# Sleep and Breathing in the General Population - Chemical Stimuli

**NCT04720547**

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**Study Protocol**

*Recruitment*

Participants will be recruited via flyers, recruitment letters, and word of mouth. Additionally, hospital databases will be searched to identify patients who completed polysomnography (PSG) studies at a sleep clinic and were diagnosed with CSA. Patients with no record of a previous PSG study or who underwent a PSG study earlier than 2 years at the screening date will have to undergo an in-laboratory PSG study to determine eligibility. Furthermore, patients who underwent medical procedures, surgeries, or had changes in health conditions or active medication that may affect sleep following the most recent PSG, will also undergo an in-lab PSG study irrespective of the date of the previous PSG study. Eligibility criteria include patients with an apnea–hypopnea index (AHI)≥15 and a central AHI (CAHI)≥5. Patients with OSA (AHI≥15) and narrow CO2 reserve (>−2.0 mmHg) will also be eligible due to their increased propensity to develop CSA [1]. Participants whose control night study does not meet the above criteria will be excluded. Additionally, patients with a history of severe respiratory, cardiac, renal, and neurologic disease and those with co-morbid sleep conditions will be excluded.

*Randomization and Study Procedures*

Eligible participants will sign an informed consent and complete an in-laboratory night study on 5 mg Zolpidem and a control night study with no medication. The dose of Zolpidem of 5 mg was selected according to current FDA recommendations to avoid adverse effects [2]. The order of the night studies (Zolpidem and control) will be randomized according to a randomized crossover study design. The randomization sequence for treatment order will be generated via Microsoft Excel. Participants and lab staff performing the night studies will not be blinded to the treatment order. Analysis of physiologic parameters and sleep studies scoring will be performed by lab personnel and reviewed by the principal investigator or a co-investigator, all of whom will be blinded to the study treatment arm at the time of the scoring, analysis, and review. The study statistician will also be blinded.

Night studies will be scheduled based on participants' availability and must be within 6 months of each other. Zolpidem has a short elimination half-life, and a washout period for a single 5 mg dose is unnecessary. When possible, consecutive night studies will be scheduled. Participants will be contacted by phone, and their medical records will be reviewed during each sleep study to ensure that no changes in medical conditions or medications occurred.

After the participant consents to take part of the study, the participant will completed the Epworth Sleepiness Scale (ESS), the Fatigue Severity Scale (FSS) questionnaire, the Pittsburgh Sleep Quality Index (PSQI) questionnaire, and the Berlin questionnaire which help us to assess their sleep patterns and daily functional outcomes.

*In-laboratory Night Studies*

As part of standard care, a polysomnography (PSG) is a test conducted record an individual's sleep study along with audio and video recording. A PSG is a test conducted to study sleep and to diagnose a variety of sleep disorders. A PSG is used not only to help diagnose a variety of sleep disorders, but also to learn whether adjustments to treatment plans are needed or if current treatment plan is effective. An enhanced PSG will be performed during both nights including electrooculography, surface electromyography, electrocardiography, and pulse oximetry (Carefusion, SomnoStar z4 Sleep System, San Diego, CA, USA) consistent with the technical criteria of the American Academy of Sleep Medicine (AASM) [3]. Additionally, a nasal mask will be connected to an in-line pneumotachometer (Hans Rudolph; model 3700A, Shawnee, KS, USA). An RSS 100HR Research Pneumotach System will acquire data (Hans Rudolph) to achieve airflow, pressure, and volume measurements. The end-tidal partial pressure of carbon dioxide (PETCO2) will be measured by connecting a tube placed in the nasal vestibule to a respiratory gas analyzer (CWE, Inc., GEMINI Respiratory Monitor, Ardmore, PA, USA). Airflow and PETCO2 will be recorded by a PowerLab data acquisition system (AD Instruments, Inc., model 16SP, Colorado Springs, CO, USA). Tidal volume (VT) is derived by integrating the airflow channel, and minute ventilation (VE) is calculated by multiplying VT by breathing frequency (FB). Arterial oxygen saturation will be monitored by an ear clip oximeter (Ohmeda Medical Inc., Biox 3740, Laurel, MD, USA). PSG variables, including apnea, arousal, and desaturation indices, will all be calculated during both nights. Sleep staging and arousals will be measured and scored according to standard criteria using oximetry, EEG, EOG, and EMG and standard PSG methods.

*Physiologic parameters*

In addition to PSG, a noninvasive positive air pressure ventilation protocol will be used to calculate the CO2 reserve and the controller gain. The CO2 reserve is defined as the difference between the eupneic end-tidal CO2 pressure and the end-tidal CO2 pressure (PETCO2) induced by the ventilation protocol that is sufficient to trigger a central apnea as defined by the AASM. If we are not able to acquire a period of stable eupneic breathing due to the persistence of spontaneous central events, we will administer a 40% CO2 gas mixture balanced with nitrogen to stabilize breathing. The combination will be administered at 5-min intervals in 0.5 L/min increments. The volume per unit time of the mixture gas required to resolve central events will be determined, and PETCO2 allowed to return to baseline. We will perform three 5-min trials at the therapeutic volume per unit of the mixture gas separated by sufficient time to return to baseline PETCO2. Here, the CO2 reserve is defined as the difference between baseline PETCO2 and the PETCO2 during the administration of the gas mixture at which central events were resolved. Controller gain is calculated by dividing the difference in minute ventilation between the post-mechanical ventilation induced by the ventilation protocol and steady-state respiration by the difference in the end-tidal CO2 pressure between the mechanical ventilation and steady-state respiration. In participants administered the gas mixture as described above, the controller gain will not be calculated due to the absence of mechanical ventilation in that protocol. Steady-state plant gain is calculated from the ratio of end-tidal CO2 to minute ventilation during stable respiration. All physiologic parameters will be calculated during non-rapid eye movement (non-REM) sleep in both the control and the zolpidem night studies.

During both nights, a supraglottic catheter will be inserted in the patient's nostril to measure epiglottic pressure throughout the PSG portion of the night study. The epiglottic nadir pressure occurring immediately before cortical arousal and during an obstructive respiratory event is defined by the AASM mark one instance of effort sufficient to trigger the arousal. These instances will be measured for all obstructive events followed by arousals during the PSG portion and averaged to produce the respiratory arousal threshold during REM and non-REM sleep.

*Outcomes*

The primary endpoint is the frequency of respiratory-related arousals, or the respiratory arousal index (R-ArI). R-ArI represents the number per hour of arousals resulting from respiratory events. Clinical outcomes will also compared between the two-night studies and included the total respiratory arousal index (ArI), AHI, and CAHI. The total ArI represents the number per hour of all arousals, whether spontaneous or due to a respiratory event. Lastly, physiologic outcomes, including the CO2 reserve, plant gain, controller gain, and arousal threshold, will be calculated and sleep and desaturation parameters will be reported as well.

*Statistical analysis*

A crossover design is used to investigate the potential influence of sequence (the order of medication administration) and period (the time of medication administration) on the effects of the two treatments (control and Zolpidem) on the clinical outcomes. The significance level will be set at a p-value equal to or less than 0.05. For the primary endpoint and clinical outcomes, the difference between the control night and the intervention night will be calculated for each participant, and Grubb's test may be utilized to identify outliers (alpha=0.05). Statistical analyses were carried out using SPSS, SAS, and R.