



Effect of 1 month of zopiclone on obstructive sleep apnoea severity and symptoms: a randomised controlled trial

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1 month of nightly zopiclone does not worsen OSA severity or symptoms in individuals with low-moderate arousal thresholds <http://ow.ly/9JD230khJpl>

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ABSTRACT Hypnotic use in obstructive sleep apnoea (OSA) is contraindicated due to safety concerns. Recent studies indicate that single-night hypnotic use worsens hypoxaemia in some and reduces OSA severity in others depending on differences in pathophysiology. However, longer clinical trial data are lacking. This study aimed to determine the effects of 1 month of zopiclone on OSA severity, sleepiness and alertness in patients with low-moderate respiratory arousal thresholds without major overnight hypoxaemia.

69 participants completed a physiology screening night with an epiglottic catheter to quantify arousal threshold. 30 eligible patients (apnoea-hypopnoea index (AHI) 22 ± 11 events·h⁻¹) then completed standard in-laboratory polysomnography (baseline) and returned for two additional overnight sleep studies (nights 1 and 30) after receiving either nightly zopiclone (7.5 mg) or placebo during a 1-month, double-blind, randomised, parallel trial (ANZCTR identifier ANZCTR12613001106729).

The change in AHI from baseline to night 30 was not different between zopiclone *versus* placebo groups (-5.9 ± 10.2 *versus* -2.4 ± 5.5 events·h⁻¹; $p=0.24$). Similarly, hypoxaemia, next-day sleepiness and driving simulator performance were not different.

1 month of zopiclone does not worsen OSA severity, sleepiness or alertness in selected patients without major overnight hypoxaemia. As the first study to assess the effect of a hypnotic on OSA severity and sleepiness beyond single-night studies, these findings provide important safety data and insight into OSA pathophysiology.

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Introduction

Hypnotic use is common, with 3–5.5% of the general population reporting hypnotic use within the past month [1, 2]. Use is higher in obese individuals (7.2%) and the elderly (9.1%) [1], two major risk factors for obstructive sleep apnoea (OSA), an increasingly common sleep-related breathing disorder with major adverse health and safety consequences [3–5]. Over 40% of OSA patients also have insomnia symptoms [6, 7].

Historically, hypnotics have been contraindicated in OSA. Major concerns have been that central nervous system depression will impair “life-saving” arousals to respiratory stimuli and worsen pharyngeal muscle contractility to promote respiratory event prolongation and hypoxaemia [8]. Indeed, certain hypnotics at high doses or in very severe, obese individuals can worsen hypoxaemia [9–11]. However, recent advances in understanding OSA pathogenesis indicate that frequent arousals destabilise sleep and breathing, and contribute to OSA [12, 13]. Waking up too easily during airway narrowing (low respiratory arousal threshold) may be a key contributor to OSA pathogenesis in up to 50% or more of OSA patients [12–17]. Contrary to previous beliefs, standard doses of common hypnotics (temazepam, trazodone, zopiclone and zolpidem) do not systematically reduce pharyngeal muscle contractility or increase upper airway collapsibility [11, 18, 19]. However, in two recent small physiology studies, trazodone and zopiclone did not change the apnoea–hypopnoea index (AHI), and zopiclone increased mean overnight hypoxaemia by 1% in individuals with severe OSA [11, 19]. In contrast, eszopiclone and trazodone have been shown to promote sleep and reduce AHI without worsening event duration or hypoxaemia during single-night studies [14, 20]. Reductions in AHI were invariable in individuals with low arousal thresholds in the eszopiclone study [14]. Eszopiclone combined with oxygen also markedly reduces AHI, with greater reductions in patients with lower arousal thresholds and less anatomical compromise [21].

