recruitment only after permission is obtained from their primary care provider or treating clinician, as appropriate, before contact by the study team. To protect participant privacy, study staff will not leave voicemail messages identifying an individual's medical condition or potential eligibility for the study and will not send emails to participants' personal email addresses outside of the MyChart system.

Participants will undergo screening to determine eligibility. Screening procedures will include review of inclusion and exclusion criteria, which can generally be performed by asynchronous review of the screening information by the study team, with follow-up communication to verify any incomplete or unclear responses. Individuals not meeting eligibility criteria will be notified through secure communication methods. Individuals meeting eligibility criteria will be invited for a baseline visit.During the baseline visit, written informed consent will be obtained prior to any reseach procedures. Following consent, additional information will be obtained including demographics, medical and sleep history, medication review, physical examination, vital signs, height, weight, BMI, and questionnaires/study testing. A baseline overnight polysomnography (PSG) will be performed if a qualifying PSG has not been completed within the prior 6 months or if there has been a clinically significant change in medical or sleep-related status, as determined by the study investigator. If needed, the baseline visit and PSG can be performed on separate visits, ideally within 2 weeks. Participants with AHI3A >/= 5 events/hr will be eligible to continue in the study. Those with AHI3A <5 events/hr will be notified that they are no longer eligible to participate.

Eligible participants will then undergo an oxygen titration PSG. During this overnight visit, PSG monitoring will be used to assess sleep architecture, respiratory events, oxygenation, and ventilatory physiology. Transcutaneous carbon dioxide ($TcCO_2$) monitoring will be performed to assess nocturnal hypercapnia. Participants with $TcCO_2$ >55 mmHg for >10 minutes during the titration PSG will be excluded from subsequent randomization.

Eligible participants will then proceed to a randomization visit, which can be performed the morning following oxygen titration PSG, or on a separate visit. Participants will be randomized in a 1:1 ratio to one of two treatment sequences: supplemental oxygen followed by sham air, or sham air followed by supplemental oxygen. Randomization will be conducted in a double-blind

manner. Participants and study staff will remain blinded to treatment assignment. Participants will receive study device training and home-use instructions at the randomization visit.

Each participant will complete two treatment periods in a cross-over design. Treatment Period 1 will consist of approximately 7 consecutive nights of at-home use of the assigned intervention, either supplemental oxygen or sham air. Participants will be instructed to use the assigned device nightly during sleep. Study staff will conduct scheduled telephone calls approximately 24 hours after initial setup and one additional time during each treatment phase to assess adherence, answer device-related questions, and review adverse events.

At the end of Treatment Period 1, participants will return for an in-laboratory overnight PSG to evaluate the physiologic effects of the assigned intervention. Procedures will include PSG monitoring, $TcCO_2$ monitoring, questionnaires/study testing, morning psychomotor vigilance testing adherence review, and adverse event assessment.

Following Treatment Period 1, participants will complete a washout period of approximately 2 weeks, during which no study intervention will be used. Participants will then begin Treatment Period 2 and will receive the alternate intervention for approximately 7 consecutive nights at home. As in Treatment Period 1, participants will use the assigned device nightly during sleep and will receive scheduled study contacts to assess adherence and adverse events.

At the conclusion of Treatment Period 2, participants will return for a final in-laboratory overnight PSG to assess physiologic outcomes under the alternate intervention. Procedures will be consistent with the end-of-period PSG assessments and will include PSG monitoring, $TcCO_2$ monitoring, questionnaires/study testing, morning PVT adherence review, and adverse event assessment.

The study includes two intervention conditions, supplemental oxygen and sham air, within a cross-over design, with each participant serving as their own control. The total duration of study participation is approximately 6–10 weeks. The study will be conducted at a single site, UC San Diego. Details regarding oxygen dosing and administration are provided in Section 6.1.2.

Participant compensation

- Baseline visit, without PSG: $50
- Baseline visit with PSG, if needed: $200
- Oxygen Titration PSG: $200
- Randomization Day Visit, if separate visit needed: $50
- End of Treatment Period 1 PSG: $200
- End of Treatment Period 2 PSG: $200
- If an additional daytime visit is needed for data collection: $50
- If data are inconclusive and an additional polysomnography night is required, participants will receive an additional $200.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study is designed to evaluate the physiologic effects of nocturnal supplemental oxygen on ventilatory stability in adults with chronic opioid use and sleep-disordered breathing (SDB). A randomized, double-blind, sham-controlled, cross-over design was selected to allow each participant to serve as their own control, thereby reducing inter-individual variability in ventilatory control and improving statistical efficiency.

The use of a sham control is necessary to account for potential placebo effects and to maintain blinding, particularly given the subjective components of sleep quality and symptom reporting. Double-blinding of participants and study staff further minimizes bias in both intervention delivery and outcome assessment.

The cross-over design is particularly appropriate for this study because the physiologic effects of supplemental oxygen are expected to be reversible, allowing for direct within-subject comparison between treatment conditions. A washout period of approximately two weeks is included to minimize potential carryover effects between treatment phases.

Polysomnography (PSG) is performed at baseline (if needed) and at the end of each treatment period to provide objective, gold-standard assessment of sleep architecture, respiratory events, and ventilatory physiology. The inclusion of physiologic measures such as loop gain, respiratory pattern variability, and gas exchange allows for mechanistic evaluation of how supplemental oxygen influences ventilatory control.

The duration of each treatment period (approximately 7 nights) was selected to allow sufficient exposure to the intervention while minimizing participant burden. This timeframe is expected to capture steady-state physiologic effects of supplemental oxygen during sleep.

Overall, this study design allows for rigorous evaluation of both mechanistic and clinical effects of supplemental oxygen while minimizing bias and variability.

4.3 JUSTIFICATION FOR DOSE

Supplemental oxygen will be administered via nasal cannula during sleep. The nasal cannula route is selected as it is the standard, non-invasive method for delivering low-flow oxygen therapy in both clinical and research settings. This route is well tolerated, widely used, and allows for consistent overnight delivery without interfering significantly with sleep.

The planned starting and maximum dose of supplemental oxygen is up to 4 liters per minute (L/min), delivered continuously during sleep. Oxygen flow will be titrated during an in-laboratory overnight titration study prior to randomization to achieve adequate oxygenation while minimizing the risk of hypercapnia. This titration approach allows individualized dosing based on physiologic response and is consistent with clinical practice.

The selected dosing range is supported by prior studies demonstrating that low-flow supplemental oxygen (typically 1–4 L/min) is sufficient to improve oxygenation and stabilize ventilatory control without significantly increasing the risk of carbon dioxide retention in appropriately screened individuals. Participants with evidence of significant hypercapnia during screening or titration will be excluded to further reduce risk.

The dosing regimen consists of nightly use during sleep for approximately 7 consecutive nights per treatment period, consistent with the study's cross-over design. This duration is sufficient to assess the physiologic effects of supplemental oxygen while minimizing participant burden.

The control condition will consist of sham air delivered via an identical nasal cannula system, with airflow that mimics the experience of oxygen delivery but does not provide supplemental oxygen. The sham intervention is necessary to maintain blinding and control for potential placebo effects.

This dosing and administration strategy is designed to provide a safe, physiologically relevant exposure to supplemental oxygen while allowing for rigorous evaluation of its effects on ventilatory stability and sleep-disordered breathing (SDB).

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all study procedures, including both treatment periods, the washout period, and the final overnight polysomnography (PSG) visit, as outlined in the Schedule of Activities (SoA), Section 1.3.

Participants who withdraw early or are discontinued from the study prior to completing all required procedures will be considered not to have completed the study.

The end of the study is defined as the completion of the final study visit or procedure (i.e., the last participant's final overnight PSG or associated assessments) as specified in the SoA.

5 STUDY POPULATION

5.1

Participants must meet all of the following criteria to be eligible for enrollment:

1. Age 18 to 75 years

2. Chronic opioid use for ≥3 months with a daily opioid dose equivalent to at least 20 mg of oral morphine (morphine equivalent daily dose [MEqD]). Examples include approximately 13 mg oxycodone, 20 mg hydrocodone, 100 mg tramadol, or equivalent doses of other opioids.
3. Ability and willingness to comply with all study procedures, including overnight polysomnography and home use of study equipment
4. Ability to provide written informed consent
5. For participants able to become pregnant: agreement to use a highly effective method of contraception (e.g., licensed hormonal or intrauterine method, or an effective barrier method) during study participation.
6. Recruitment will target approximately equal numbers of males and females to enable consideration of sex as a biological variable, consistent with NIH policy.

In addition to enrollment criteria, participants must meet the following criterion to be eligible for randomization:

1. Diagnosis of sleep-disordered breathing (SDB), defined as AASM-recommended apnea–hypopnea index (AHI3A) ≥ 5 events per hour on a qualifying sleep study. AHI3A includes hypopnea definition ≥ 30% airflow reduction lasting ≥ 10seconds, accompanied by ≥3% SpO2 desaturation or arousal.

5.2 EXCLUSION CRITERIA

Participants will be excluded if any of the following criteria are met:

1. Body mass index (BMI) >35 kg/m²
2. Requirement for supplemental oxygen therapy outside of the study
3. Current use of positive airway pressure (PAP) therapy that cannot be safely discontinued for study participation
4. Known severe pulmonary disease (e.g., advanced chronic obstructive pulmonary disease) that, in the opinion of the investigator, may increase the risk of oxygen-induced hypercapnia
5. Unstable or clinically significant cardiopulmonary disease, including but not limited to decompensated heart failure, unstable angina, or clinically significant arrhythmia
6. Recent hospitalization (within the past 30 days) or anticipated need for hospitalization during the study period
7. Recreational or non-prescribed opioid use
8. Alcohol use exceeding 2 standard drinks per day or evidence of substance use disorder that may interfere with study participation
9. Presence of other sleep disorders or neurologic conditions that significantly affect breathing during sleep (e.g., neuromuscular disease), in the opinion of the investigator
10. Pregnancy or breastfeeding, or planning to become pregnant during the study period

11. Positive pregnancy test at screening (serum or urine) for participants able to become pregnant. A pregnancy test will be repeated prior to each in-laboratory PSG visit; a positive test triggers withdrawal from further study procedures.
12. Hospitalization for respiratory failure within the prior 12 months.
13. Severe untreated insomnia (Insomnia Severity Index >22) likely to preclude completion of in-laboratory PSG visits.
14. Inability to communicate in English sufficient for informed consent and study procedures, where a qualified interpreter consistent with UCSD HRPP policy is not available.
15. Inability to tolerate nasal cannula or study procedures
16. Inability to provide informed consent or comply with study procedures
17. Any medical, psychiatric, or social condition that, in the opinion of the investigator, would interfere with safe participation or interpretation of study results
18. Prisoners or individuals who are involuntarily incarcerated.
19. Current smoking or a home environment that, in the opinion of the investigator, does not permit the safe use or storage of home oxygen equipment (e.g., indoor smoking, open flames, or other significant fire hazards).

In addition to the enrollment exclusion criteria, participants will be excluded from randomization if any of the following criteria are met:

1. Evidence of significant hypercapnia, defined as transcutaneous carbon dioxide ($TcCO_2$) >55 mmHg for >10 minutes during screening or oxygen titration polysomnography (PSG)

5.3 LIFESTYLE CONSIDERATIONS

Participants will be instructed to maintain their usual daily routines, including diet, physical activity, and sleep schedules, throughout the study period. Participants will be asked to avoid initiating new medications or therapies that may affect sleep or respiratory function unless medically necessary. Participants should not change prescribed opioid dosing unless directed by their treating clinician.

Participants will be instructed to avoid alcohol consumption, recreational drug use, and excessive caffeine intake on the days of in-laboratory polysomnography (PSG) visits, as these substances may affect sleep architecture and respiratory parameters.

Participants will also be instructed to use the study device only during sleep and not during daytime hours. Any changes in medications, health status, or lifestyle factors that may affect sleep or breathing should be reported to the study team.

5.4 SCREEN FAILURES

Potential participants may undergo screening activities prior to informed consent to assess preliminary eligibility. Screening activities may include review of medical records, prior sleep studies, medication records, clinic notes, laboratory results, referral information, and responses to study questionnaires or REDCap screening surveys, in accordance with IRB approval and applicable HIPAA regulations, as described in Section 8.1 and DSMP §3.3 (Protections Against Risk).

Individuals determined to be ineligible prior to informed consent will be considered screen failures and will not be enrolled in the study.

