Original Article

The effect of nonbenzodiazepines sedative hypnotics on apnea–hypopnea index: A meta-analysis

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Abstract:

INTRODUCTION: Nonbenzodiazepine (non-BZD) sedative hypnotics (NBSH) refer to non-BZD sedatives that act as BZD receptor agonists such as zolpidem, zaleplon, and eszopiclone. Today, there is a high prevalence of insomnia with or without concurrent obstructive sleep apnea (OSA). Our goal was to study how NBSH use impacts the baseline apnea–hypopnea index (AHI) in patients with or without OSA.

METHODS: PubMed/MEDLINE, Scopus, Web of Science and Cochrane Library databases were searched.

RESULTS: Seventeen studies comprising a cumulative total of 2099 patients were identified in the last 30 years (between 1988 and 2017) that evaluated the effect of NBSH on respiratory parameters during sleep. The AHI mean (M) ± standard deviation (SD) in NBSH group was 13.17 ± 16.27 versus 15.94 ± 19.31 (mean difference [MD]-95% confidence interval [CI], 2.77 [1.463–4.076]). Six studies (100 patients) compared zolpidem with either placebo or no medication and demonstrated an AHI MD of −0.61 events/h (95% CI − 1.94, 0.71), overall effect Z = 0.9, $P = 0.36$. Four studies (362 patients) compared eszopiclone with placebo and demonstrated an AHI MD of −5.73 events/h0 (95% CI − 8.90, −0.2.57). Two large studies (979 patients) compared both zolpidem and eszopiclone to no medication and found AHI MD of −1.66 events/h (95% CI − 5.87, 0.2.55).

CONCLUSIONS: The majority of patients using NBSH did not develop any worsening of existing AHI, when using NBSH, regardless of their baseline AHI values (mild, moderate, severe, or no OSA). On average, the AHI improved minimally with NBSH and eszopiclone showed the largest difference in AHI with an MD of −5.73 events/h.

Keywords:

Apnea–hypopnea index, continuous positive airway pressure, eszopiclone, nonbenzodiazepine sedative hypnotics, obstructive sleep apnea, placebo, zolpidem, zopiclone

Nonbenzodiazepine (non-BZD) sedative hypnotics (NBSH) are drugs that are structurally non-BZD compounds that act as BZD receptor agonists and bind preferentially to the ω1-BZD receptor of the BZD receptor component of the GRSC (gamma-aminobutyric acid [GABA]-receptor-mediated chloride ionophore supramolecular complex).[1] NBSH group of medications includes imidazopyridine zolpidem, cyclopyrrolone zopiclone, S-isomer of racemic zopiclone called eszopiclone, and pyrazolopyrimidine zaleplon. These medications differ pharmacokinetically in their therapeutic half-lives. Zolpidem is one of the most common and widely used NBSHs today, in an era where the use of prescription medications for use in insomnia is on the rise.[2] Zolpidem is chemically an imidazopyridine (N, N,6-trimethyl-2-[4-methylphenyl] imidazo (1,2-a) pyridine-3-acetamide hemitartrate) that binds selectively and with high affinity to the α-1-containing GABAA

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receptors but with much lower affinity to α-2 and α-3 and not at all to α-5.[3] This is in contrast to zopiclone and eszopiclone that have similar affinity for GABA receptors containing α1, α2, α3, and α5 subunits.[4] Currently, NBSH medications are US Food and Drug Administration approved for the treatment of insomnia in adults only. The limited clinical data on zolpidem in children has raised concerns about lack of efficacy and side effects (dizziness, headache, and hallucination).[5]