Given that >50% of OSA patients fail to comply with the first-line therapy, continuous positive airway pressure [5, 17, 22] and second-line therapies have variable and unpredictable efficacy [23], and there is increasing interest in a personalised approach to pharmacotherapy for OSA [24]. Thus, to gain important safety knowledge and understand the potential therapeutic utility of certain hypnotics for selected OSA patients, there is a need to determine if reductions in AHI are stable over time. Accordingly, the primary aim of this study was to determine if 1 month of nightly zopiclone reduces OSA severity compared with placebo in patients with low–moderate respiratory arousal thresholds and mild overnight hypoxaemia. As there is potential for residual next-day sleepiness with hypnotics, secondary aims were to assess changes in sleep parameters, daytime sleepiness and alertness to establish the safety profile of extended hypnotic use in this group of patients. Finally, to advance clinical translation, in a secondary *post hoc* analysis we assessed whether a recently developed clinical tool to estimate the respiratory arousal threshold from standard polysomnography (PSG) variables yielded similar findings to the gold standard, but somewhat invasive, pressure catheter approach [16].

Methods

Participants

Otherwise healthy individuals with untreated or suspected OSA aged 18–65 years were recruited *via* advertisement using flyers on local notice boards. Newly diagnosed patients or those who failed other therapies were also recruited from NeuRA’s research volunteer database or from local sleep clinic referrals (Prince of Wales Hospital and Woolcock Sleep clinics), all located in Sydney, Australia. To be randomised, patients had to have AHI ≥ 5 events·h⁻¹, nadir arterial blood oxygen saturation (SaO₂) $\geq 75\%$ and a respiratory arousal threshold ≥ -25 cmH₂O (determined during an overnight screening physiology study, as outlined later). Other exclusion criteria included any medication that may affect breathing, sleep or pharyngeal muscle activity, pregnant or nursing mothers and known allergy to hypnotics. Participants were also asked not to consume alcohol for the duration of the 1-month trial and to allow sufficient time for sleep opportunity each night after taking the study medication.

Informed consent was provided as approved by the South Eastern Sydney Local Health District Human Research Ethics Committee. This study is registered at ANZCTR with identifier number ANZCTR12613001106729.

Protocol and key measurements

Initially, an overnight screening physiology study (Spike 2; Cambridge Electronic Design, Cambridge, UK) with standard PSG equipment (see later) plus an epiglottic pressure catheter (Millar, Houston, TX, USA) and nasal mask was performed to quantify the arousal threshold to determine eligibility [11]. Eligible participants (AHI ≥ 5 events·h⁻¹, nadir SaO₂ $\geq 75\%$ and a respiratory arousal threshold ≥ -25 cmH₂O) then completed a standard overnight PSG without an epiglottic pressure catheter. Recording equipment included: electroencephalogram, electro-oculogram, ECG, surface submental is electromyogram, pulse

oximeter, chest and abdominal motion, position monitor, and nasal pressure and thermistor airflow sensors (REMLogic; Natus Medical, Pleasanton, CA, USA) to re-confirm eligibility criteria and quantify baseline sleep characteristics and OSA severity in the absence of an epiglottic pressure catheter. Following the screening physiology study and baseline PSG, participants were randomised to either 1 month of nightly placebo or zopiclone (7.5 mg) according to a double-blind, parallel design (figure 1). Participants returned for a standard PSG on the first (night 1) and the last (night 30) night of the 1-month trial to investigate potential changes in sleep parameters from baseline between conditions. Pill counts at night 30 were taken to assess adherence. The Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ) and Karolinska Sleepiness Scale (KSS) were administered 1.5 h prior to sleep at

