SCIENTIFIC INVESTIGATIONS

Eszopiclone and Zolpidem Do Not Affect the Prevalence of the Low Arousal Threshold Phenotype

Patrick R. Smith, DO1; Karen L. Sheikh, BA2; Camille Costan-Toth, MD3; Derek Forsthoefer, MD1; Edward Bridges, MD1; Teotimo F. Andrada, MS1; LTC Aaron B. Holley, MD1

1Department of Pulmonary, Critical Care, and Sleep Medicine Walter Reed National Military Medical Center Bethesda, MD; 2Respira Medical, Inc, Walter Reed National Military Medical Center; 3Department of Pulmonary, Critical Care, and Sleep Medicine, Walter Reed National Military Medical Center

Study Objectives: We sought to determine whether non benzodiazepine sedative hypnotics (NBSH) reduce the occurrence of the low arousal threshold (LAT) phenotype.

Methods: Consecutive patients with suspected obstructive sleep apnea (OSA) referred for polysomnography (PSG) had demographic and PSG data abstracted. LAT was estimated using PSG criteria. After adjusting for pretest probability (PTP) for OSA, we calculated the effect that premedication with NBSHs has on LAT prevalence.

Results: Five hundred seventy-nine patients with a mean age and body mass index of 42.2 ± 10.1 y and 28.9 ± 4.5 kg/m², respectively, had data available for analysis. Most patients (444, or 80.9%) had a LAT, and administering a NBSH (zolpidem or eszopiclone) on the same night as the PSG did not change LAT prevalence (NBSH: 339 (83.3%) versus no drug: 100 (80.6%); p = 0.50). Adjusting for PTP, neither administration of eszopiclone (odds ratio 0.80 (95% confidence interval: 0.33–2.0)); 0.69) nor zolpidem (odds ratio 1.65 (95% confidence interval: 0.8–3.5); p = 0.19) reduced the odds that a patient had a LAT. NBSHs did not change the mean SpO₂ nadir, percentage hypopneas, or apnea-hypopnea index. There was no association between zolpidem or eszopiclone dosing and SpO₂ nadir (zolpidem: β = −0.69, p = 0.80; eszopiclone: β = −1.53, p = 0.68), percentage hypopneas (zolpidem: β = 2.2, p = 0.43; eszopiclone β = −6.2, p = 0.46), or apnea-hypopnea index (zolpidem: β = 3.1, p = 0.22; eszopiclone: β = 2.6, p = 0.39).

Conclusions: The LAT is common in our population and NBSH premedication does not alter its occurrence. Further studies are needed to determine how the LAT can be optimally managed to improve OSA treatment.

Keywords: arousal threshold, sleep apnea, non benzodiazepine sedative hypnotics


INTRODUCTION

Obstructive sleep apnea (OSA) is a commonly diagnosed sleep disorder associated with a decline in neurocognitive function, excessive daytime sleepiness and an elevated risk for cardiovascular disease.1–3 Continuous positive airway pressure is recommended as the first-line treatment for OSA. Unfortunately, adherence to therapy is poor,4 particularly in military5,6 and veteran populations.7,8

Active-duty military populations referred to sleep clinics show a high prevalence of OSA, but on average patients are younger and thinner, and disease symptoms tend to be milder.5,9 Younger, thinner patients with milder disease are more likely to meet criteria for having a low arousal threshold (LAT).10,11 The presence of a LAT can predispose a patient to sleep disruptions and respiratory instability.11 Some groups are advocating therapy targeting the specific physiologic traits contributing to OSA in a given patient, including providing sedative medications for those patients with a LAT.12,13 Data from one small trial showed that treatment with the non benzodiazepine sedative hypnotic (NBSH) eszopiclone improved the apnea-hypopnea index (AHI) in all patients with a LAT.14

BRIEF SUMMARY

Current Knowledge/Study Rationale: The non benzodiazepine sedative hypnotic eszopiclone increases the respiratory arousal threshold in small studies of patients with severe OSA. We sought to determine whether zolpidem and eszopiclone affect the arousal threshold in a large cohort of patients with mild-to-moderate disease.

Study Impact: After adjustment for pretest probability of OSA, patients who received zolpidem or eszopiclone prior to PSG were just as likely to have a low arousal threshold as those who were not premedicated. Our study suggests that for non-selected patients with mild-to-moderate disease, neither drug is likely to increase the arousal threshold.