The association between obstructive sleep apnea (OSA) and insomnia is strong and often interdependent. Insomnia-related complaints are predominant in 39%–58% of patients with OSA; and reciprocally a substantial proportion (29%–67%) of patients with insomnia have some severity of sleep apnea (as defined by apnea–hypopnea index [AHI] of 5 events/h or higher).[6] Given NBSH like zolpidem are one of the most commonly prescribed sedative-hypnotics, it would be prudent to determine if this class of medications can ameliorate the severity of existing sleep-disordered breathing or even iatrogenically worsen existing AHI (in a nonsleep apneic patient) in the range of clinical sleep apnea. To date, only one meta-analysis has been conducted that evaluated the effect of NBSH on sleep apnea severity.[7] That meta-analysis included eight studies with a cumulative total of 448 patients. Since this was an early meta-analysis, it did not capture the results of studies conducted in the last 6 years. Given the recent increase in prescription of NBSH medications, we felt necessary that the pertinent research data be revisited, revised, and updated. We present a robust review comprised of 17 studies conducted over the last 30 years including a total of 2099 patients to comprehensively assess the effects of NBSH on the existing AHI in patients with and without prior diagnosis of sleep-disordered breathing.[8-24]

Methods

Search strategy

The following search strategy was used in PubMed/MEDLINE, other versions were used in the additional databases after being tailored to the specific requirements: (hypnotics odds ratio [OR] sedatives OR "non-BZD hypnotics" OR "NBSH" OR non-BZD OR pyrazolopyrimidine OR zaleplon OR eszopiclone OR cyclopyrrolone OR zopiclone OR imidazopyridine OR zolpidem) AND ("sleep apnea" OR "sleep apnoea" OR "AHI" OR "apnoea-hypopnoea index" OR "respiratory disturbance index [RDI]" OR AHI OR RDI). Please refer to Figure 1 for details.

Inclusion and exclusion criteria

Inclusion criteria: (1) All studies that included patients being administered an NBSH medication followed by determination or discussion of the subsequent AHI compared to nonusers or placebo treatment. (2) Sleep studies conducted in-lab or at home to determine AHI. (3) Studies including patients treated with NBSH as a pretreatment to calibrate continuous positive airway pressure (CPAP) titration for a diagnosis of OSA. (4) Studies including patients treated with NBSH for insomnia, with or without concurrent diagnosis of OSA. (5) Studies including patients treated with NBSH for idiopathic central sleep apnea (ICSA).

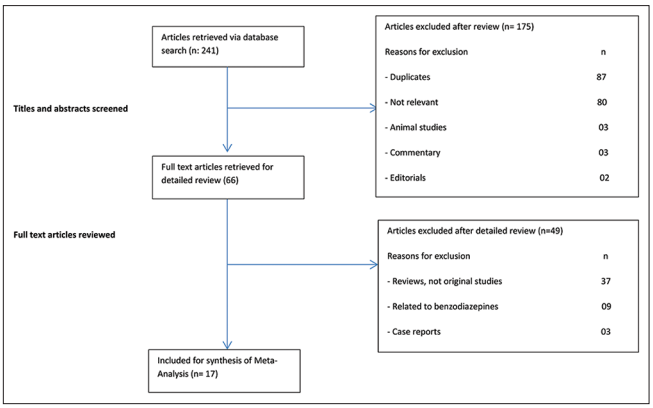

Figure 1: Flow diagram demonstrating selection of pertinent studies through multiple database search

Exclusion criteria: (1) Studies that mentioned AHI values neither quantitatively nor qualitatively, while reporting NBSH effects on sleep architecture in patients with or without sleep-disordered breathing. (2) Studies discussing NBSH effects on AHI on patients at high altitudes. (3) Studies that discussed AHI effects of NBSH in pediatric patients.

Results

Based on the criteria described above 17 studies were included in this meta-analysis.[8-24] These represented a cumulative sample size of 2099 patients. The results are representative of global AHI outcomes providing data for patients exposed to different varieties and dosages of NBSH medications. Twelve studies were conducted in the United States, and one study from each of the following countries: Canada, France, Italy, Brazil, and Australia. Three studies used the definition for hypopnea at ≥3% oxygen desaturation from preevent baseline while eight studies used ≥4% oxygen desaturation from preevent baseline to categorize them as hypopneas. The remaining studies did not mention, what hypopnea definition was used to arrive at the final calculation for AHI. The majority of the identified studies were randomized, double-blind cross-over studies, whereas four studies were retrospective reviews. Ten studies had 100% enrollees with OSA, one study had 82% patients with OSA, and at least two studies had no enrollees with OSA. Five studies found NBSH use could increase the

final AHI; four studies found NBSH use could decrease the final AHI and eight studies found NBSH use did not affect the final AHI.