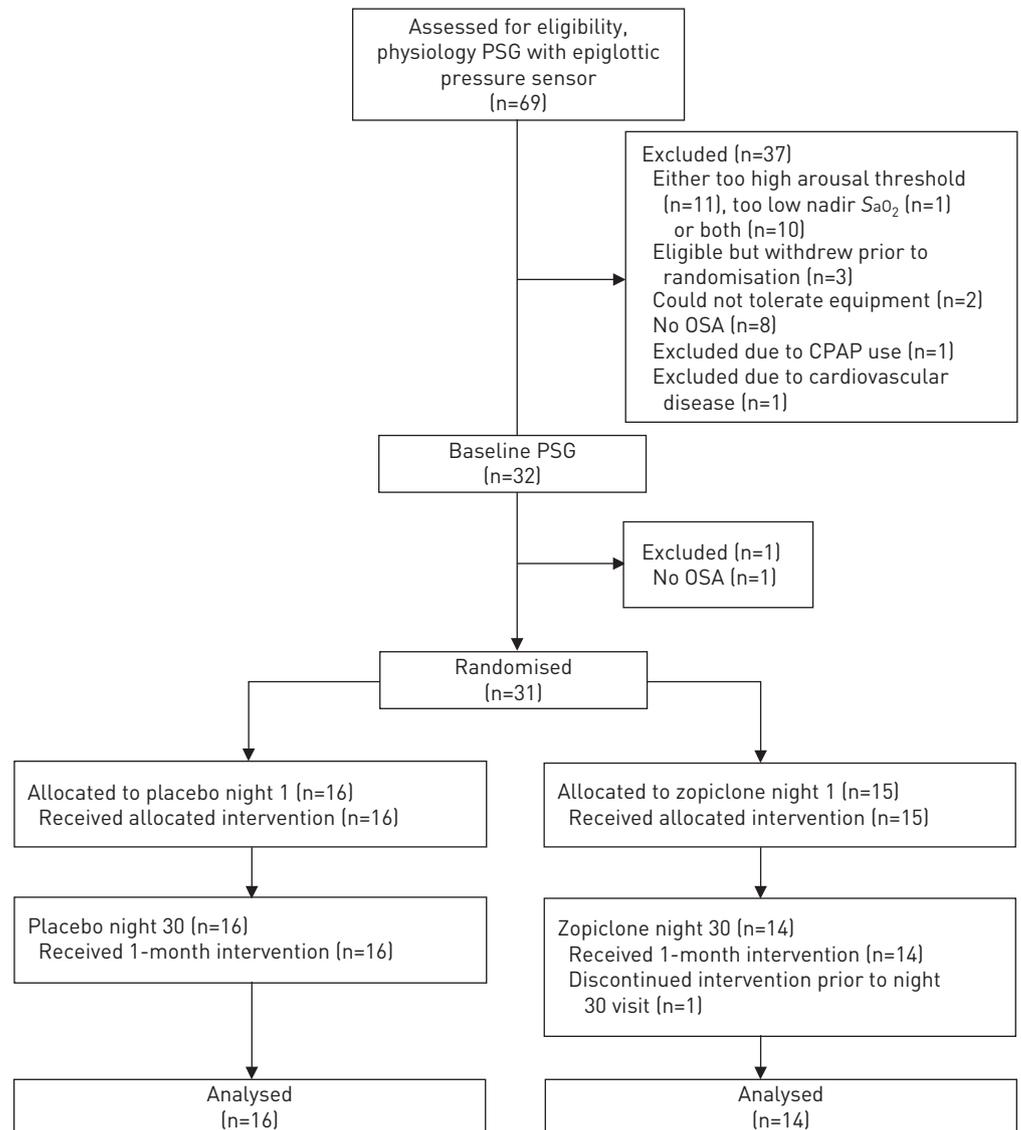


FIGURE 1 CONSORT flow diagram indicating the enrolment, randomisation, allocation, follow-up and analysis procedures for this double-blind, placebo-controlled, parallel trial. Initially, participants with a confirmed diagnosis or clinical suspicion of OSA responded to a research advertisement or were contacted via a research volunteer database. Participants attended an in-laboratory physiology screening PSG to determine eligibility for the trial. Eligible patients (untreated OSA (apnoea-hypopnoea index ≥ 5 events \cdot h $^{-1}$), overnight nadir $S_{aO_2} \geq 75\%$ and low-moderate respiratory arousal threshold ≥ -25 cmH $_2$ O) that were otherwise healthy) attended a standard in-laboratory baseline PSG. If still eligible following baseline, patients were then randomised to either the placebo or zopiclone condition. Participants received either once-nightly placebo or 7.5 mg of zopiclone just prior to bed for 1 month. Participants attended two standard in-laboratory PSGs on the first (night 1) and last night (night 30) of the treatment nights. One patient was excluded from the study after the baseline PSG as they were found not to have OSA. One patient discontinued involvement in the study prior to completing night 30 due to an unrelated personal issue. PSG: polysomnography; S_{aO_2} : arterial blood oxygen saturation; OSA: obstructive sleep apnoea; CPAP: continuous positive airway pressure.