At the Walter Reed National Military Medical Center our sleep laboratory sees predominantly active-duty patients. Many of our sleep physicians routinely use NBSHs prior to PSG because data from our laboratory showed this improves the quality of studies and positive airway pressure titrations.15,16 Using two years of PSG data from our sleep center, we sought to determine the prevalence of the LAT (defined by PSG variables)10 for our population. We wanted to identify clinical and demographic characteristics that predict this physiologic trait, and to see whether pre-PSG NBSH administration reduces the occurrence of the LAT.
This was a retrospective review of consecutive patients undergoing level I PSG at our sleep center from September 2012 through February 2014. We abstracted clinical and PSG data on all patients. Although our clinic does not require the providers to use a particular OSA pretest probability (PTP) assessment tool, we calculated PTP for all patients using a validated score to better characterize our population. This tool uses snoring, body mass index (BMI), age, and sex to establish the probability for OSA. This study was considered a performance improvement (PI) project and formal submission to the institutional review board at our hospital was waived.

**Polysomnography**

By design, all patients in our review had an attended, overnight level I PSG. We did not exclude patients based on the presence of comorbid disease. The AHI was used to diagnose OSA and assess severity when disease was present. Hypopneas were defined according to the recommended criteria in the American Academy of Sleep Medicine scoring guidelines published in 2012. For split-night titrations we used only the diagnostic portion of the study to characterize OSA and calculate the LAT. Patients were split when they met published criteria during the first half of the night.

All PSGs were scored by a certified sleep technician in accordance with published American Academy of Sleep Medicine guidelines, and interpreted by a board-certified sleep physician. Relevant PSG data were abstracted, including oxygen saturation nadir, total time with oxygen saturation less than 90%, and percentage of hypopneas. We recorded the presence or absence of NBSH administration prior to the study. If an NBSH was given, the specific drug and dose were collected. The respiratory arousal threshold is the level of respiratory effort, assessed as negative intrathoracic pressure generated in cm H2O, required to produce an arousal on the electroencephalogram. A patient is labeled as having an LAT when rapid eye movement sleep and a lower percentage of N1. The respiratory efforts less negative than −15 cm H2O intrathoracic pressure trigger electroencephalogram arousal. Investigators recently defined PSG criteria that have good sensitivity and specificity for predicting an LAT less negative than −15 cm H2O. We used their definition to identify patients with LAT:

At least two of the following conditions must be present:

- > 85% of all respiratory events are hypopneas
- > 82.5% oxygen saturation (SpO2) nadir
- Mild to moderate OSA (AHI ≥ 5 but < 30 events/h)

**Statistics**

Variables with normal and nonnormal distributions are expressed as means ± standard deviation and median with interquartile range, respectively. Continuous variables were assessed using the two-sample t-test for normally distributed continuous variables, and the Mann-Whitney rank-sum test for skewed variables. Categorical variables were compared using the Fisher exact test.

To assess overall effect of NBSHs on arousal threshold, we compared arousal threshold PSG characteristics in patients who received the drug with those who did not. Previous studies have shown that BMI, age, and OSA presence and severity all affect the arousal threshold. In order to reduce bias when comparing the arousal threshold in patients who received NBSHs to those who did not, we chose a validated OSA PTP score that contained both age and BMI in its calculation to control for differences between the groups. When modeling the effect that NBSHs had on the LAT, we used logistic regression to control for the effects of baseline PTP when the dependent variable was dichotomous (high arousal threshold versus LAT) and linear regression when the dependent variable was continuous (AHI, percentage hypopneas, and oxygen saturation nadir). Data were analyzed using SPSS 21.0 (IBM Inc, Chicago, IL).

**RESULTS**

A total of 579 patients had data available for analysis. Mean age was 42.2 ± 10.1 y, mean BMI was 28.9 ± 4.5 kg/m2, 416 patients (85.4%) were male, and the median AHI was 13.2 (6.5–26.0) breathing events per hour. Among the group, 100 (17.4%) had no OSA, whereas 219 (38.1%), 128 (22.3%), and 128 (22.3%) had mild, moderate, and severe disease, respectively. Most patients, 261 (58.7%), had a high PTP for OSA. There were 429 patients (76.6%) who received an NBSH (100 eszopiclone and 328 zolpidem) and 131 (23.4%) who took no medication prior to PSG.