Meta-analysis results

Polysomnography outcomes for NBSH versus placebo or no medications revealed that the AHI was slightly decreased in NBSH group as compared to placebo or no medications (non-NBSH). Overall, M ± SD in NBSH group was 13.17 ± 16.27 versus 15.94 ± 19.31 (mean difference [MD] – 95% confidence interval [CI], 2.77 [1.463–4.076]) [Table 1]. A subanalysis using random effects modeling was performed for a total of 12 studies (1441 patients) in which M ± SD were reported, and the AHI MD was – 2.20 events/h (95% CI – 3.54, –0.86), overall effect Z = 3.21, $P = 0.001$, Q statistic $P = 0.00001$ (significant heterogeneity), $I^2 = 90\%$ (high inconsistency) [Figure 2]. The funnel plot for the AHI MD was scattered asymmetrically and only mildly distributed into an inverted funnel shape. The AHI standardized MD was – 0.37 (95% CI – 0.61, –0.13) (small magnitude of effect), overall effect Z = 3.0, $P < 0.003$, Q statistic $P < 0.00001$ (significant heterogeneity), $I^2 = 84\%$ (high inconsistency) [Figure 3]. The funnel plot for standardized mean difference was significantly clustered toward the center of the funnel.

There was significant persistent heterogeneity and inconsistency among the included studies in this meta-analysis. The authors performed a sensitivity analysis and could not identify any specific studies contributing to the heterogeneity. However, the studies conducted by Berry and Patel, Gatti *et al*., Rosenberg *et al*., and Smith *et al*. demonstrated the least heterogeneity. The studies by Coyle *et al*., Eckert *et al*., Lettieri *et al*., Quadri *et al*., Quera-Salva *et al*., Smith *et al*., and Steens *et al*. demonstrated the most heterogeneity among the studies included in this meta-analysis. Excluding aforementioned studies yielded no significant heterogeneity (Q statistic $P = 0.12$) and medium inconsistency ($I^2 = 48\%$).

A subanalysis using random effects modeling among six studies (100 patients) which compared zolpidem with either placebo or no medication (Berry *et al*., Coyle *et al*., Gatti *et al*., Quadri *et al*., Quera-Salva *et al*., and Steens *et al*.) demonstrated an AHI MD of –0.61 events/h (95% CI – 1.94, 0.71), overall effect Z = 0.9, $P = 0.36$, Q statistic $P = 0.00001$ (significant heterogeneity), $I^2 = 89\%$ (high inconsistency).

A subanalysis using random effects modeling among four studies (362 patients) which compared eszopiclone with placebo (Eckert *et al*., Lettieri *et al*. 2008 and 2009, and Rosenberg *et al*.) yielded an AHI MD of –5.73 events/h (95% CI –8.90, –0.2.57), overall effect Z = 3.55, $P = 0.0004$, Q statistic $P = 0.07$ (no significant heterogeneity), $I^2 = 58\%$ (moderate inconsistency).