Participants who provide informed consent but are subsequently found to be ineligible prior to randomization, or who are unable or unwilling to continue participation prior to randomization, will be classified as early discontinuations prior to randomization rather than screen failures. Reasons may include failure to meet subsequent inclusion/exclusion criteria, withdrawal of consent, adverse events, safety concerns identified during study procedures, protocol-defined exclusion findings, or investigator determination that continued participation is not appropriate.

A minimal set of information may be retained for participants who consent but do not proceed to randomization in order to support study tracking, CONSORT reporting, safety oversight, and regulatory requirements. This information may include demographics, eligibility status, reason for discontinuation or non-randomization, and any adverse events (AEs) or serious adverse events (SAEs) occurring during the screening or pre-randomization period, consistent with DSMP §§4 and 6.

Participants who do not proceed to randomization will not undergo additional study procedures beyond those required for eligibility determination or participant safety. Re-screening may be permitted if the reason for ineligibility or discontinuation is temporary and has resolved, as determined by the investigator.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

This study will evaluate two study interventions: supplemental oxygen and a sham air control, administered in a randomized, double-blind, cross-over design.

Both interventions will be delivered using visually identical oxygen concentrators connected to a standard wall electrical outlet and administered through a standard nasal cannula. Participants will receive both interventions in a randomized sequence, with each intervention administered

during separate treatment periods. Each treatment period will consist of approximately 7 consecutive nights of at-home use during sleep, separated by a washout period of approximately 14 days.

The supplemental oxygen intervention will deliver oxygen at the individualized flow rate determined during the in-laboratory oxygen titration study. The sham intervention will deliver room air through the same concentrator and nasal cannula setup while maintaining continuous airflow to mimic the experience of oxygen delivery. Device configuration will be performed by designated unblinded study personnel who are not involved in participant assessments or outcome evaluation. Participants, investigators, and study staff responsible for data collection and outcome assessment will remain blinded to treatment assignment throughout the study.

6.1.2 DOSING AND ADMINISTRATION

Supplemental Oxygen

Supplemental oxygen will be delivered using an oxygen concentrator connected to a standard wall electrical outlet and administered through a nasal cannula during sleep. Oxygen flow will be titrated during an in-laboratory overnight titration study prior to randomization to determine the appropriate individualized flow rate for each participant. The maximum flow rate will be up to 4 liters per minute (L/min).

Participants will receive instruction on proper equipment setup, operation, and home oxygen safety before beginning home treatment. Participants will be instructed to use the oxygen concentrator nightly during sleep for approximately 7 consecutive nights during each assigned treatment period.

Sham Control (Air)

The sham intervention will be delivered using an identical oxygen concentrator connected to a standard wall electrical outlet and administered through an identical nasal cannula. The concentrator will be configured to deliver room air rather than supplemental oxygen while providing continuous airflow through the nasal cannula to mimic the experience of oxygen delivery and maintain participant blinding.

The sham intervention will be administered using the same schedule, equipment, participant instructions, and treatment duration as the supplemental oxygen intervention. Device configuration will be performed by designated unblinded study personnel to preserve the study blind. Participants, investigators, and study staff involved in outcome assessment will remain blinded to treatment assignment throughout the study.

Prior to home use, participants will receive verbal and written instruction regarding the safe operation, storage, and handling of the oxygen concentrator and associated equipment. Study

staff will review home oxygen safety precautions, including avoidance of smoking, open flames, heat sources, and other fire hazards, and will confirm that the home environment is appropriate for safe use of the study equipment.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Study oxygen equipment, including oxygen concentrators and any associated supplies, will be maintained, tracked, and distributed by study personnel. Equipment accountability will be documented throughout the study.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Oxygen equipment and associated supplies will remain labeled in accordance with manufacturer requirements and applicable institutional safety policies. Required safety labels and warnings will not be removed or altered.

6.2.3 PRODUCT STORAGE AND STABILITY

Oxygen equipment will be stored, transported, and used according to manufacturer recommendations and institutional safety procedures. Participants will receive instruction regarding safe home storage and operation of oxygen equipment, including maintaining adequate ventilation, avoiding heat sources, smoking, and open flames.

6.2.4 PREPARATION

Not applicable

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants who meet eligibility criteria will be randomized in a 1:1 ratio to one of two treatment sequences: (1) supplemental oxygen followed by sham air or (2) sham air followed by supplemental oxygen.

Randomization will be performed using a computer-generated randomization schedule prepared by study personnel not directly involved in participant enrollment or outcome assessment. Allocation will be concealed until the time of assignment.

This study will be conducted in a double-blind manner. Participants, investigators, and study staff involved in data collection and outcome assessment will remain blinded to treatment assignment throughout the study.

Blinding will be maintained through the use of identical or visually indistinguishable devices for both supplemental oxygen and sham air delivery. Device configuration and preparation will be performed by designated unblinded study personnel who are not involved in outcome assessment.

The cross-over design further minimizes bias by allowing each participant to serve as their own control, reducing the impact of inter-individual variability in ventilatory control and sleep physiology.

Unblinding will only occur in the event of a medical emergency or when knowledge of the intervention is necessary for clinical management. Any unblinding will be documented and reported in accordance with study procedures. In addition, events requiring unblinding will undergo expedited reporting to the DSMB.

6.4 STUDY INTERVENTION COMPLIANCE

Participant compliance with the study intervention will be assessed through participant self-report, review of device usage logs, and study staff check-ins during each treatment period.

Study staff will conduct scheduled contacts (e.g., telephone or electronic communication) during each treatment period to assess adherence, address device-related questions, and monitor for adverse events.

Compliance will also be indirectly assessed during in-laboratory polysomnography (PSG) visits conducted at the end of each treatment period, during which the physiologic effects of the assigned intervention will be evaluated.

Participants will be asked to report any missed nights of device use or difficulties with the study intervention. Reasons for non-compliance will be documented.

Participants who are unable or unwilling to comply with study procedures, including consistent use of the study intervention, may be withdrawn from the study at the discretion of the investigator.

6.5 CONCOMITANT THERAPY

For this protocol, concomitant therapy includes all prescription medications, over-the-counter medications, supplements, complementary and alternative therapies, and medical treatments or procedures used by participants during the study.

All concomitant medications and therapies will be recorded in the case report forms (CRFs), including medication name, indication, dose, frequency, and duration of use. This information will be collected at screening and updated at each study visit, including randomization and overnight polysomnography (PSG) visits, as well as during scheduled study contacts.

Participants will be encouraged to maintain a stable medication regimen, including opioid therapy, throughout the study unless changes are medically necessary. Any changes in medications, including opioid dose, sedatives, or other agents that may affect sleep or respiratory function, will be documented throughout the study.

Initiation of new therapies that may significantly affect sleep-disordered breathing (SDB) or ventilatory control (e.g., positive airway pressure [PAP] therapy, supplemental oxygen outside of the study, or respiratory depressant medications) should be avoided during study participation unless clinically indicated. Participants who require initiation of such therapies may be withdrawn from the study at the discretion of the investigator for safety reasons.

The potential effects of concomitant therapies will be addressed through documentation of medication use, efforts to maintain stable regimens during the study period, and consideration of medication changes during data analysis. Where appropriate, analyses may account for changes in medications or baseline medication use to distinguish the effects of the study intervention from those of concomitant therapies.

6.5.1 RESCUE MEDICINE

Not applicable.

If a participant requires initiation of clinically indicated positive airway pressure (PAP) therapy, supplemental oxygen outside of the study, or a respiratory-depressant medication during the study period, study intervention is discontinued and the participant may be withdrawn per Section 7.1.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Criteria and procedures for discontinuation of study intervention are provided in DSMP §9.3 (Individual Participant Discontinuation and Withdrawal Criteria), incorporated here by reference.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Criteria and procedures for participant discontinuation from the study and full withdrawal are provided in DSMP §9.3 (Individual Participant Discontinuation and Withdrawal Criteria), incorporated here by reference.

7.3 LOST TO FOLLOW-UP

Criteria, contact-attempt sequence, documentation, and analytical handling of participants lost to follow-up are provided in DSMP §9.4 (Lost to Follow-Up), incorporated here by reference.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

This section describes study procedures and evaluations performed to assess the physiologic effects of nocturnal supplemental oxygen on ventilatory stability and sleep-disordered breathing (SDB) in adults with chronic opioid use. The timing of study procedures is detailed in the Schedule of Activities (SoA), Section 1.3.

Screening Procedures

To determine preliminary eligibility, study personnel may review existing medical records, including prior sleep studies, medication records, clinic notes, laboratory results, and other relevant clinical information. Access to protected health information (PHI) for screening purposes will be conducted in accordance with institutional policy, IRB approval, and applicable HIPAA regulations. A partial waiver of HIPAA authorization may be used, as approved by the IRB, to permit review of records necessary to identify potentially eligible participants prior to obtaining informed consent.

Screening procedures will be conducted within 28 days prior to enrollment to determine participant eligibility.

Screening assessments may include:

- Review of inclusion and exclusion criteria
- Limited Medical and sleep history
- Limited Concomitant medication review
- Review of prior diagnostic sleep studies, if available
- Assessment of the home environment to ensure safe use and storage of supplemental oxygen equipment, including evaluation of smoking, open flames, fire hazards, electrical safety, and the participant's ability to safely operate and store the equipment.

Baseline visit Procedures

A baseline visit will be performed, during which the following will be obtained:

- Informed consent
- Re-Review of inclusion and exclusion criteria
- Detailed Medical and sleep history
- Vitals and focused physical examination
- Detailed Concomitant medication review
- Questionnaires
- Blood draw

A baseline overnight polysomnography (PSG) will be performed if a qualifying PSG has not been completed within the prior 6 months or if there has been a clinically significant change in medical or sleep-related status.

Eligibility for further participation will be based on continued fulfillment of inclusion and exclusion criteria, including confirmation of sleep-disordered breathing (AHI3A ≥ 5 events/hour).

Oxygen Titration Procedure

Eligible participants will undergo an overnight oxygen titration PSG prior to randomization.

Supplemental oxygen will be titrated to achieve adequate oxygenation while minimizing risk of hypercapnia. Transcutaneous carbon dioxide ($TcCO_2$) monitoring will be performed during titration.

Participants demonstrating significant hypercapnia ($TcCO_2$ >55 mmHg for >10 minutes) will be excluded from further participation.

Oxygen Intervention Procedures

Participants will be randomized to receive supplemental oxygen or sham air in a double-blind cross-over design.

Each treatment period will consist of approximately 7 consecutive nights of at-home use of the assigned intervention during sleep.

Participants will:

- Receive instruction on device setup and use
- Participants will receive written home oxygen safety instructions in addition to verbal training at the time study equipment is provided.
- Use the assigned intervention nightly during sleep

- Participate in scheduled study contacts for adherence review and adverse event monitoring

Post-Intervention Assessments

At the end of each treatment period, participants will undergo an overnight PSG to assess physiologic responses to the assigned intervention.

Assessments may include:

- Sleep architecture
- Respiratory events, including AHI and AHIflow
- Oxygenation and gas exchange
- Ventilatory control measures
- $TcCO_2$ monitoring
- Morning Psychomotor Vigilance Test (PVT)
- Questionnaires and patient-reported outcomes
- Adherence review
- Adverse event assessment

Following overnight PSG visits, participants will undergo a standardized morning release assessment, including evaluation of alertness and fitness to drive, in accordance with the DSMP.

Questionnaires and Patient-Reported Outcomes

Validated patient-reported outcome measures will be administered to assess sleep quality, daytime functioning, and related symptoms.

The patient-reported outcome (PRO) battery is harmonized with the NIH HEAL Initiative Common Data Elements (CDEs) for adult chronic pain research. The full battery and its schedule are described below; instrument-level recall windows are noted for transparency and for selection of follow-up subsets in time-constrained intervention windows.

HEAL CDE core (adult chronic pain):

- Pain intensity and interference — PEG (3-item; past week).
- Physical functioning — PROMIS Physical Functioning Short Form 6b (current ability).
- Sleep — PROMIS Sleep Disturbance Short Form 6a (past 7 days).
- Pain catastrophizing — Pain Catastrophizing Scale Short Form (6-item or 13-item; situational).
- Depression — PHQ-9 (past 2 weeks).
- Anxiety — GAD-7 (past 2 weeks).
- Global satisfaction / impression of change — Patient Global Impression of Change (PGIC; change since baseline).
- Substance-use screener — TAPS-1 (past 12 months).