each visit. The KSS, Leeds Sleep Evaluation Questionnaire (Leeds) and a 30-min AusEd driving simulator task were performed each morning 30 min after awakening to assess next-day sleepiness and alertness [25]. At the end of the trial, participants were also asked several questions as to how they felt during the study and whether or not they believed they were in the zopiclone *versus* placebo arm.

Data analyses

All analyses were performed blinded to the study intervention. Sleep staging, respiratory event and arousal scoring were performed by a single experienced sleep technician according to the American Academy of Sleep Medicine recommended criteria version 2.1 [26]. Up to 20 (or as many as were available) cortical arousals that occurred in conjunction with increasing epiglottic pressure swings with obstructive apnoeas or hypopnoeas were selected at random to calculate the arousal threshold for each participant during the initial physiology screening PSG. Specifically, the nadir epiglottic pressure immediately prior to a cortical arousal was determined for each respiratory event (figure 2) and averaged to quantify the arousal threshold as described previously [11, 14]. As an exploratory *post hoc* analysis, the utility of a simple validated clinical tool to estimate the arousal threshold from standard PSG variables [16] was used to determine if those with low-moderate arousal thresholds at baseline could be accurately identified.

Statistical procedures

Based on previous data (standard deviation of the difference in AHI of $6.3 \text{ events}\cdot\text{h}^{-1}$ between conditions) [14], our sample size of $n=15$ in each group (zopiclone and placebo) was selected to detect a change of $7 \text{ events}\cdot\text{h}^{-1}$ from baseline to night 30 (primary outcome) between conditions with $>80\%$ power with a two-tailed, unpaired t-test [14]. Similarly, all normally distributed (Shapiro-Wilk) data for secondary outcomes were compared using a two-tailed, unpaired t-test. Nonnormally distributed data were compared using a Wilcoxon signed-rank test. $p<0.05$ was considered significant. Data are reported as mean with standard deviation or median (interquartile range) for nonnormally distributed variables.

Results

Participant characteristics

Of the 69 individuals who participated in the overnight screening physiology study, 38 were ineligible due to their arousal threshold being $\leq -25 \text{ cmH}_2\text{O}$ and/or their nadir S_{aO_2} being $\leq 75\%$, or did not meet other inclusion criteria. Of these 38 individuals, 27 had predominantly severe OSA (AHI $48\pm 25 \text{ events}\cdot\text{h}^{-1}$), nine did not have OSA (AHI $<5 \text{ events}\cdot\text{h}^{-1}$) and AHI could not be quantified in two participants due to