Table 1: Summary of demographic and polysomnographic characteristics of patients included in the meta-analysis

Author, Year	Patient characteristics			Apnea Hypopnea Index (mean/sd, except^)		
	n	Age, Years	BMI Kg/m^2	Without-NBSH	With-NBSH	MD (95% CI)
Smith *et al*., 2017^	579	42.2±10.1	28.9±4.5	18.8±20.7	19.4±19	0.60(-2.894-1.694)
Carter-Berger *et al*., 2016^	12	49.3±10.1	28 (26-33)	40.8	49.1	-
Gatti *et al*., 2016	15	59.1±7.6	25.5±3.7	22.81±16.31	22.16±17.72	0.65 (12.087-13.387)
Loh *et al*., 2014	300	-	-	-	61.7, 18.0, 20.3	-
Park *et al*., 2013^	134	49.8±11.3	-	-	-	-
Eckert *et al*., 2011	17	45±4	36±7	31±5	24±4	7.0 (3.84-10.16)
Collen *et al*., 2009	400	47±7.7	30.3±13.4	9.8±10.7	6.1±7	3.70 (2.444-4.956)
Quadri *et al*., 2009	20	55.0±9	-	30±18.1	13.5±13.3	16.50 (6.333-26.667)
Lettieri *et al*., 2009	98	44.9.0±6.70	32.5±7.5	34.2±27.6	24.1±21	10.10 (3.191-17.009)
Lettieri *et al*., 2008	226	43.5±10.0	30.3±3.8	11.9±19.6	5.7±10.3	6.2 (3.306-9.094)
Rosenberg *et al*., 2007	21	48.4±9	-	16.5±9.3	16.7±8.1	0.20 (-5.639-5.239)
Berry *et al*., 2006	16	49.4±12.4	36.1±4.8	4.8±1.4	2.7±0.47	2.10 (1.346-2.854)
Lettieri *et al*., 2005	200	43.9±9.9	-	-	27	-
Coyle *et al*., 2005	15	-	-	7.5±1.0	7.2±0.8	0.30 (-0.377-0.977)
Quera-Salva., 1994	10	42	26.5	1.5±1.5	3±3	1.50 (-3.728-0.728)
Steens *et al*., 1993	24	58.2±5.5	-	4.7±0.8	4.9±0.8	0.20 (-0.665-0.265)
Cirignotta *et al*., 1988	12	49	-	16.9	29.9	-
Total Patients	2099					
Included in Meta-Analysis	1441					
Combined Means/SD/MDs	1441			15.94±19.34	13.17±16.23	2.77 (1.463-4.076)
	1416	46.57±8.98				
	1372		30.73±10.40			

^: Represents Mean/Median AHI with Interquartile range, NBSH: Non benzodiazepines Sedative Hypnotics, BMI: Body Mass Index, SD: Standard Deviation, MD: Mean Difference, CI: Confidence interval