PSG parameters for patients who took no drug, zolpidem, or eszopiclone are listed in Table S1 in the supplemental material. Table 1 provides a comparison of clinical and PSG parameters in patients with and without the LAT. Most patients (444, or 80.9%) had a LAT according to previously defined PSG criteria. For all patients, values for oxygen, AHI, and percentage hypopneas were expected to be different based on the LAT definition. LAT patients were younger and had a lower BMI and central apnea index. They had a higher percentage of rapid eye movement sleep and a lower percentage of N1. There was no significant difference in PTP for OSA between patients with and without LAT (p = 0.64). There were 98 patients (16.9%) who had a split PSG performed and 39 (40.2%) had a LAT. Among those with an AHI ≥ 5, 345 (76.7%) had a LAT. Table 2 provides a breakdown of the LAT based on the presence and severity of disease. All patients without OSA had a LAT, and the prevalence of the LAT decreased as disease severity increased.

Administering a NBSH (zolpidem or eszopiclone) prior to PSG did not change the prevalence of the clinically defined LAT (NBSH: 339 [83.3%] versus no drug: 100 [80.6%]; p = 0.50). Examining each drug individually, the prevalence of the LAT with zolpidem was 84.8% (263 of 310 patients) and 78.1% (75 of 95 patients) with eszopiclone, p = 0.32 and p = 0.74, respectively, for comparison to patients who were not premedicated. After adjustment for PTP, neither administration of any NBSH (odds ratio (OR) 1.4; 95% confidence interval (CI) 0.7–2.8; p = 0.35) eszopiclone (OR 0.80; 95% CI 0.33–2.0; p = 0.69) or zolpidem (OR 1.65; 95% CI 0.8–3.5; p = 0.19) was associated with the presence of a LAT. Table 3 lists the mean values for oxygen saturation nadir, AHI, and
repeating this analysis using only patients with a high PTP for OSA (data not shown), NBSHs still did not change the mean SpO2 nadir, percentage hypopneas, or AHI. Table S2 in the supplemental material provides a comparison between patients premedicated with zolpidem or eszopiclone and shows there were no differences in prevalence of the LAT or in variables associated with the LAT.

Table 4 lists the dosages administered for each drug. Entering each drug separately into a linear regression model and controlling for PTP, we tested to see whether increasing dosing would affect SpO2 nadir, percentage hypopneas, or AHI. After adjusting for PTP, there was no association between zolpidem or eszopiclone dosing and SpO2 nadir (zolpidem: \( \beta = -0.69, p = 0.80 \); eszopiclone: \( \beta = -1.53, p = 0.68 \)), percentage hypopneas (zolpidem: \( \beta = 2.2, p = 0.43 \); eszopiclone \( \beta = -6.2, p = 0.03 \)).
This was based on studies showing that sedatives increase the arousal threshold. If NBSHs were affecting the arousal threshold, we would have expected to see a decrease in the arousal threshold. For example, if a patient started with an arousal threshold of −8 cm H₂O and the drug increased the threshold to −10 cm H₂O, we would have expected to see a decrease in the arousal threshold.

DISCUSSION

In this paper we provide prevalence data for the LAT trait for a large group of consecutive patients who had sleep studies ordered at a tertiary academic medical facility. We found that most patients, with or without OSA, had a LAT. Consistent with previous studies, patients with LAT were younger and had lower BMIs, but the use of a NBSH did not decrease the occurrence of the LAT phenotype.

Given the mean age, BMI, and AHI in our population, the high prevalence of a LAT was expected. The decreasing LAT prevalence with increasing OSA severity that we found has been described, and the lower BMI and younger age associations have also been published. Because the PSG LAT score performed as expected, we believe our data indirectly provide external validation for the score.