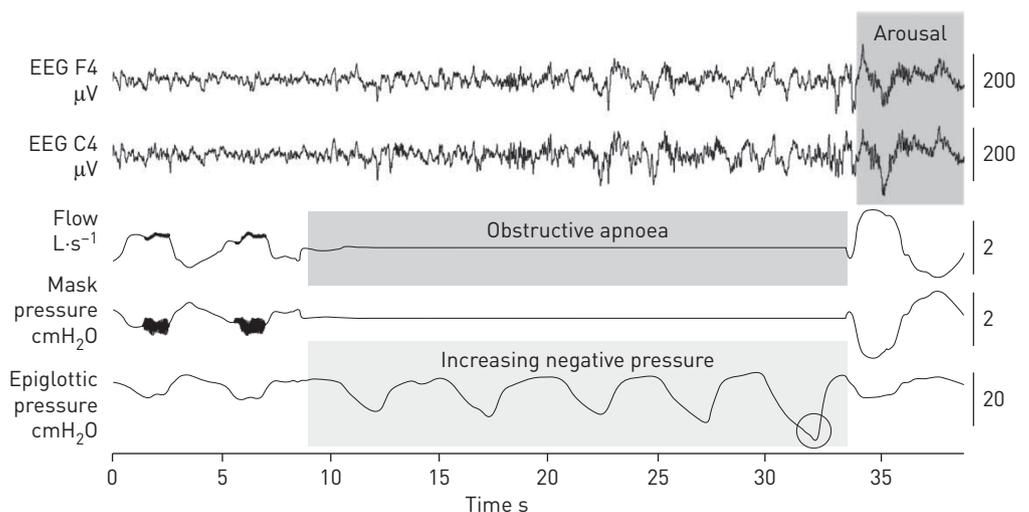


FIGURE 2 Polysomnographic recordings in an individual patient demonstrating how the respiratory arousal threshold measures were obtained. This example shows an ~40-s epoch of non-rapid eye movement N2 sleep in which the 35-year-old male patient [apnoea-hypopnoea index $20 \text{ events}\cdot\text{h}^{-1}$; body mass index $32.2 \text{ kg}\cdot\text{m}^{-2}$] experienced an ~25-s respiratory event [shaded area of the respiratory flow channel labelled "Obstructive apnoea"] that ended with a cortical arousal from sleep [shaded area of the two EEG channels labelled "Arousal"]. The respiratory arousal threshold is quantified as the nadir epiglottic pressure during the respiratory effort occurring immediately prior to arousal [circled area on the epiglottic pressure channel, in this example approximately $-32 \text{ cmH}_2\text{O}$]. Flow is the nasal airflow measured *via* a mask and pneumotachograph; mask pressure is the pressure at the nasal mask measured using a pressure transducer. EEG: electroencephalogram.

inability to sleep with the recording equipment during the physiology screening night (see figure 1 for further details). 31 individuals were randomised; 30 completed all 4 nights of the trial and were included in the final analyses (figure 1). Baseline anthropometric and sleep parameters were well matched between placebo and zopiclone groups (table 1). Anthropometric characteristics did not change during the 1-month trial (supplementary table E1). Adherence with the study intervention was high for both zopiclone and placebo groups ($93.7\pm 9.7\%$ and $93.4\pm 11.0\%$, respectively). Adverse events were uncommon during the 1-month trial, and all but one was minor and not related to the study medication (table 2). Table 3 summarises participant perceptions of the study medication (placebo or zopiclone) at the end of the 1-month trial. During zopiclone compared with placebo, 79% *versus* 56% reported improved sleep, 36% *versus* 31% said that they would continue with the study medication if available and 79% *versus* 69% correctly perceived which study medication they were taking.

Respiratory events and sleep parameters

The change in AHI from baseline to night 30 was not different between zopiclone and placebo conditions ($p=0.24$) (figure 3). The mean reduction in AHI at night 30 compared with baseline during zopiclone was -5.9 ± 10.2 ($p=0.048$) *versus* -2.4 ± 5.5 events·h⁻¹ during placebo ($p=0.098$). Percentage reductions in AHI with zopiclone were similar in those with moderate < -15 and > -25 cmH₂O) and low (≥ -15 cmH₂O) respiratory arousal thresholds (29% *versus* 21%) (table 4).