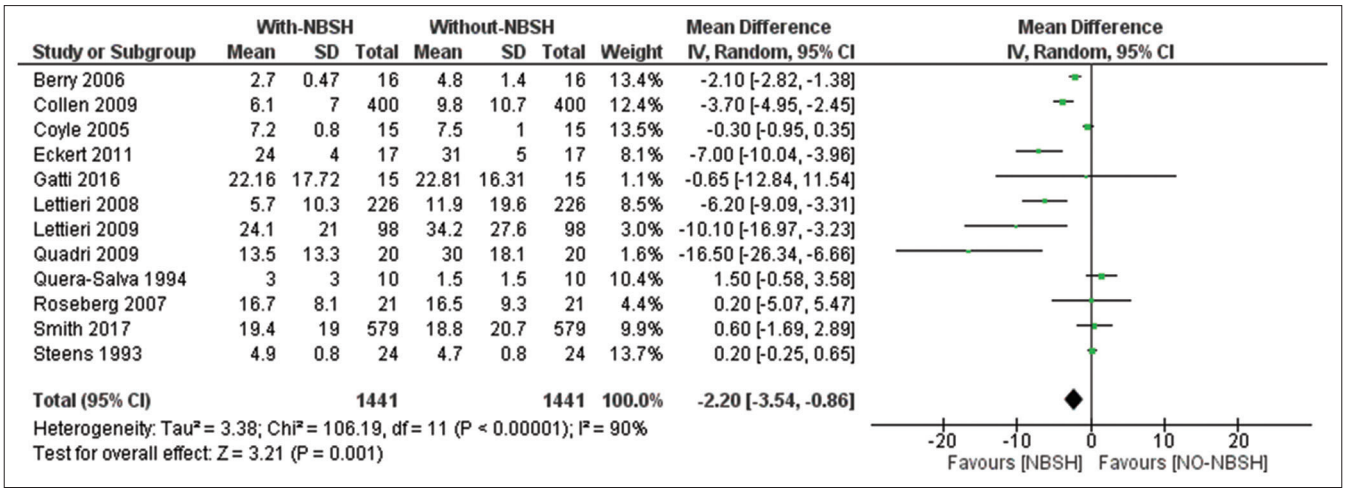

Figure 2: A subanalysis using random effects modeling to determine apnea–hypopnea index mean differences

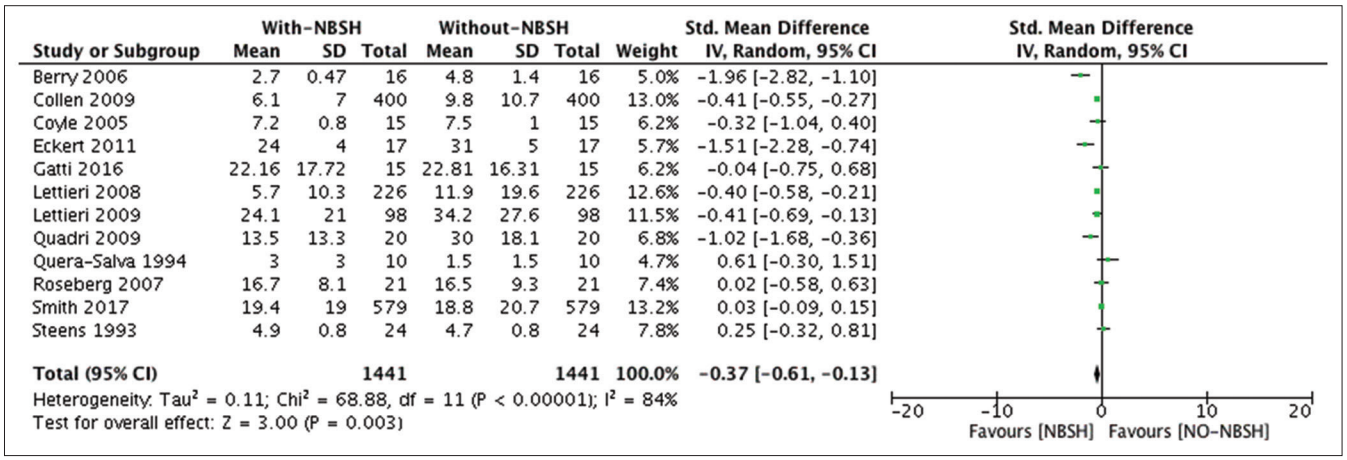

Figure 3: A subanalysis using random effects modeling to determine the standardized apnea–hypopnea index mean differences

To further identify the heterogeneity, a subanalysis using random effects modeling was performed incorporating the two largest constituent studies (Smith *et al*. and Collen *et al*.), totaling 979 patients. These two studies compared usage of both zolpidem and eszopiclone in their studies against no medication, the AHI MD was −1.66 events/h (95% CI − 5.87, 0.2.55), overall effect Z = 0.77, *P* = 0.44, Q statistic *P* = 0.001 (significant heterogeneity), I^2 = 90% (high inconsistency).

Discussion

Effect of nonbenzodiazepines sedative hypnotics on apnea–hypopnea index in cohorts composed exclusively of patients without sleep apnea

At least two studies were composed of all participants devoid of baseline OSA where baseline AHI was <5 events/h. Quera-Salva *et al*. studied "heavy snorers" without baseline OSA, while Steens *et al*. studied chronic obstructive pulmonary disease patients without OSA. When compared to placebo, both these studies observed at best a marginal, few indices rise in baseline AHI with use of zolpidem that was either statistically significant (Quera-Salva *et al*.) or insignificant (Steens *et al*.). Despite this nominal rise in AHI, most patients did not develop polysomnographically validated OSA due to use of zolpidem.