- Health-related quality of life — WHOQOL-BREF (past 2 weeks).

Sleep and fatigue adjuncts:

- PROMIS Sleep-Related Impairment Short Form 8a (past 7 days).
- PROMIS Fatigue Short Form 8a (past 7 days).
- Epworth Sleepiness Scale (ESS; usual lifestyle, trait measure).
- Pittsburgh Sleep Quality Index (PSQI, past month; includes the sleep-duration items).
- Insomnia Severity Index (ISI; past 2 weeks).

Opioid use, misuse, and safety screens:

- Current Opioid Misuse Measure (COMM; past 30 days).
- Suicide-risk screening: PHQ-9 item 9 monitored at every administration.
- Karolinska Sleepiness Scale (KSS) is administered the morning after every in-laboratory PSG before discharge, consistent with DSMP §4.2.

Prescription opioid quantification: Name of opioid, dose, prescription duration, total days exposed, and daily dose in morphine milligram equivalents (MME) will be captured for every prescribed opioid. MME calculations will use the NIH HEAL Morphine Milligram Equivalent Online Calculator (research-mme.wakehealth.edu), which provides evidence-based mapping factors for 29 opioids (traditional full agonists, partial agonists, and mixed-mechanism agents) and supports four standardized time-window calculation methods (Total Days Supply, On-therapy Days, Fixed Observation Window, and Maximum Daily Dose). For pre-specified analyses involving large datasets or offline use, the companion R package mmequiv (CRAN) will be used to replicate the same calculations. MME outputs are used for research characterization only and do not inform clinical prescribing. Citation: Adams MCB, Sward KA, Perkins ML, Hurley RW. Standardizing research methods for opioid dose comparison: the NIH HEAL morphine milligram equivalent calculator. PAIN. 2025;166(8) (doi:10.1097/j.pain.0000000000003529).

Collection schedule:

Full HEAL-aligned battery is collected at the baseline visit. At the end-of-week-1 and end-of-week-2 PSG visits (the oxygen and sham follow-up visits, approximately 7 nights of at-home intervention each), only PRO instruments with a recall window ≤1 week are administered, in order to match the recall window to the intervention exposure period. The follow-up subset consists of: PEG (past week); PROMIS Sleep Disturbance Short Form 6a (past 7 days); PROMIS Sleep-Related Impairment Short Form 8a (past 7 days); PROMIS Fatigue Short Form 8a (past 7 days); PROMIS Physical Functioning Short Form 6b (current ability); PGIC (change since start of the assigned-arm period); and KSS the morning after the PSG. Instruments with longer recall windows (PSQI, ESS, ISI, PHQ-9, GAD-7, WHOQOL-BREF, COMM, TAPS-1, Pain Catastrophizing Scale) are not repeated at the 1-week follow-up PSG visits, but baseline values from the screening visit remain the reference.

Under-Mattress Cardiorespiratory Sensor

During each home intervention period, participants will use an under-mattress cardiorespiratory sensor to collect physiologic information during sleep. The sensor is placed beneath the mattress and does not come into direct contact with the participant. It continuously measures cardiorespiratory signals, including respiratory rate, heart rate, sleep-related movement, and breathing patterns. Data are transmitted securely to a research dashboard for review by authorized study personnel.

The under-mattress sensor is **not currently cleared by the U.S. Food and Drug Administration (FDA)** for clinical use; however, an FDA application is in progress. The device has previously been reviewed and approved for research use by the UC San Diego Institutional Review Board (IRB Protocol #171480) and has been used in both hospital and home research settings, including studies involving pregnant individuals and pediatric participants. To date, no device-related safety incidents have been reported during several years of research use at UC San Diego.

The sensor is used **for research data collection only** and is **not used to diagnose medical conditions or direct participant care**. Data collected from the device do not automatically trigger clinical decisions or treatment changes. If study personnel identify a potential safety concern during routine review of the research data, the information may prompt a telephone call to the participant to assess symptoms and determine whether additional medical evaluation is appropriate. Any decisions regarding medical care remain under the supervision of qualified study clinicians and are not made by the device itself.

The performance of the sensor has been evaluated against in-laboratory polysomnography (PSG), the clinical gold standard for sleep assessment. Validation studies demonstrated a mean absolute error of **0.6 breaths per minute** for respiratory rate and **1.2 beats per minute** for heart rate. The device has also demonstrated excellent performance for identifying sleep apnea, with an area under the receiver operating characteristic curve (ROC AUC) of **0.96 for severe sleep apnea** and **0.92 for moderate-to-severe sleep apnea**. Three-stage sleep classification accuracy is approximately **90%** based on ongoing validation studies. These validation results support the use of the device as a research monitoring tool but do not establish it as a substitute for clinical polysomnography.

Use of Existing Medical Data

Existing medical records and prior diagnostic studies may be used for screening and study data collection, as applicable. All data collection will comply with HIPAA regulations and institutional policies.

Qualified Personnel and Standardization

All study procedures, including PSG acquisition and scoring, physiologic monitoring, and neurobehavioral testing, will be performed by trained and qualified personnel using standardized procedures designed to minimize variability across study visits.

Biological Specimen Collection and Laboratory Evaluations

Blood samples will be collected at the Baseline Visit for measurement of opioid levels to characterize participant exposure and assess potential relationships between opioid use and study outcomes.

Samples will be processed and analyzed using standard laboratory methods and institutional procedures. Where applicable, testing will be conducted in CLIA-compliant laboratories.

Serum opioid concentrations will be measured by multiplex liquid chromatography–tandem mass spectrometry (LC–MS/MS) overseen by Dr. Jeremiah Momper (UCSD Pharmacometrics and Analytical Chemistry Core).

8.2 SAFETY AND OTHER ASSESSMENTS

Safety monitoring will be performed throughout study participation in accordance with the protocol-defined monitoring schedule.

Screening/Baseline: History, physical exam, medication review, vital signs, mood screening, opioid misuse screening, laboratory review, and confirmation of eligibility for supplemental O_2 exposure.

Baseline PSG night: Real-time technologist monitoring; $TcCO_2$ and SpO_2 review; PI review of PSG findings prior to randomization; exclusion if $TcCO_2$ >55 mmHg for >10 minutes or other protocol-defined safety criteria.

Oxygen titration night (PSG): Physician-supervised titration under PSG; real-time $TcCO_2$, SpO_2, and respiratory pattern review; safety exclusions reapplied before home exposure; prescribed fixed-flow determined.

Morning release assessment: Standardized release criteria (Section 4.2) after each overnight visit.

Home intervention week—automated text check-in: Assessment of sedation, respiratory symptoms, mood change, symptoms suggestive of nocturnal hypoventilation/hypercapnia, and device intolerance. Positive responses trigger same-day staff follow-up and PI review when indicated.

Home intervention week—under-mattress cardiorespiratory sensor: Nightly remote surveillance of heart rate, respiratory rate, and movement; research staff review incoming data with pre-specified escalation thresholds for abnormal values (i.e., mean HR <40 or >110, RR <8 or >22) or major night-to-night change (i.e., >30% from prior mean values); provides monitoring for potential breathing-pattern changes related to oxygen use.

Mid-week phone call: Coordinator-administered symptom review, adherence reinforcement, confirmation of safe continuation; troubleshooting of equipment issues; PI notification of nonadherence or device malfunction.

Oxygen/sham concentrator compliance: Concentrator usage-hour review; participant confirmation of prescribed flow and duration; PI notification of nonadherence or device malfunction.

End-of-week PSG night: Real-time technologist monitoring; PI review of outcome PSG and any safety signals prior to crossover or study completion.

AE capture and PI review: AE CRF review; severity, expectedness, and relatedness adjudication; reporting per Section 8.3

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32(a)).

For this study, an Adverse Event (AE) is defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to participation (OHRP guidance; ICH E6 Good Clinical Practice). AEs encompass physical and psychological harms.

Adverse event (AE), serious adverse event (SAE), and unanticipated problem (UP) monitoring and reporting will be conducted in accordance with the study Data and Safety Monitoring Plan (DSMP).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious Adverse Event (SAE): Any AE temporally associated with research participation that results in: death; life-threatening event; inpatient hospitalization or prolongation of hospitalization; persistent or significant disability/incapacity; congenital anomaly/birth defect; or any other event that may jeopardize participant health and require medical or surgical intervention to prevent these outcomes.

Mental health crises, suspected overdose, clinically significant withdrawal, respiratory deterioration, or other events that may jeopardize participant safety will be reviewed urgently and may qualify as SAEs or unanticipated problems (UPs) even if hospitalization has not yet occurred. If uncertainty exists about seriousness or reportability, the event will be managed as reportable pending final determination.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

AE severity will be classified using CTCAE v5.0:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization indicated.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

Relationship of each adverse event to the study intervention will be classified as follows:

- **Definitely Related:** Clearly related to investigational procedure in temporal sequence, with no other plausible explanation.
- **Possibly Related:** Follows reasonable temporal sequence from research procedures but could have been produced by other factors.
- **Not Related:** Another cause is most plausible; causal relationship is biologically implausible.

8.3.3.3 EXPECTEDNESS

Expectedness of adverse events will be determined by the Principal Investigator using the study protocol, DSMP, published literature, and known risks associated with study procedures and supplemental oxygen administration, as described in DSMP §§3 and 6.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

All adverse events (AEs) will be reviewed by the Principal Investigator typically within one business day, and the same day for any event meeting red-flag criteria or potentially meeting the definition of a serious adverse event (SAE) or unanticipated problem (UP). The Principal Investigator will adjudicate the final severity, expectedness, and relatedness classifications.

Each event will be tracked longitudinally until resolution, stabilization, or determination that no further follow-up is feasible. Any new information altering the seriousness, expectedness, or relatedness assessment will trigger an updated report to the appropriate oversight bodies.

Adverse event case report form review, severity, expectedness, and relatedness adjudication, and reporting will occur on an ongoing basis, with review at each participant contact, in accordance with the protocol-defined monitoring schedule.

8.3.5 ADVERSE EVENT REPORTING

All adverse events (AEs) will be documented in the study records. The Principal Investigator will review every AE, adjudicate final severity, expectedness, and relatedness classifications, and determine whether the event meets the definition of a serious adverse event (SAE) or unanticipated problem (UP).

Events meeting SAE or UP criteria will be reported to the IRB, NHLBI, and DSMB on the timelines specified in Section 7. All other AEs will be tabulated and reported to the DSMB at each scheduled review meeting and to the IRB at continuing review. Each event will be tracked longitudinally until resolution, stabilization, or determination that no further follow-up is feasible, and any new information altering the seriousness, expectedness, or relatedness assessment will trigger an updated report to the appropriate oversight bodies.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The Principal Investigator will review every AE — typically within one business day, and same-day for any event meeting red-flag criteria (Section 4.3.3) or potentially meeting SAE or unanticipated problem definitions — and will adjudicate final severity, expectedness, and relatedness classifications. Events meeting SAE or UP criteria will be reported to the IRB, NHLBI, and DSMB on the timelines specified in Section 7; all other AEs will be tabulated and reported to the DSMB at each scheduled review meeting and to the IRB at continuing review.

Each event will be tracked longitudinally until resolution, stabilization, or determination that no further follow-up is feasible, and any new information altering the seriousness, expectedness, or relatedness assessment will trigger an updated report to the appropriate oversight bodies.

Event	Initial Timeline	Reported By	Reported To
Fatal or life-threatening unexpected suspected SAE	DSMB: within 24 hours; IRB and NHLBI: within 7 calendar days	PI or delegated investigator	DSMB, IRB, NHLBI
Non-fatal unexpected suspected SAE	Within 15 calendar days of initial receipt	PI or delegated investigator	IRB, DSMB, NHLBI
Unanticipated problem not an SAE	Within 10 working days of awareness	PI or delegated investigator	IRB, DSMB, NHLBI
All other AEs	DSMB: At scheduled DSMB review IRB: Annually at time of renewal	PI or delegated investigator	DSMB, IRB

Any IRB action involving suspension, termination, reportable noncompliance, major safety-related revision, or other determination materially affecting participant safety will be forwarded to NHLBI. Any protocol or consent amendment that may alter subject risk, monitoring intensity, study arms, stopping rules, or remote monitoring procedures will be submitted to the IRB and provided to NHLBI and the DSMB, as applicable, after IRB approval and before implementation unless necessary to eliminate immediate hazard.