Prior to analyzing our data we had hypothesized that after adjustment for PTP of OSA, patients who had been premedicated with a NBSH would have a lower prevalence of the LAT. This was based on studies showing that sedatives increase the respiratory arousal threshold by 24% to 33% and improve the AHI for some OSA patients who have a LAT. There was no difference in LAT prevalence when either zolpidem or eszopiclone were administered. One possible explanation for this finding is that NBSHs did increase the arousal threshold in our population, but not enough to cross the −15 cm H₂O threshold. For example, if a patient started with an arousal threshold of −8 cm H₂O and achieved a 24% to 33% increase, the arousal threshold would increase to −10 to −11 cm H₂O. The drug would have increased the arousal threshold but the patient would still have a LAT (less negative than −15 cm H₂O). Table 3 was an attempt to account for this. In the study by Edwards et al., AHIs were similar between their administration and the mean/medians of these three PSG variables. Table 3 shows this was not the case. A dose response might also be expected, with higher doses having more effect on the individual variables making up the score. Again, this was not observed among our patients.

Our study is difficult to compare with those that have shown a sedative effect on the arousal threshold and AHI. Studies of agents considered to be without myorelaxant properties, mainly eszopiclone and trazodone, have enrolled small numbers of patients with mean AHIs that were much higher than the median AHI in our population. These studies assessed the effect of sedatives on the AT within individual patients (PSG with drug versus PSG without drug in the same patient), whereas we compared effects between patients after adjusting for PTP.

The trazodone studies have had conflicting results. One study showed a reduction in AHI without an increase in the arousal threshold whereas another showed the opposite, an increase in arousal threshold but no change in AHI. A third study with a slightly different design showed a change in the arousal response to carbon dioxide but not to mechanical airway occlusion. Last, we were unable to find previously published data on zolpidem and the arousal threshold, and most of our patients received this drug. Though our data indirectly suggest that NBSHs do not affect the arousal threshold for our population, we still know relatively little about the interactions between sedatives, specific patients, and the factors that dictate their arousal threshold.

Our study has several limitations. First, we used a PSG score to estimate AT, and this score has yet to be externally validated. As discussed earlier, based on patient demographics and disease severity the score classified patients as expected, so we assume it performs reasonably well. Our study was retrospective, and although many of the providers in our clinic routinely premedicate their patients with NBSHs, there are some who do not (their patients made up our comparison group). We suspect this is an issue of provider preference, but there may be systematic differences between patients who did and did not receive premedication. We think this is unlikely to have influenced results because we adjusted for PTP, which includes the factors previously shown to affect AT (age, BMI, and an overall, validated prediction of OSA). The mean AHI in our study was low, and like many military populations, age and BMI were also comparatively low. Although this may limit overall generalizability, our results should be applicable to patients with mild to moderate OSA, and these categories of severity are much more common than the more severe forms of the disease. Most patients in our study used zolpidem, and this drug’s short half-life may have diminished effects on the arousal threshold. Finally, we did not exclude patients in whom disorders of arousal have been diagnosed, such as posttraumatic stress disorder or insomnia. Because neither diagnosis has been proven to alter the respiratory arousal threshold, it is not clear whether their inclusion affects our results.

In summary, we found a high prevalence of the LAT in a population referred for PSG at a military medical facility.
Several authors have suggested that manipulating the arousal threshold for patients with a LAT should be part of individualized therapy for OSA. Given our high prevalence of LAT this approach could potentially benefit our population. We found that zolpidem and eszopiclone prescribed at standard doses do not alter the prevalence of LAT. Further study will be required to determine whether proper patient selection can identify patients likely to benefit from NBSHs, or whether different or higher dosing of sedative medications might be required.

**ABBREVIATIONS**

AHI, apnea-hypopnea index  
BMI, body mass index  
CAI, central apnea index  
CI, confidence interval  
LAT, low arousal threshold  
N1, stage 1 sleep  
N2, stage 2 sleep  
N3, stage 3 sleep  
NBSH, non benzodiazepine sedative hypnotics  
OR, odds ratio  
OSA, obstructive sleep apnea  
PI, performance improvement  
PSG, polysomnography  
PTP, pretest probability  
REM, rapid-eye movement sleep  
SpO₂, oxygen saturation  
TST, total sleep time  
WASO, wake after sleep onset

**REFERENCES**


**SUBMISSION & CORRESPONDENCE INFORMATION**

Submitted for publication March, 2016  
Submitted in final revised form September, 2016  
Accepted for publication September, 2016

**DISCLOSURE STATEMENT**

This was not an industry supported study. The authors have indicated no financial conflicts of interest. The views expressed in this paper are those of the authors and do not reflect the official policy of the Department of the Army, Department of Defense, or the US Government.