Effect of nonbenzodiazepines sedative hypnotics on apnea–hypopnea index in cohorts composed exclusively/predominantly of patients with sleep apnea

At least ten studies claimed 100% participants having baseline OSA. Majority of these studies found no significant change in AHI (Carter *et al*., Rosenberg *et al*., Park *et al*., Berry *et al*., and Coyle *et al*.) or even a statistically significant decrease in AHI (Eckert *et al*. and Collen *et al*.) when compared to placebo/no medication cohort. Of note, Berry *et al*. and Rosenberg *et al*. also happened to be studies with least heterogeneity. Only one study (Loh *et al*.) found a statistically significant increase in AHI following use of NBSH compared to

no medication. Of note, Loh *et al*. data were presented as a meeting abstract. The authors here conceded that the rise in AHI noted could have been partly related to selection bias, given that the providers, who prescribed NBSH to their patients had a different referral pattern than providers, who did not prescribe any hypnotics to their patients. The study with the largest sample size in this meta-analysis was that of Smith *et al*. with 579 participants, and majority of the participants had OSA. This study concluded that use of NBSH during polysomnogram does not change the mean AHI. In addition to these nine studies, another study in this meta-analysis was that of Quadri *et al*. who studied patients with ICSA. They found that in patients with ICSA, with use of NBSH, central apneas and hypopneas decreased significantly, without any significant worsening of OSA.

Effect of nonbenzodiazepines sedative hypnotics on apnea–hypopnea index including all patient populations regardless of comorbidities

NBSH use most likely results in no numerically prominent or statistically significant changes in AHI for the vast majority of patients, while in some participants, it may increase or decrease the baseline AHI. Figure 4 provides some hypothetical possibilities as to how NBSH medications could alter the baseline AHI.

Few studies reported increased AHI on night patients were exposed to NBSH compared to placebo or no use of NBSH medication. Like BZDs, could NBSH lead to relaxation of upper airway muscles leading to elevation of AHI as their sedative effects permeate?[25] This is likely not the case, especially when NBSH involved is zolpidem. While the selective binding of zolpidem on the α-1-containing GABAA receptors is not absolute, its strong preference and affinity for the above receptor subunit may explain the relative absence of myorelaxant effect related to this drug. Unlike classical BZDs where sedative and myorelaxant effects occurring at any given dose are mutual and inextricable (given almost equal binding to all receptor subunits), in case of zolpidem, the preferential and selective binding to α-1-subunit of GABAA receptors ensures that the sedative/hypnotic effect kicks in at a much lower dose than do the other pharmacological effects attributed to BZD-site action such as their myorelaxant properties.[26]

First of all, the most studies that arrived at this conclusion conceded that the iatrogenic numerical rise in AHI was small and/or insignificant (Cirignotta *et al*., Steens *et al*., and Lettieri *et al*. [2005]). Second, selection bias at least in part may be contributing to the elevated AHI reported with NBSH use. This was exemplified in the study by Loh *et al*. as discussed above. Third, up to 15% patients with OSA will