FDA reportability: no IND or IDE is currently held for any aim of this study based on the current protocol; therefore no expedited FDA reporting is required. If a protocol change introduces an FDA-regulated investigational use, the study will not proceed with that change until (i) an IND or IDE has been obtained, (ii) FDA expedited reporting timelines per 21 CFR 312.32 are incorporated into this DSMP, and (iii) the revised DSMP has been approved by the IRB and NHLBI.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Participants will be informed of adverse events (AEs) and clinically important findings identified during study procedures by the Principal Investigator (PI) or designee in a timely manner. Clinically important incidental findings will be promptly reviewed and disclosed to the participant. A summary letter will be generated and, upon request, will be sent to the participant's primary care or treating physician. For incidental findings such as a new diagnosis of sleep-disordered breathing (SDB), cardiac arrhythmia, or significant hypoxemia, participants will be counseled regarding the importance and potential consequences of the finding, including motor vehicle accident risk and cardiovascular risk, and appropriate referral pathways will be provided, as described in DSMP Section 3.3.

Participants will be informed of AEs and clinically important findings identified during study procedures by the PI or designee in a timely fashion. A summary letter will be generated and, upon request, will be sent to the participant's primary care or treating physician. For incidental findings such as new diagnosis of SDB, cardiac arrhythmia, or significant hypoxemia, participants will be counseled on the importance and potential consequences of the finding, including motor vehicle accident risk and cardiovascular risk, and referral pathways will be provided per DSMP §3.3.

8.3.8 EVENTS OF SPECIAL INTEREST

Events of special interest may include prolonged respiratory events, worsening hypercapnia, worsening hypoventilation, severe oxygen desaturation, respiratory deterioration, device intolerance, significant equipment malfunction affecting participant safety, hospitalization, or other clinically significant respiratory or sleep-related events requiring additional evaluation or intervention.

8.3.9 REPORTING OF PREGNANCY

Pregnancy occurring during study participation will be reported to the Principal Investigator and managed in accordance with institutional policy and IRB requirements. Participants who become pregnant may be withdrawn from study intervention or additional study procedures if continued participation is not considered appropriate or safe, consistent with DSMP §9.3.

Pregnancy will be detected by the protocol-specified pregnancy testing schedule described in Section 5.2 (serum or urine pregnancy test at screening and prior to each in-laboratory PSG visit for participants able to become pregnant) or by participant self-report at any time. Pregnancy will be reported to the IRB within 10 working days consistent with DSMP §7.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

An unanticipated problem (UP) is any incident, experience, or outcome that is: (1) unexpected in nature, severity, or frequency given the research procedures and the participant population; (2) related or possibly related to participation in the research; and (3) suggests that the research places participants or others at a greater risk of harm than was previously known or recognized.

Events meeting the definition of an unanticipated problem will be reviewed by the Principal Investigator to determine reportability and managed in accordance with the study Data and Safety Monitoring Plan (DSMP), applicable institutional policies, and federal regulations

8.4.2 UNANTICIPATED PROBLEM REPORTING

Unanticipated problems (UPs) will be reviewed by the Principal Investigator to determine reportability. Events meeting the definition of a UP will be reported in accordance with the reporting procedures and timelines described in Section 8.3.6 and the study Data and Safety Monitoring Plan (DSMP). Follow-up information will be submitted as it becomes available until the event is resolved, stabilized, or no further follow-up is feasible.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be informed in a timely manner of any unanticipated problem that may affect their safety, willingness to continue study participation, or medical care. The Principal Investigator or designee will promptly review and disclose clinically important information to the participant, provide appropriate counseling regarding the nature and potential consequences of the finding, and facilitate referral for appropriate clinical evaluation or treatment when indicated. Participants will be informed of any new information that may affect their willingness to continue participation in the study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint

The primary hypothesis is that nocturnal supplemental oxygen will reduce the severity of sleep-disordered breathing (SDB) compared to sham air, as measured by the apnea–hypopnea index based on airflow (AHIflow).

- **Null hypothesis (H_0):** There is no difference in AHIflow between oxygen and sham conditions.
- **Alternative hypothesis (H_1):** AHIflow is significantly lower during oxygen compared to sham air.

This will be evaluated as a **superiority comparison** in a randomized, double-blind, cross-over design.

Secondary Efficacy Endpoints

Secondary hypotheses are that supplemental oxygen will:

- Improve ventilatory stability (e.g., loop gain, arousal threshold)
- Reduce respiratory pattern variability
- Improve oxygenation (e.g., time with SpO_2 <90%)
- Affect nocturnal hypercapnia ($TcCO_2$)
- Improve neurobehavioral performance (Psychomotor Vigilance Test)
- Improve patient-reported sleep outcomes

These analyses are considered **secondary and exploratory**.

9.2 SAMPLE SIZE DETERMINATION

The study will enroll approximately 62 participants, with an anticipated 52 evaluable participants, to provide adequate statistical power for detecting a clinically meaningful difference in the primary endpoint (AHIflow). With 52 evaluable participants (58 enrolled at 10% attrition; 62 at 15% attrition), the study has 80% power to detect a minimum standardized effect size of 0.4. There will be no planned interim efficacy or futility analyses; however, the DSMB may modify this during ongoing safety monitoring

The sample size is based on:

- Primary outcome: AHIflow
- Design: Within-subject cross-over (each participant serves as their own control)
- Statistical test: Paired comparison / linear mixed-effects model
- Type I error (alpha): 0.05 (two-sided)
- Power: Approximately 80%

The cross-over design reduces inter-subject variability and increases statistical efficiency.

Allowances have been made for:

- Participant dropout
- Missing data
- Non-adherence

9.3 POPULATIONS FOR ANALYSES

The following analysis populations will be defined:

- Intention-to-Treat (ITT): All randomized participants
- Modified ITT: Participants completing at least one treatment period with evaluable PSG data
- Per-Protocol: Participants completing both treatment periods with adequate adherence
- Safety Population: All participants who receive any study intervention

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics:

- Continuous variables: mean ± standard deviation or median (IQR)
- Categorical variables: counts and percentages

Inferential testing:

- Two-sided tests
- Significance level: $p < 0.05$
- 95% confidence intervals

Analyses will account for the cross-over design and repeated measures.

A formal Statistical Analysis Plan (SAP) will be finalized prior to database lock and unblinding.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint (AHIflow) will be analyzed using a linear mixed-effects model appropriate for a cross-over design.

The model will include:

- Fixed effects for treatment (oxygen vs sham)
- Period effect
- Sequence (if applicable)
- Random effect for participant

Results will be presented as:

- Adjusted mean differences between treatment conditions
- 95% confidence intervals

This approach appropriately accounts for within-subject correlation.

Missing data will be handled using mixed-model methods under the assumption of missing at random.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints will be analyzed using:

- Linear mixed-effects models for continuous outcomes
- Appropriate transformations or nonparametric methods if assumptions are not met

Results will be reported as:

- Adjusted means or effect estimates
- 95% confidence intervals

These analyses are considered exploratory and hypothesis-generating.

9.4.4 SAFETY ANALYSES

Safety analyses will be descriptive.

- Adverse events (AEs) will be coded using MedDRA
- AEs will be summarized by:

- Frequency
- Severity
- Relationship to study intervention

Serious adverse events and discontinuations will be summarized separately.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics will be summarized using descriptive statistics.

No formal hypothesis testing will be performed for baseline comparisons.

9.4.6 PLANNED INTERIM ANALYSES

No formal interim efficacy analyses are planned.

Safety data will be periodically reviewed by the Data and Safety Monitoring Board (DSMB), which may recommend modifications if safety concerns arise.

9.4.7 SUB-GROUP ANALYSES

Exploratory subgroup analyses may include:

- Sex
- Age
- Opioid exposure levels

These analyses will be considered hypothesis-generating.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data may be listed by measure and time point, as appropriate.

9.4.9 EXPLORATORY ANALYSES

Exploratory analyses may evaluate:

- Relationships between opioid levels and ventilatory control
- Mechanistic physiologic responses to oxygen

These analyses will not be used for confirmatory conclusions.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 STUDY DISCONTINUATION AND CLOSURE

The Principal Investigator (PI), Institutional Review Board (IRB), NHLBI, or Data and Safety Monitoring Board (DSMB) may suspend or terminate the study or an individual study aim if participant safety is compromised, if new information indicates that study procedures present an unacceptable risk, if study objectives can no longer be achieved, or for administrative, regulatory, funding, or scientific reasons.

Recommendations for suspension or termination may be considered if there is an unexpected pattern of study-related Grade 3 or higher adverse events, any study-related death or life-threatening event attributable to research procedures, repeated clinically significant respiratory deterioration attributable to study procedures, oxygen administration, or other study interventions, or other evidence demonstrating that continuation of the study would not be in the best interest of participant safety.

Individual participants may discontinue study intervention or be withdrawn from study participation at their request, because of loss of capacity or inability to provide ongoing consent, pregnancy when continued participation is not appropriate, nonadherence creating a safety risk, a request from the treating clinician, determination by the PI that continued participation is unsafe, or at the direction of the DSMB, IRB, or NHLBI. Participants in the OPIO2 study may also be withdrawn for clinically significant hypercapnia or respiratory instability, or if clinically indicated positive airway pressure (PAP) therapy or supplemental oxygen outside of the study becomes necessary.

Whenever feasible, participants who discontinue study intervention will be encouraged to complete study follow-up assessments to support participant safety and preserve study data. Study records will be maintained in accordance with institutional policies, sponsor requirements, and applicable federal regulations.

Details regarding study discontinuation and closure are provided in DSMP §9.2 (Trial Stopping Rules), incorporated here by reference.

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality will be maintained throughout the study in accordance with applicable federal regulations, the Health Insurance Portability and Accountability Act (HIPAA), National Institutes of Health (NIH) requirements, and University of California, San Diego (UC San Diego) policies.

Participants will be assigned a unique study identification number. Identifiable information will be maintained separately from research data whenever possible.

Signed informed consent forms and any other paper records containing identifiable participant information will be stored in locked file cabinets within secure, access-controlled UC San Diego research offices. Access to these records will be limited to authorized study personnel.

Participant enrollment logs and documents linking participant names with study identification numbers will be maintained separately from research data in secure, password-protected, HIPAA-compliant electronic files on UC San Diego-managed systems. Access will be restricted to authorized study personnel through individual password-protected accounts with role-based access.

Research data will be captured using secure electronic case report forms in REDCap, direct participant questionnaire entry where appropriate, and secure UC San Diego-managed network resources. Overnight polysomnography (PSG) files, physiologic signal files, concentrator adherence downloads, remote monitoring summaries, laboratory records, and other electronic study data will be identified only by study identification number whenever possible and stored on secure, password-protected UC San Diego-managed servers.

Documents linking participant identifiers to study identification numbers will be stored separately from research data. Data generated outside REDCap will be transferred only through secure UC San Diego-approved systems. Electronic research data will be protected using institutional security measures, including password protection, restricted user access, and HIPAA-compliant data storage.

The study team will perform routine data quality checks for completeness, consistency, protocol compliance, intervention adherence, and timely completion of study procedures. Access to study records will be limited to authorized study personnel.

Participant confidentiality will be protected in all presentations and publications by reporting only aggregate or de-identified data. Adverse event reports and DSMB summaries will use coded participant identifiers unless disclosure of identifiable information is required for participant safety or regulatory reporting.

Study staff are mandatory reporters under California law. Confidentiality may be limited in circumstances involving imminent risk of serious harm to self or others, suspected abuse or neglect of a child, dependent adult, or elder, court order or other disclosures required by law, or

disclosures required under the NIH Certificate of Confidentiality regulations. These limits to confidentiality will be described during the informed consent process.

Because this is an NIH-funded study, an NIH Certificate of Confidentiality automatically applies. The Certificate helps protect identifiable research information from compelled disclosure in legal proceedings except as required by law or as otherwise permitted under NIH policy.

Detailed data-acquisition, transmission, storage, role-based access, mandatory-reporter limits to confidentiality, and the NIH Certificate of Confidentiality (CoC) statement for this NIH-funded study (NHLBI R01 HL179220) are provided in DSMP §5 (Data Acquisition, Transmission, Confidentiality, and Quality Control), incorporated here by reference.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Study data and residual specimens collected under this protocol may be retained after completion of the study for future research use, as described in the informed consent document and approved by the UC San Diego IRB/HRPP. Future use is part of the study consent and will not be offered as a separate optional activity. Individuals who do not agree to the storage and future use of study data and residual specimens described in the consent document may choose not to participate in the study.