PSG data at baseline and night 30 during both conditions are summarised in table 4. The increase in sleep efficiency from baseline to night 1 was significantly greater with zopiclone compared with placebo ($8.8\pm 0.1\%$ *versus* $1.2\pm 0.1\%$; $p=0.02$) (supplementary table E2). A comparable increase of $6.9\pm 0.1\%$ in sleep efficiency from baseline to night 30 with zopiclone occurred, but did not reach statistical significance ($p=0.06$). The delta change from baseline to night 30 was not different between conditions (table 4). The amount of wake after sleep onset was reduced from baseline to night 1 with zopiclone *versus* placebo (-41 ± 45 *versus* -8 ± 38 min; $p=0.004$) (supplementary table E2), but not compared with night 30 (table 4). There were no between-condition differences in the majority of the other sleep parameters, including sleep onset latency, percentage total sleep time (TST) spent in non-rapid eye movement (REM) or REM sleep, arousal index, percentage TST supine, supine AHI, or respiratory event duration. Mean SaO₂ during sleep at baseline was ~1% lower in the zopiclone group ($p=0.03$). However, zopiclone did not alter mean or nadir SaO₂. Sleep and respiratory parameters at night 1 were similar to night 30 (supplementary table E2).

Sleepiness and alertness

Sleepiness and alertness data from baseline to night 30 for placebo and zopiclone conditions are summarised in table 5. There were no differences in any measure of sleepiness or alertness, including ESS, FOSQ, Leeds, KSS or AusEd driving simulator performance, between conditions. Similarly, apart from an increase in the standard deviation from the median of the lane position during the driving task with zopiclone from baseline to night 1 compared with placebo (6.7 ± 8.4 *versus* -5.4 ± 12.1 cm; $p=0.004$) (supplementary table E3), measures of alertness and sleepiness on night 1 were not different between conditions.

TABLE 1 Participant anthropometric and sleep characteristics

	Placebo	Zopiclone
Participants	16	14
Sex		
Male	13	12
Female	3	2
Age years	46±13	50±8
BMI kg·m⁻²	29±4	28±4
Mean AHI events·h⁻¹	21±10	23±12
AHI range events·h⁻¹	6–38	6–53
Arousal threshold cmH₂O	-16±5	-16±7

Data are presented as n or mean±SD, unless otherwise stated. Group anthropometric and baseline obstructive sleep apnoea severity data acquired from the baseline and physiology (for respiratory arousal threshold data only) overnight sleep studies. BMI: body mass index; AHI: apnoea–hypopnoea index.

TABLE 2 Adverse events reported during the 1-month trial

	Placebo		Zopiclone [#]		Related to zopiclone [¶]
	Minor	Serious	Minor	Serious	
Abnormal dreams	2/16		1/15		Probably
Abscess drainage				1/15	No
Anxiety			1/15		Possibly
Balance disorder			1/15		Probably
Bradycardia	1/16				
Change in sleep pattern	3/16				
Constipation	1/16				
Decreased appetite			2/15		Probably
Diarrhoea			1/15		Probably
Disturbance in memory or attention			2/15		Probably
Dysgeusia			3/15		Definite
Fatigue or asthenia	1/16		1/15		Probably
Feeling abnormal			2/15		Probably
Headache or migraine			2/15		Probably
Insomnia			2/15		Possibly
Joint swelling			1/15		No
Loss of libido			1/15		Probably
Muscle ache or injury	1/16		1/15		No
Nasopharyngitis	2/16		1/15		No
Oral ulcer	1/16				
Rash	2/16				
Stress			1/15		Possibly
Weight loss			2/15		Possibly

Data represent adverse events reported during the 1-month trial or during the week after completion. None of these events required withdrawal from the study. A total of seven out of 16 participants randomised to placebo and 14 out of 15 randomised to zopiclone reported adverse events during the 1-month trial. Six participants in the placebo group and eight in the zopiclone group reported more than one adverse event. [#]: one participant from the zopiclone group withdrew from the study prior to completing the 1-month trial due to nonmedical issues; [¶]: whether each adverse event was related to zopiclone was determined by a physician according to the following criteria: not related ("No"), unlikely, possibly, probably or definitely.