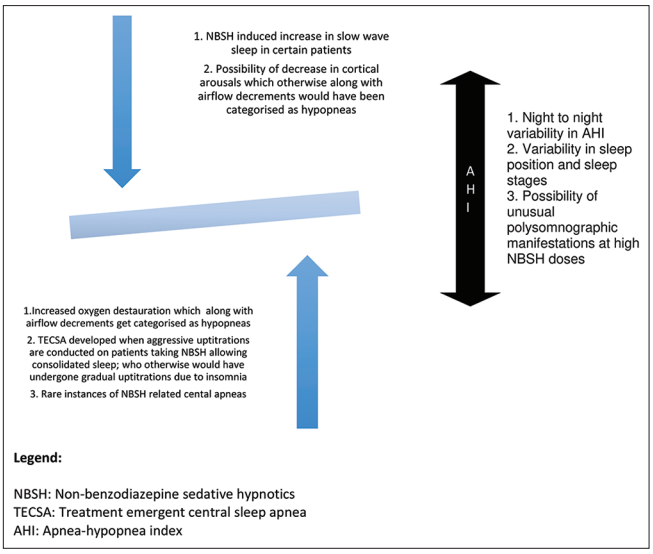

Figure 4: Possible parameters influencing apnea–hypopnea index fluctuations on exposure to nonbenzodiazepine sedative hypnotics

demonstrate considerable night-to-night variability in their recorded AHI, which could have affected the final AHI on the night of NBSH administration.[27] Finally, a higher proportion of supine sleep or higher proportion of rapid eye movement sleep on the night of NBSH medication administration could also lead to a higher final AHI on such nights.[28] Of note, one study (in case of Quera-Salva *et al*.) showed a small, yet statistically significant rise in AHI with use of zolpidem when compared to placebo. In this study, they even noticed that one patient had a RDI that was "almost pathological with zolpidem" (RDI of 10 events/h), whereas in the remaining participants, the RDIs were far from being abnormal with zolpidem (RDI <5 events/h). One possibility is the development of idiosyncratic reaction to zolpidem resulting from GABAA receptor subunit mutation leading to altered sensitivity and affinity toward zolpidem. In such rare patients, we wonder if there could have been zolpidem-related rise in central apneas, causing a secondary rise in baseline AHI similar to the phenomenon of treatment-emergent central sleep apnea (TECSA) or could there be a higher chance of development of TECSA in patients undergoing CPAP titration with use of zolpidem? This is plausible given that NBSH creates a favorable sleep architecture allowing consolidated sleep, creating the environment and opportunity for rapid and aggressive uptitrations which otherwise would have been slow and cautious in OSA patients with insomnia.[29,30] More experimental research into polysomnographic effects of zolpidem is needed to answer these questions definitively.

On the other end of the spectrum, some studies demonstrated an effective reduction in AHI, when NBSH was used compared to patients who used placebo or did not use any medications. Again, this

could be indicative of night-to-night variability described above.[27] Slow-wave sleep has been found to profoundly reduce obstructive events (and hence AHI), especially in patients with OSA.[31] However, the effects of zolpidem on slow-wave sleep have been inconsistent so far with some studies reporting a reduction,[32] some reporting an elevation[33] and some reporting no change[34-36] in amount of slow-wave sleep in a hypnogram when patients are exposed to zolpidem. The way zolpidem affects the proportion of slow-wave sleep in a particular patient could in part explain the secondary rise or fall in AHI with use of the NBSH medications. Administration of placebo medications can also subjectively improve sleep quality and efficiency with somewhat favorable projections on polysomnographic variables as evidenced by previous studies, although it remains unclear if this could affect the subsequent AHI in such patients.[37] Furthermore, it has been demonstrated that zolpidem blocks the "histamine hub" that otherwise would have created arousals and wakefulness.[38] It is possible that borderline airflow decrements which along with cortical arousals may have been classified otherwise as hypopneas would not be contributing to hypopnea index anymore under altered spectral power density EEG effects mediated by zolpidem.[39] More research work is required to better understand the convoluted role of zolpidem in altering the baseline AHI.

Conclusion

The majority of patients using NBSH did not develop any polysomnographically evident worsening of existing AHI when using NBSH, regardless of their baseline AHI values (mild, moderate, severe, or no OSA). On the contrary, use of NBSH in many cases may even result in a marginal improvement in baseline AHI, when compared to no medications or placebo groups. On average, the AHI improved minimally with NBSH and eszopiclone showed the largest difference in AHI with an MD of − 5.73 events/h.

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Conflicts of interest
There are no conflicts of interest.

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