Study data generated under this protocol may include demographic information, medical and sleep history, medication information, opioid exposure data, questionnaire responses, psychomotor vigilance testing results, polysomnography and physiologic signal data, study-device use data, adverse-event information, and derived analytic variables. Blood specimens collected for opioid level measurement will be used for the purposes described in this protocol. Residual blood specimens remaining after protocol-specified testing may be retained for future research related to sleep-disordered breathing, ventilatory control, opioid-related respiratory physiology, nocturnal oxygenation and ventilation, sleep, pain, neurobehavioral performance, cardiopulmonary physiology, and related health outcomes.

Stored data and residual specimens will be labeled with a study code rather than direct identifiers whenever feasible. The code key linking participant identifiers to coded data or specimens will be maintained within REDCap with access only available to authorized UC San Diego study personnel. Identifiable information will be stored on UC San Diego–managed secure systems or in locked study files with access limited to authorized study personnel. Electronic data will be stored in secure institutional systems, including REDCap and/or UC San Diego–managed secure network storage, with role-based access controls. Physiologic signal files and analytic datasets will be maintained on UC San Diego–managed secure servers or other UC San Diego–approved secure platforms. Physical specimens, if retained, will be stored in a UC San Diego–approved research laboratory or biorepository with access limited to authorized personnel.

Study records will be retained for at least the minimum period required by UC San Diego policy, NIH/NHLBI requirements, applicable regulations, and sponsor requirements. Coded data and residual specimens approved for future use may be stored indefinitely unless a shorter retention period is required by the IRB, sponsor, institutional policy, or applicable law.

Future research using stored identifiable or coded data or residual specimens will occur only as permitted by the informed consent document, UC San Diego IRB/HRPP requirements, NIH/NHLBI requirements, institutional policy, and applicable laws. Future studies using identifiable or coded data or specimens will be submitted for IRB review, exemption determination, or other HRPP determination as required before use. De-identified datasets may be shared with collaborators or repositories only as permitted by the consent form, IRB/HRPP requirements, NIH data-sharing requirements, institutional policy, and applicable data-use agreements. Shared datasets will not include direct identifiers unless specifically approved by the IRB/HRPP and permitted by the consent form.

Participants may withdraw from the study at any time. If a participant withdraws, the study team may continue to use data and specimens already collected to the extent permitted by the informed consent document, IRB/HRPP requirements, institutional policy, and applicable regulations, including for study integrity, safety reporting, regulatory documentation, and analyses already completed or underway. The study team will not collect additional research data or specimens after withdrawal unless the participant provides permission or such collection is otherwise permitted by the IRB/HRPP.

No genetic testing or genomic analysis will be performed under this protocol. Stored specimens will not be used for genetic testing or genomic analysis unless a future IRB-approved protocol and consent or re-consent process permits such testing.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Jeremy Orr, MD, Associate Professor
UC San Diego Altman Clinical and Translational Research Institute
9452 Medical Center Drive, La Jolla, CA 92037
(858) 692-6556
j1orr@health.ucsd.edu

In addition, study oversight is provided by an NHLBI-appointed Data and Safety Monitoring Board (DSMB) covering all aims of R01 HL179220 under a single integrated DSMP. The DSMB will review safety data and study conduct at least semi-annually and will provide recommendations to the PI and to NHLBI.

10.1.5 SAFETY OVERSIGHT

Safety oversight will be conducted in accordance with the separately submitted Data and Safety Monitoring Plan (DSMP). The PI will review adverse events, serious adverse events, unanticipated problems, protocol deviations, and any clinically significant safety concerns. Additional oversight, including DSMB review if applicable, will occur as described in the DSMP.

10.1.6 CLINICAL MONITORING

Clinical monitoring will be conducted to ensure participant safety, protocol compliance, data integrity, and adherence to applicable regulatory requirements, institutional policies, Good Clinical Practice (GCP), and the study Data and Safety Monitoring Plan (DSMP). The PI will serve as the primary study monitor with close DSMB oversight as outlined in the DSMP.

Monitoring activities may include review of:

- Informed consent documentation
- Protocol compliance and study conduct
- Adverse event (AE) and serious adverse event (SAE) reporting
- Participant eligibility and source documentation
- Data accuracy, completeness, and timeliness
- Study records and regulatory documentation
- Adherence to study procedures and safety monitoring requirements

Monitoring will be performed by qualified study personnel and/or DSMB at intervals appropriate for the level of study risk and study activity, as outlined in the DSMP.

10.1.7 DATA HANDLING AND RECORD KEEPING

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of trained study personnel under the supervision of the Principal Investigator.

Study data will be entered into REDCap, a secure, 21 CFR Part 11-compliant electronic data capture system. The system includes password protection and internal quality checks to identify incomplete or inconsistent data.

Source documents will be maintained for all participants, and data entered into the electronic system will be verified against source documentation.

Access to study data will be restricted to authorized personnel. The Principal Investigator is responsible for ensuring the accuracy, completeness, and timeliness of all data collected.

10.1.7.2 STUDY RECORDS RETENTION

Study records will be retained in accordance with institutional and regulatory requirements.

All study documents will be maintained for a minimum of three (3) years following submission of the final study report or longer if required by applicable regulations or sponsor requirements, or as justified by scientific rationale.

No study records will be destroyed without appropriate authorization.

10.1.8 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to NIH Institute during the annual review. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.2 ADDITIONAL CONSIDERATIONS

IND/IDE Status

No Investigational New Drug application (IND) or Investigational Device Exemption (IDE) is planned for this study.

The study intervention is nocturnal supplemental oxygen delivered by nasal cannula using commercially available oxygen-delivery equipment. Supplemental oxygen is a lawfully marketed medical gas used in clinical care, and this study is not intended to support a new FDA indication, a significant change in product labeling, or a significant change in advertising for any oxygen product or device. The study is designed to evaluate physiologic and sleep-disordered breathing responses to supplemental oxygen compared with sham air in adults using chronic opioids.

The planned oxygen exposure uses a standard route of administration, nasal cannula, and a clinically familiar dose range, with oxygen titrated during an attended polysomnography visit and limited to a maximum flow rate of 4 L/min. Based on these features, the study is considered exempt from IND requirements under 21 CFR 312.2(b)(1), because it involves a lawfully marketed product, is not intended to support FDA labeling or advertising changes, is not intended for promotion or commercialization, and does not involve a route of administration, dosage level, patient population, or other factor that is expected to significantly increase the risks or decrease the acceptability of risks associated with the product.

Appendix - Data and Safety Monitoring Plan
The Data and Safety Monitoring Plan (DSMP v1.0, 1 June 2026 revision) is attached as Appendix A and is referenced throughout this protocol using the form ‘DSMP §X’ for the specified section. The DSMP is the single source of truth for safety oversight, informed consent procedures, participant withdrawal criteria, conflict-of-interest management, AE/SAE/UP definitions and reporting, data and confidentiality procedures, stopping rules, and DSMB roles and operations.

10.3 ABBREVIATIONS

AE — Adverse Event
AHI — Apnea–Hypopnea Index
$AHI_{(flow)}$ — Apnea–Hypopnea Index based on airflow
ANCOVA — Analysis of Covariance
BMI — Body Mass Index
CFR — Code of Federal Regulations
CLIA — Clinical Laboratory Improvement Amendments
CMP — Clinical Monitoring Plan
COC — Certificate of Confidentiality
CONSORT — Consolidated Standards of Reporting Trials
CRF — Case Report Form
DHHS — Department of Health and Human Services
DSMB — Data and Safety Monitoring Board
eCRF — Electronic Case Report Form
ESS — Epworth Sleepiness Scale
FDA — Food and Drug Administration

FDAAA — Food and Drug Administration Amendments Act of 2007
FFR — Federal Financial Report
GCP — Good Clinical Practice
GLP — Good Laboratory Practice
GMP — Good Manufacturing Practice
HIPAA — Health Insurance Portability and Accountability Act
ICH — International Conference on Harmonisation
ICMJE — International Committee of Medical Journal Editors
IRB — Institutional Review Board
ITT — Intention-to-Treat
LSMEANS — Least-Squares Means
MedDRA — Medical Dictionary for Regulatory Activities
MOP — Manual of Procedures
NCT — ClinicalTrials.gov Identifier
NIH — National Institutes of Health
NIH IC — National Institutes of Health Institute or Center
OHRP — Office for Human Research Protections
PI — Principal Investigator
PSG — Polysomnography
PVT — Psychomotor Vigilance Test
QA — Quality Assurance
QC — Quality Control
REDCap — Research Electronic Data Capture (secure web-based application for data collection)
SAE — Serious Adverse Event
SAP — Statistical Analysis Plan
CoC — Certificate of Confidentiality
COWS — Clinical Opiate Withdrawal Scale
KSS — Karolinska Sleepiness Scale
MEqD — Morphine Equivalent Dose per Day
SABV — Sex as a Biological Variable
SOWS — Subjective Opiate Withdrawal Scale
SDB — Sleep Disordered Breathing
SOA — Schedule of Activities
SOC — System Organ Class
SpO_2 — Peripheral Oxygen Saturation
SOP — Standard Operating Procedure
$TcCO_2$ — Transcutaneous Carbon Dioxide
UP — Unanticipated Problem
US — United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	1 June 2026	Initial version.	

11 REFERENCES

1. Kinnard EN, Philbin MM, Beletsky L. Government Actions to Curb the Opioid Epidemic. JAMA. 2018;319(15):1619–20. doi: 10.1001/jama.2018.0741. PubMed PMID: 29677294.

2. van den Berg-Wolf M. Government Actions to Curb the Opioid Epidemic. JAMA. 2018;319(15):1619. doi: 10.1001/jama.2018.0737. PubMed PMID: 29677293.

3. Kolodny A, Frieden TR. Government Actions to Curb the Opioid Epidemic-Reply. JAMA. 2018;319(15):1620–1. doi: 10.1001/jama.2018.0745. PubMed PMID: 29677298.

4. Filiatrault ML, Chauny JM, Daoust R, Roy MP, Denis R, Lavigne G. Medium Increased Risk for Central Sleep Apnea but Not Obstructive Sleep Apnea in Long-Term Opioid Users: A Systematic Review and Meta-Analysis. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2016;12(4):617–25. doi: 10.5664/jcsm.5704. PubMed PMID: 26943709; PubMed Central PMCID: PMC4795290.

5. Jones GH, Bruera E, Abdi S, Kantarjian HM. The opioid epidemic in the United States-Overview, origins, and potential solutions. Cancer. 2018;124(22):4279–86. doi: 10.1002/cncr.31713. PubMed PMID: 30299538.

6. DuPont RL. The opioid epidemic is an historic opportunity to improve both prevention and treatment. Brain Res Bull. 2018;138:112–4. Epub 20170613. doi: 10.1016/j.brainresbull.2017.06.008. PubMed PMID: 28627395.

7. Amoroso P, Langford R. The opioid epidemic: a wake-up call for us all. BJU Int. 2018;122(5):719–20. doi: 10.1111/bju.14544. PubMed PMID: 30358934.

8. Skolnick P. The Opioid Epidemic: Crisis and Solutions. Annu Rev Pharmacol Toxicol. 2018;58:143–59. doi: 10.1146/annurev-pharmtox-010617-052534. PubMed PMID: 28968188.

9. McGregor AJ. The Opioid Epidemic: Overcoming Challenges by Using a Sex and Gender Lens. Clin Ther. 2018;40(2):188–9. doi: 10.1016/j.clinthera.2018.01.007. PubMed PMID: 29395291.

10. Kurland M. The Opioid Epidemic: The Crisis That Hits Home. Prof Case Manag. 2018;23(5):280–1. doi: 10.1097/NCM.0000000000000314. PubMed PMID: 30059470.

11. Mitchell AM. The Opioid Epidemic: What's Inside This Issue. J Addict Nurs. 2018;29(3):153–4. doi: 10.1097/JAN.0000000000000244. PubMed PMID: 30179998.

12. Hedegaard H, Minino AM, Spencer MR, Warner M. Drug Overdose Deaths in the United States, 1999-2020. NCHS Data Brief. 2021(426):1–8. PubMed PMID: 34978529.

13. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Prescription of Long-Acting Opioids and Mortality in Patients With Chronic Noncancer Pain. JAMA. 2016;315(22):2415–23. Epub 2016/06/15. doi: 10.1001/jama.2016.7789. PubMed PMID: 27299617; PubMed Central PMCID: PMC5030814.

14. Kao D, Bucher Bartelson B, Khatri V, Dart R, Mehler PS, Katz D, et al. Trends in reporting methadone-associated cardiac arrhythmia, 1997-2011: an analysis of registry data. Annals of internal medicine. 2013;158(10):735–40. doi: 10.7326/0003-4819-158-10-201305210-00008. PubMed PMID: 23689766.

15. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, et al. The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention WorkshopEffectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain. Annals of Internal Medicine. 2015;162(4):276–86. doi: 10.7326/m14-2559.

16. Carman WJ, Su S, Cook SF, Wurzelmann JI, McAfee A. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. Pharmacoepidemiology and drug safety. 2011;20(7):754–62. Epub 2011/05/14. doi: 10.1002/pds.2131. PubMed PMID: 21567652.

17. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. Journal of internal medicine. 2013;273(5):511–26. Epub 2013/01/22. doi: 10.1111/joim.12035. PubMed PMID: 23331508.

18. Pontes C, Marsal JR, Elorza JM, Aragón M, Prieto-Alhambra D, Morros R. Analgesic Use and Risk for Acute Coronary Events in Patients With Osteoarthritis: A Population-based, Nested Case-control Study. Clinical Therapeutics. 2018;40(2):270–83. doi: https://doi.org/10.1016/j.clinthera.2017.12.011.

19. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The Comparative Safety of Analgesics in Older Adults With ArthritisComparative Safety of Analgesics in Arthritis. Archives of internal medicine. 2010;170(22):1968–78. doi: 10.1001/archinternmed.2010.391.

20. Wiese AD, Grijalva CG. The use of prescribed opioid analgesics & the risk of serious infections. Future microbiology. 2018;13:849–52. Epub 2018/06/14. doi: 10.2217/fmb-2018-0101. PubMed PMID: 29896976; PubMed Central PMCID: PMC6060396.

21. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain - United States, 2022. MMWR Recomm Rep. 2022;71(3):1–95. Epub 20221104. doi: 10.15585/mmwr.rr7103a1. PubMed PMID: 36327391; PubMed Central PMCID: PMC9639433.

22. Chou R, Deyo R, Devine B, Hansen R, Sullivan S, Jarvik JG, et al. The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. Evid Rep Technol Assess (Full Rep). 2014(218):1–219. doi: 10.23970/AHRQEPCERTA218. PubMed PMID: 30313000.

23. Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. Jama. 2018;320(23):2448–60. doi: 10.1001/jama.2018.18472. PubMed PMID: 30561481; PubMed Central PMCID: PMC6583638.

24. Zhu W, Chernew ME, Sherry TB, Maestas N. Initial Opioid Prescriptions among U.S. Commercially Insured Patients, 2012–2017. New England Journal of Medicine. 2019;380(11):1043–52. doi: doi:10.1056/NEJMsa1807069.

25. Schieber LZ, Guy GP, Jr., Seth P, Young R, Mattson CL, Mikosz CA, et al. Trends and Patterns of Geographic Variation in Opioid Prescribing Practices by State, United States, 2006-2017Geographic Variation in Opioid Prescribing Practices by US State, 2006-2017Geographic Variation in Opioid Prescribing Practices by US State, 2006-2017. JAMA Network Open. 2019;2(3):e190665–e. doi: 10.1001/jamanetworkopen.2019.0665.

26. Wakeman SE, Larochelle MR, Ameli O, Chaisson CE, McPheeters JT, Crown WH, et al. Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder. JAMA Netw Open. 2020;3(2):e1920622. Epub 20200205. doi: 10.1001/jamanetworkopen.2019.20622. PubMed PMID: 32022884; PubMed Central PMCID: PMC11143463.

27. Tentindo GS, Fishman SM, Li CS, Wang Q, Brass SD. The prevalence and awareness of sleep apnea in patients suffering chronic pain: an assessment using the STOP-Bang sleep apnea questionnaire. Nat Sci Sleep. 2018;10:217–24. Epub 20180801. doi: 10.2147/NSS.S167658. PubMed PMID: 30123015; PubMed Central PMCID: PMC6078087.

28. Cao M, Javaheri S. Effects of Chronic Opioid Use on Sleep and Wake. Sleep Med Clin. 2018;13(2):271–81. Epub 20180312. doi: 10.1016/j.jsmc.2018.02.002. PubMed PMID: 29759277.

29. Wang D, Teichtahl H, Drummer O, Goodman C, Cherry G, Cunnington D, et al. Central sleep apnea in stable methadone maintenance treatment patients. Chest. 2005;128(3):1348–56. doi: 10.1378/chest.128.3.1348. PubMed PMID: 16162728.

30. Walker JM, Farney RJ, Rhondeau SM, Boyle KM, Valentine K, Cloward TV, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2007;3(5):455–61. PubMed PMID: 17803007; PubMed Central PMCID: PMC1978331.

31. Mubashir T, Nagappa M, Esfahanian N, Botros J, Arif AA, Suen C, et al. Prevalence of Sleep Disordered Breathing in Opioid Users With Chronic Pain: A Systematic Review and Meta-Analysis. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2020. Epub 2020/02/28. doi: 10.5664/jcsm.8392. PubMed PMID: 32105208.

32. Javaheri S, Randerath WJ, Badr MS, Javaheri S. Medication-Induced Central Sleep Apnea: A Unifying Concept. Sleep. 2024. Epub 20240209. doi: 10.1093/sleep/zsae038. PubMed PMID: 38334297.

33. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet. 2014;383(9918):736–47. doi: 10.1016/S0140-6736(13)60734-5. PubMed PMID: 23910433; PubMed Central PMCID: 3909558.

34. Jelic S. Direct characterization of the vascular endothelium in sleep apnea. Chest. 2011;140(6):1400–1. doi: 10.1378/chest.11-1376. PubMed PMID: 22147815.

35. Jelic S, Le Jemtel TH. Inflammation, oxidative stress, and the vascular endothelium in obstructive sleep apnea. Trends Cardiovasc Med. 2008;18(7):253–60. doi: 10.1016/j.tcm.2008.11.008. PubMed PMID: 19232954.

36. Jelic S, Lederer DJ, Adams T, Padeletti M, Colombo PC, Factor PH, et al. Vascular inflammation in obesity and sleep apnea. Circulation. 2010;121(8):1014–21. Epub 20100216. doi: 10.1161/CIRCULATIONAHA.109.900357. PubMed PMID: 20159829; PubMed Central PMCID: PMC2864627.

37. O. Donnell C, King ED, Schwartz AR, Robotham JL, Smith PL. Relationship between blood pressure and airway obstruction during sleep in the dog. J Appl Physiol. 1994;77(4):1819–28.

38. Khayat RN, Abraham WT, Patt B, Pu M, Jarjoura D. In-hospital treatment of obstructive sleep apnea during decompensation of heart failure. Chest. 2009;136(4):991–7. Epub 2009/07/02. doi: 10.1378/chest.09-0597. PubMed PMID: 19567491; PubMed Central PMCID: PMC2771043.

39. Khayat RN, Xie A, Patel AK, Kaminski A, Skatrud JB. Cardiorespiratory effects of added dead space in patients with heart failure and central sleep apnea. Chest. 2003;123(5):1551–60.

40. Somers VK. Debating sympathetic overactivity as a hallmark of human obesity: an opposing position. J Hypertens. 1999;17(8):1061–4.

41. Somers VK. To sleep, perchance to breathe. Implications for the failing heart. American journal of respiratory and critical care medicine. 1999;160(4):1077–8. Epub 1999/10/06. PubMed PMID: 10508791.

42. Somers VK. Sleep--a new cardiovascular frontier. The New England journal of medicine. 2005;353(19):2070–3. Epub 2005/11/12. doi: 353/19/2070 [pii]

10.1056/NEJMe058229. PubMed PMID: 16282183.

43. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. American journal of epidemiology. 2013;177(9):1006–14. doi: 10.1093/aje/kws342. PubMed PMID: 23589584; PubMed Central PMCID: 3639722.

44. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med. 2015. doi: 10.1016/S2213-2600(15)00043-0. PubMed PMID: 25682233.

45. Guilleminault C, Cao M, Yue HJ, Chawla P. Obstructive sleep apnea and chronic opioid use. Lung. 2010;188(6):459–68. Epub 20100724. doi: 10.1007/s00408-010-9254-3. PubMed PMID: 20658143.

46. Ahmad A, Ahmad R, Meteb M, Ryan CM, Leung RS, Montandon G, et al. The relationship between opioid use and obstructive sleep apnea: A systematic review and meta-analysis. Sleep medicine reviews. 2021;58:101441. Epub 20210121. doi: 10.1016/j.smrv.2021.101441. PubMed PMID: 33567395.

47. Orr JE, Malhotra A, Gruenberg E, Marin T, Sands SA, Alex RM, et al. Pathogenesis of sleep disordered breathing in the setting of opioid use: A multiple mediation analysis using physiology. Sleep. 2024. Epub 20240412. doi: 10.1093/sleep/zsae090. PubMed PMID: 38605676.

48. Orr JE, Malhotra A, Sands SA. Pathogenesis of central and complex sleep apnoea. Respirology. 2017;22(1):43–52. Epub 20161031. doi: 10.1111/resp.12927. PubMed PMID: 27797160; PubMed Central PMCID: PMC5161664.

49. Morgenthaler TI, Kuzniar TJ, Wolfe LF, Willes L, McLain WC, 3rd, Goldberg R. The complex sleep apnea resolution study: a prospective randomized controlled trial of continuous positive airway pressure versus adaptive servoventilation therapy. Sleep. 2014;37(5):927–34. Epub 20140501. doi: 10.5665/sleep.3662. PubMed PMID: 24790271; PubMed Central PMCID: PMC3985095.

50. Mogri M, Nadler J, Khan T, Mador MJ. Complex sleep apnea in patients with obstructive sleep apnea on opioids for chronic pain. Sleep and Biological Rhythms. 2014;12(2):127–34. doi: 10.1111/sbr.12051.

51. Javaheri S, Smith J, Chung E. The prevalence and natural history of complex sleep apnea. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2009;5(3):205–11. Epub 2009/12/08. PubMed PMID: 19960639; PubMed Central PMCID: PMC2699163.

52. Davis MP, Behm B, Balachandran D. Looking both ways before crossing the street: Assessing the benefits and risk of opioids in treating patients at risk of sleep -disordered breathing for pain and dyspnea. J Opioid Manag. 2017;13(3):183–96. doi: 10.5055/jom.2017.0385. PubMed PMID: 28829519.

53. Rowsell L, Wong KKH, Yee BJ, Eckert DJ, Somogyi AA, Duffin J, et al. The effect of acute morphine on obstructive sleep apnoea: a randomised double-blind placebo-controlled crossover trial. Thorax. 2019;74(2):177–84. doi: 10.1136/thoraxjnl-2018-211675. PubMed PMID: 30166422.

54. Lam KK, Kunder S, Wong J, Doufas AG, Chung F. Obstructive sleep apnea, pain, and opioids: is the riddle solved? Curr Opin Anaesthesiol. 2016;29(1):134–40. doi: 10.1097/ACO.0000000000000265. PubMed PMID: 26545144; PubMed Central PMCID: PMC4927322.

55. Robinson RW, et al. Effects of oral narcotics on sleep-disordered breathing in healthy adults. Chest. 1987;91(2):197–203.

56. Gupta K, Nagappa M, Prasad A, Abrahamyan L, Wong J, Weingarten TN, et al. Risk factors for opioid-induced respiratory depression in surgical patients: a systematic review and

meta-analyses. BMJ Open. 2018;8(12):e024086. Epub 20181214. doi: 10.1136/bmjopen-2018-024086. PubMed PMID: 30552274; PubMed Central PMCID: PMC6303633.

57. Mubashir T, Nagappa M, Esfahanian N, Botros J, Arif AA, Suen C, et al. Prevalence of sleep-disordered breathing in opioid users with chronic pain: a systematic review and meta-analysis. Journal of Clinical Sleep Medicine. 2020;16(6):961–9. doi: doi:10.5664/jcsm.8392.

58. Sun X, Thörn Pérez C, Halemani D N, Shao XM, Greenwood M, Heath S, et al. Opioids modulate an emergent rhythmogenic process to depress breathing. Elife. 2019;8:e50613. doi: 10.7554/eLife.50613. PubMed PMID: 31841107.

59. Mellen NM, Janczewski WA, Bocchiaro CM, Feldman JL. Opioid-induced quantal slowing reveals dual networks for respiratory rhythm generation. Neuron. 2003;37(5):821–6. doi: 10.1016/s0896-6273(03)00092-8. PubMed PMID: 12628172.

60. Gray PA, Rekling JC, Bocchiaro CM, Feldman JL. Modulation of respiratory frequency by peptidergic input to rhythmogenic neurons in the preBotzinger complex. Science. 1999;286(5444):1566–8. doi: 10.1126/science.286.5444.1566. PubMed PMID: 10567264; PubMed Central PMCID: PMC2811082.

61. Rose AR, Catcheside PG, McEvoy RD, Paul D, Kapur D, Peak E, et al. Sleep disordered breathing and chronic respiratory failure in patients with chronic pain on long term opioid therapy. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2014;10(8):847–52. Epub 2014/08/16. doi: 10.5664/jcsm.3950. PubMed PMID: 25126029; PubMed Central PMCID: PMC4106937.

62. Mellen NM, Janczewski WA, Bocchiaro CM, Feldman JL. Opioid-induced quantal slowing reveals dual networks for respiratory rhythm generation. Neuron. 2003;37(5):821–6. PubMed PMID: 12628172; PubMed Central PMCID: PMC3210017.

63. Janczewski WA, Onimaru H, Homma I, Feldman JL. Opioid-resistant respiratory pathway from the preinspiratory neurones to abdominal muscles: in vivo and in vitro study in the newborn rat. J Physiol. 2002;545(3):1017–26. doi: 10.1113/jphysiol.2002.023408. PubMed PMID: 12482904; PubMed Central PMCID: PMC2290709.

64. Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014;311(15):1547–55. Epub 2014/04/17. doi: 10.1001/jama.2014.3266. PubMed PMID: 24737367.

65. Russell IJ, Holman AJ, Swick TJ, Alvarez-Horine S, Wang YG, Guinta D. Sodium oxybate reduces pain, fatigue, and sleep disturbance and improves functionality in fibromyalgia: results from a 14-week, randomized, double-blind, placebo-controlled study. Pain. 2011;152(5):1007–17. Epub 2011/03/15. doi: 10.1016/j.pain.2010.12.022. PubMed PMID: 21397402.

66. Zgierska A, Brown RT, Zuelsdorff M, Brown D, Zhang Z, Fleming MF. Sleep and daytime sleepiness problems among patients with chronic noncancerous pain receiving long-term opioid therapy: a cross-sectional study. J Opioid Manag. 2007;3(6):317–27. doi: 10.5055/jom.2007.0020. PubMed PMID: 18290583.

67. Affleck G, Urrows S, Tennen H, Higgins P, Abeles M. Sequential daily relations of sleep, pain intensity, and attention to pain among women with fibromyalgia. Pain. 1996;68(2):363–8. doi: https://doi.org/10.1016/S0304-3959(96)03226-5.

68. Roseen EJ, Gerlovin H, Femia A, Cho J, Bertisch S, Redline S, et al. Yoga, Physical Therapy, and Back Pain Education for Sleep Quality in Low-Income Racially Diverse Adults with Chronic Low Back Pain: a Secondary Analysis of a Randomized Controlled Trial. J Gen Intern Med. 2020;35(1):167–76. Epub 2019/11/02. doi: 10.1007/s11606-019-05329-4. PubMed PMID: 31667747; PubMed Central PMCID: PMC6957649.

69. Haack M, Lee E, Cohen DA, Mullington JM. Activation of the prostaglandin system in response to sleep loss in healthy humans: potential mediator of increased spontaneous pain. Pain. 2009;145(1-2):136–41. doi: 10.1016/j.pain.2009.05.029. PubMed PMID: 19560866; PubMed Central PMCID: PMC2737342.

70. Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. Sleep. 2007;30(9):1145–52. PubMed PMID: 17910386; PubMed Central PMCID: PMC1978405.

71. Weingarten JA, Dubrovsky B, Basner RC, Redline S, George L, Lederer DJ. Polysomnographic Measurement of Sleep Duration and Bodily Pain Perception in the Sleep Heart Health Study. Sleep. 2016;39(8):1583–9. Epub 2016/05/12. doi: 10.5665/sleep.6026. PubMed PMID: 27166228; PubMed Central PMCID: PMC4945318.

72. Khalid I, Roehrs TA, Hudgel DW, Roth T. Continuous Positive Airway Pressure in Severe Obstructive Sleep Apnea Reduces Pain Sensitivity. Sleep. 2011;34(12):1687–91. doi: 10.5665/sleep.1436.

73. Zhao YY, Wang R, Gleason KJ, Lewis EF, Quan SF, Toth CM, et al. Effect of Continuous Positive Airway Pressure Treatment on Health-Related Quality of Life and Sleepiness in High Cardiovascular Risk Individuals With Sleep Apnea: Best Apnea Interventions for Research (BestAIR) Trial. Sleep. 2017;40(4). doi: 10.1093/sleep/zsx040.

74. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: Pathophysiology and treatment. Chest. 2007;131(2):595–607. Epub 2007/02/14. doi: 10.1378/chest.06.2287. PubMed PMID: 17296668; PubMed Central PMCID: 2287191.

75. Peppard PE, Szklo-Coxe M, Hla KM, Young T. Longitudinal association of sleep-related breathing disorder and depression. Archives of internal medicine. 2006;166(16):1709–15. Epub 2006/09/20. doi: 166/16/1709 [pii]

10.1001/archinte.166.16.1709. PubMed PMID: 16983048.

76. Baxley C, Weinstock J, Lustman PJ, Garner AA. The influence of anxiety sensitivity on opioid use disorder treatment outcomes. Exp Clin Psychopharmacol. 2019;27(1):64–77. Epub 20180806. doi: 10.1037/pha0000215. PubMed PMID: 30080059.

77. Memtsoudis S, Liu SS, Ma Y, Chiu YL, Walz JM, Gaber-Baylis LK, et al. Perioperative pulmonary outcomes in patients with sleep apnea after noncardiac surgery. Anesthesia and analgesia. 2011;112(1):113–21. Epub 2010/11/18. doi: ANE.0b013e3182009abf [pii]

10.1213/ANE.0b013e3182009abf. PubMed PMID: 21081775.

78. Memtsoudis SG, Cozowicz C, Nagappa M, Wong J, Joshi GP, Wong DT, et al. Society of Anesthesia and Sleep Medicine Guideline on Intraoperative Management of Adult Patients With Obstructive Sleep Apnea. Anesthesia and analgesia. 2018;127(4):967–87. doi: 10.1213/ANE.0000000000003434. PubMed PMID: 29944522; PubMed Central PMCID: PMC6135479.

79. Halbert BT, Davis RB, Wee CC. Disproportionate longer-term opioid use among U.S. adults with mood disorders. Pain. 2016;157(11):2452–7. Epub 2016/10/19. doi: 10.1097/j.pain.0000000000000650. PubMed PMID: 27472400; PubMed Central PMCID: PMC5069117.

80. Redline S, Adams N, Strauss ME, Roebuck T, Winters M, Rosenberg C. Improvement of mild sleep-disordered breathing with CPAP compared with conservative therapy. American journal of respiratory and critical care medicine. 1998;157(3 Pt 1):858–65.

81. Redline S, Strohl KP. Recognition and consequences of obstructive sleep apnea hypopnea. Clinics in chest medicine. 1998;19(1):1–19.

82. Redline S, Young T. Epidemiology and natural history of obstructive sleep apnea. Ear Nose Throat J. 1993;72(1):20–1, 4–6.

83. Gottlieb DJ, et al. Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study. Am J Respir Crit Care Med. 1999;159(2):502–7.

84. Crombie KM, Brellenthin AG, Hillard CJ, Koltyn KF. Psychobiological Responses to Aerobic Exercise in Individuals With Posttraumatic Stress Disorder. J Trauma Stress. 2018;31(1):134–45. Epub 20180201. doi: 10.1002/jts.22253. PubMed PMID: 29388710.

85. Crombie KM, Brellenthin AG, Hillard CJ, Koltyn KF. Endocannabinoid and Opioid System Interactions in Exercise-Induced Hypoalgesia. Pain Med. 2018;19(1):118–23. doi: 10.1093/pm/pnx058. PubMed PMID: 28387833; PubMed Central PMCID: PMC6454785.

86. Brellenthin AG, Lee DC. Physical Activity and the Development of Substance Use Disorders: Current Knowledge and Future Directions. Prog Prev Med (N Y). 2018;3(3). doi: 10.1097/pp9.0000000000000018. PubMed PMID: 30345414; PubMed Central PMCID: PMC6192057.

87. Djonlagic IE, Guo M, Igue M, Kishore D, Stickgold R, Malhotra A. Continuous Positive Airway Pressure Restores Declarative Memory Deficit in Obstructive Sleep Apnea. American journal of respiratory and critical care medicine. 2021;203(9):1188–90. doi: 10.1164/rccm.202011-4253LE. PubMed PMID: 33347378; PubMed Central PMCID: PMC8314910.

88. Costello R, Deegan P, Fitzpatrick M, McNicholas WT. Reversible hypercapnia in chronic obstructive pulmonary disease: A distinct pattern of respiratory failure with a favorable prognosis. The American Journal of Medicine. 1997;102(3):239–44. doi: http://dx.doi.org/10.1016/S0002-9343(97)00017-X.

89. Kohnlein T, Windisch W, Kohler D, Drabik A, Geiseler J, Hartl S, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med. 2014;2(9):698–705. doi: 10.1016/S2213-2600(14)70153-5. PubMed PMID: 25066329.

90. Guilleminault C, Simmons FB, Motta J, Cummiskey J, Rosekind M, Schroeder JS, et al. Obstructive sleep apnea syndrome and tracheostomy. Long-term follow-up experience. Archives of internal medicine. 1981;141(8):985–8. Epub 1981/07/01. PubMed PMID: 7247605.

91. Nowbar S, Burkart KM, Gonzales R, Fedorowicz A, Gozansky WS, Gaudio JC, et al. Obesity-Associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. The American Journal of Medicine. 2004;116(1):1–7. doi: https://doi.org/10.1016/j.amjmed.2003.08.022.

92. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. JAMA. 2017;317(21):2177–86. doi: 10.1001/jama.2017.4451. PubMed PMID: 28528348.

93. Sajkov D, McEvoy RD. Obstructive Sleep Apnea and Pulmonary Hypertension. Progress in Cardiovascular Diseases. 2009;51(5):363–70.

94. Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep. 1997;20(10):835–43.

95. Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. Sleep. 2007;30(6):711–9. Epub 2007/06/22. PubMed PMID: 17580592; PubMed Central PMCID: 1978355.

96. Weaver TE, Maislin G, Dinges DF, Younger J, Cantor C, McCloskey S, et al. Self-efficacy in sleep apnea: instrument development and patient perceptions of obstructive sleep apnea risk, treatment benefit, and volition to use continuous positive airway pressure. Sleep. 2003;26(6):727–32. Epub 2003/10/24. PubMed PMID: 14572127.

97. Rosen IM, Aurora RN, Kirsch DB, Carden KA, Malhotra RK, Ramar K, et al. Chronic Opioid Therapy and Sleep: An American Academy of Sleep Medicine Position Statement. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2019. Epub 2019/10/08. PubMed PMID: 31588898.

98. Sankri-Tarbichi AG, Rowley JA, Badr MS. Expiratory pharyngeal narrowing during central hypocapnic hypopnea. American journal of respiratory and critical care medicine.

2009;179(4):313–9. Epub 2009/02/10. doi: 10.1164/rccm.200805-741OC. PubMed PMID: 19201929; PubMed Central PMCID: PMC2643080.

99. Rapoport DM, Norman RG, Goldring RM. CO2 homeostasis during periodic breathing: predictions from a computer model. Journal of applied physiology. 1993;75(5):2302–9. Epub 1993/11/01. doi: 10.1152/jappl.1993.75.5.2302. PubMed PMID: 8307889.

100. Orr JE, Edwards BA, Malhotra A. CrossTalk opposing view: Loop gain is not a consequence of obstructive sleep apnoea. J Physiol. 2014;592(Pt 14):2903–5. doi: 10.1113/jphysiol.2014.271841. PubMed PMID: 25027957.

101. Salloum A, Rowley JA, Mateika JH, Chowdhuri S, Omran Q, Badr MS. Increased Propensity for Central Apnea in Patients with Obstructive Sleep Apnea. Am J Respir Crit Care Med. 2010;181(2):189–93.

102. Chowdhuri S, Shanidze I, Pierchala L, Belen D, Mateika JH, Badr MS. Effect of episodic hypoxia on the susceptibility to hypocapnic central apnea during NREM sleep. Journal of applied physiology (Bethesda, Md : 1985). 2010;108(2):369–77. Epub 2009/11/25. doi: 10.1152/japplphysiol.00308.2009. PubMed PMID: 19940101.

103. Mateika JH, Mendello C, Obeid D, Badr MS. Peripheral chemoreflex responsiveness is increased at elevated levels of carbon dioxide after episodic hypoxia in awake humans. Journal of applied physiology (Bethesda, Md : 1985). 2004;96(3):1197–6. Epub 2003/11/14. doi: 10.1152/japplphysiol.00573.2003. PubMed PMID: 14617525.

104. Sankari A, Bascom AT, Chowdhuri S, Badr MS. Tetraplegia is a risk factor for central sleep apnea. Journal of applied physiology (Bethesda, Md : 1985). 2014;116(3):345–53. Epub 2013/10/10. doi: 10.1152/japplphysiol.00731.2013. PubMed PMID: 24114704.

105. Berger KI, Ayappa I, Sorkin IB, Norman RG, Rapoport DM, Goldring RM. Postevent ventilation as a function of CO(2) load during respiratory events in obstructive sleep apnea. Journal of applied physiology (Bethesda, Md : 1985). 2002;93(3):917–24. doi: 10.1152/japplphysiol.01082.2001. PubMed PMID: 12183486.

106. Sands SA, Edwards BA, Kee K, Turton A, Skuza EM, Roebuck T, et al. Loop Gain As a Means to Predict a Positive Airway Pressure Suppression of Cheyne-Stokes Respiration in Patients with Heart Failure. Am J Respir Crit Care Med. 2011;184(9):1067–75.

107. Stanchina M, Robinson K, Corrao W, Donat W, Sands S, Malhotra A. Clinical Use of Loop Gain Measures to Determine Continuous Positive Airway Pressure Efficacy in Patients with Complex Sleep Apnea. A Pilot Study. Annals of the American Thoracic Society. 2015;12(9):1351–7. doi: 10.1513/AnnalsATS.201410-469BC. PubMed PMID: 26214564; PubMed Central PMCID: PMC5467091.

108. Morgenthaler TI, Kagramanov V, Hanak V, Decker PS. Complex sleep apnea syndrome: is it a unique clinical syndrome? Sleep. 2006;29(9):1203–9.

109. Morgenthaler TI, Gay PC, Gordon N, Brown LK. Adaptive servoventilation versus noninvasive positive pressure ventilation for central, mixed, and complex sleep apnea syndromes. Sleep. 2007;30(4):468–75.

110. Javaheri S, Malik A, Smith J, Chung E. Adaptive pressure support servoventilation: a novel treatment for sleep apnea associated with use of opioids. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2008;4(4):305–10. PubMed PMID: 18763420; PubMed Central PMCID: PMC2542500.

111. Rao H, Thomas RJ. Complex sleep apnea. Curr Treat Options Neurol. 2013;15(6):677–91. doi: 10.1007/s11940-013-0260-7. PubMed PMID: 24136715.

112. Thomas RJ. Effect of added dead space to positive airway pressure for treatment of complex sleep-disordered breathing. Sleep Med. 2005;6(2):177–8. doi: 10.1016/j.sleep.2004.11.004. PubMed PMID: 15716223.

113. Thomas RJ, Mietus JE, Peng CK, Gilmartin G, Daly RW, Goldberger AL, et al. Differentiating obstructive from central and complex sleep apnea using an automated electrocardiogram-based method. Sleep. 2007;30(12):1756–69. PubMed PMID: 18246985; PubMed Central PMCID: PMC2276128.

114. Gilmartin GS, Daly RW, Thomas RJ. Recognition and management of complex sleep-disordered breathing. Curr Opin Pulm Med. 2005;11(6):485–93. doi: 10.1097/01.mcp.0000183061.98665.b0. PubMed PMID: 16217173.

115. Reddy M, Roopika, Adamo R, David, Kufel M, Thomas, Porhomayon M, Jahan, El-Solh M, MPH, Ali A. Treatment of opioid-related central sleep apnea with positive airway pressure: A systematic review. 2014. 2014;10(1):6. Epub 2014-01-01. doi: 10.5055/jom.2014.0192.

116. Javaheri S, Harris N, Howard J, Chung E. Adaptive servoventilation for treatment of opioid-associated central sleep apnea. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2014;10(6):637–43. doi: 10.5664/jcsm.3788. PubMed PMID: 24932143; PubMed Central PMCID: PMC4031404.

117. Ramar K, Ramar P, Morgenthaler TI. Adaptive servoventilation in patients with central or complex sleep apnea related to chronic opioid use and congestive heart failure. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2012;8(5):569–76. doi: 10.5664/jcsm.2160. PubMed PMID: 23066370; PubMed Central PMCID: PMC3459204.

118. Chowdhuri S, Ghabsha A, Sinha P, Kadri M, Narula S, Badr MS. Treatment of central sleep apnea in U.S. veterans. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2012;8(5):555–63. doi: 10.5664/jcsm.2156. PubMed PMID: 23066368; PubMed Central PMCID: 3459202.

119. Liu D, Armitstead J, Benjafield A, Shao S, Malhotra A, Cistulli PA, et al. Trajectories of Emergent Central Sleep Apnea During CPAP Therapy. Chest. 2017;152(4):751–60. doi: https://doi.org/10.1016/j.chest.2017.06.010.

120. Davis MJ, Livingston M, Scharf SM. Reversal of central sleep apnea following discontinuation of opioids. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2012;8(5):579–80. doi: 10.5664/jcsm.2164. PubMed PMID: 23066372; PubMed Central PMCID: PMC3459206.

121. Javaheri S, Patel S. Opioids Cause Central and Complex Sleep Apnea in Humans and Reversal With Discontinuation: A Plea for Detoxification. Journal of Clinical Sleep Medicine. 2017;13(06):829–33. doi: doi:10.5664/jcsm.6628.

122. Fiellin DA, Schottenfeld RS, Cutter CJ, Moore BA, Barry DT, O'Connor PG. Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. JAMA Intern Med. 2014;174(12):1947–54. doi: 10.1001/jamainternmed.2014.5302. PubMed PMID: 25330017; PubMed Central PMCID: PMC6167926.

123. Sullivan MD, Turner JA, DiLodovico C, D'Appollonio A, Stephens K, Chan YF. Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial. J Pain. 2017;18(3):308–18. Epub 20161128. doi: 10.1016/j.jpain.2016.11.003. PubMed PMID: 27908840; PubMed Central PMCID: PMC5337146.

124. Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy. Annals of Internal Medicine. 2017;167(3):181–91. doi: 10.7326/m17-0598 %m 28715848.

125. Mogri M, Desai H, Webster L, Grant BJ, Mador MJ. Hypoxemia in patients on chronic opiate therapy with and without sleep apnea. Sleep Breath. 2009;13(1):49–57. Epub 20080806. doi: 10.1007/s11325-008-0208-4. PubMed PMID: 18683000.

126. Rose AR, Catcheside PG, McEvoy RD, Paul D, Kapur D, Peak E, et al. Sleep Disordered Breathing and Chronic Respiratory Failure in Patients with Chronic Pain on Long Term Opioid Therapy. Journal of Clinical Sleep Medicine. 2014;10(08):847–52. doi: doi:10.5664/jcsm.3950.

127. Azarbarzin A, Sands SA, Stone KL, Taranto-Montemurro L, Messineo L, Terrill PI, et al. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. European heart journal. 2019;40(14):1149–57. Epub 2018/10/31. doi: 10.1093/eurheartj/ehy624. PubMed PMID: 30376054; PubMed Central PMCID: PMC6451769.

128. Hajipour M, Baumann B, Azarbarzin A, Allen AJH, Liu Y, Fels S, et al. Association of alternative polysomnographic features with patient outcomes in obstructive sleep apnea: a systematic review. Journal of Clinical Sleep Medicine. 2023;19(2):225–42. doi: doi:10.5664/jcsm.10298.

129. Panza GS, Kissane DM, Puri S, Mateika JH. The hypoxic ventilatory response and hypoxic burden are predictors of the magnitude of ventilatory long-term facilitation in humans. J Physiol. 2023;601(20):4611–23. Epub 20230828. doi: 10.1113/JP285192. PubMed PMID: 37641466; PubMed Central PMCID: PMC11006398.

130. Alex RM, Panza GS, Hakim H, Badr MS, Edwards BA, Sands SA, et al. Exposure to mild intermittent hypoxia increases loop gain and the arousal threshold in participants with

obstructive sleep apnoea. The Journal of Physiology. 2019;597(14):3697–711. doi: https://doi.org/10.1113/JP277711.

131. Mehta V, Vasu TS, Phillips B, Chung F. Obstructive sleep apnea and oxygen therapy: a systematic review of the literature and meta-analysis. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2013;9(3):271–9. Epub 20130315. doi: 10.5664/jcsm.2500. PubMed PMID: 23493498; PubMed Central PMCID: PMC3578679.

132. Aurora RN, Chowdhuri S, Ramar K, Bista SR, Casey KR, Lamm CI, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. Sleep. 2012;35(1):17–40. Epub 20120101. doi: 10.5665/sleep.1580. PubMed PMID: 22215916; PubMed Central PMCID: PMC3242685.

133. Sands SA, Edwards BA, Terrill PI, Butler JP, Owens RL, Taranto-Montemurro L, et al. Identifying obstructive sleep apnea patients responsive to supplemental oxygen therapy. European Respiratory Journal. 2018:1800674. doi: 10.1183/13993003.00674-2018.

134. Edwards BA, Sands SA, Owens RL, Eckert DJ, Landry S, White DP, et al. The Combination of Supplemental Oxygen and a Hypnotic Markedly Improves Obstructive Sleep Apnea in Patients with a Mild to Moderate Upper Airway Collapsibility. Sleep. 2016;39(11):1973–83. doi: 10.5665/sleep.6226. PubMed PMID: PMC5070751.

135. Wellman A, Malhotra A, Jordan AS, Stevenson KE, Gautam S, White DP. Effect of oxygen in obstructive sleep apnea: Role of loop gain. Respir Physiol Neurobiol. 2008;162(2):144–51. doi: 10.1016/j.resp.2008.05.019. PubMed PMID: 18577470; PubMed Central PMCID: 4332598.

136. Schmickl CN, Orr JE, Sands SA, Alex RM, Azarbarzin A, McGinnis L, et al. Loop Gain as a Predictor of Blood Pressure Response in Patients Treated for Obstructive Sleep Apnea: Secondary Analysis of a Clinical Trial. Annals of the American Thoracic Society. 2024;21(2):296–307. doi: 10.1513/AnnalsATS.202305-437OC. PubMed PMID: 37938917; PubMed Central PMCID: PMC10848904.

137. Abdo WF, Heunks LM. Oxygen-induced hypercapnia in COPD: myths and facts. Crit Care. 2012;16(5):323. Epub 20121029. doi: 10.1186/cc11475. PubMed PMID: 23106947; PubMed Central PMCID: PMC3682248.

138. Alford NJ, Fletcher EC, Nickeson D. Acute oxygen in patients with sleep apnea and COPD. Chest. 1986;89(1):30–8. Epub 1986/01/01. PubMed PMID: 3079693.

139. Flenley DC. Sleep in chronic obstructive lung disease. Clinics in chest medicine. 1985;6(4):651–61. Epub 1985/12/01. PubMed PMID: 2935359.

140. Doufas AG, Laporta ML, Driver CN, Di Piazza F, Scardapane M, Bergese SD, et al. Incidence of postoperative opioid-induced respiratory depression episodes in patients on room air or supplemental oxygen: a post-hoc analysis of the PRODIGY trial. BMC Anesthesiol. 2023;23(1):332. Epub 20231004. doi: 10.1186/s12871-023-02291-x. PubMed PMID: 37794334; PubMed Central PMCID: PMC10548743.