Simple clinical tool to estimate the arousal threshold

Of the patients included in the 1-month trial, 100% were correctly identified as being eligible using the published algorithm [16] in combination with our inclusion criteria of an arousal threshold ≥ -25 cmH₂O and nadir SaO₂ $\geq 75\%$. Applying these criteria for all screened participants, in whom data were available in n=60, we found that only 15% would have been incorrectly enrolled. Of these, all had high arousal

TABLE 3 Participant feedback at study conclusion

	Placebo	Zopiclone
Did you feel like your sleep improved or worsened?		
Improved	9/16	11/14
Worsened	1/16	1/14
Same	6/16	2/14
If available, would you continue to use the study medication?		
Yes	5/16	5/14
No	10/16	9/14
Unsure	1/16	0/14
Do you feel like you were taking the sleeping pill or the placebo during the study?		
Placebo	11/16	3/14
Zopiclone	5/16	11/14

Data are presented as counts according to participant feedback over the 1-month trial. Data were collected on the morning of the final visit (night 30).

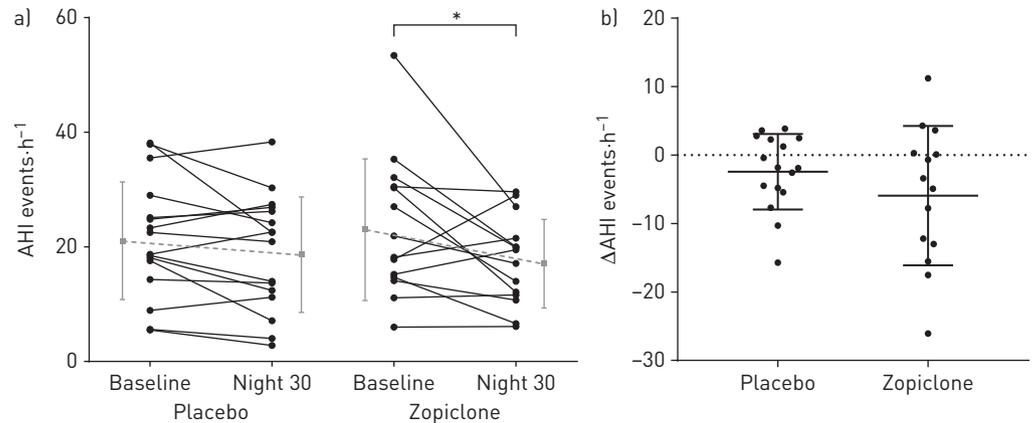


FIGURE 3 a) Apnoea-hypopnoea index (AHI) scatter plot representing each individual's AHI during placebo (n=16) versus zopiclone (n=14) conditions for baseline and night 30. Grey lines and error bars indicate mean±SD. *: significant difference from baseline. b) Scatter plot indicating each individual's change in AHI (ΔAHI) from baseline to night 30 for both conditions. Lines and error bars indicate mean±SD.

thresholds as measured with the epiglottic catheter (-32 ± 4 cmH₂O), which was underestimated by the algorithm (-21 ± 2 cmH₂O). These individuals also all had moderate to severe OSA (AHI 45 ± 13 events·h⁻¹).

Discussion

The main findings of this study are that a 1-month course of a standard 7.5 mg dose of nightly zopiclone does not worsen AHI, hypoxaemia, daytime sleepiness or morning alertness in individuals with OSA, low-moderate respiratory arousal thresholds (≥ -25 cmH₂O) and mild-moderate overnight hypoxaemia at baseline (nadir SaO₂ $\geq 75\%$). In addition, there were no major adverse events with zopiclone use in this patient population. These novel findings extend recent single-night hypnotic studies and challenge earlier concerns that hypnotics systematically worsen OSA.

TABLE 4 Placebo and zopiclone polysomnography data for the 8-h overnight sleep studies during the baseline and night 30 conditions

	Placebo [#]		Zopiclone [¶]		Delta change	p-value
	Baseline	Night 30	Baseline	Night 30		
Sleep onset latency min	10 [6–13]	6 [2–15]	9 [5–26]	16 [10–32]	6 [–11–17]	0.47
Sleep efficiency % sleep	84±7	85±10	79±13	86±6	5 [–2–13]	0.16
TST min	415±34	424±45	386±61	427±27	32 [–2–67]	0.07
Non-REM sleep N1 % TST	7±4	5±3	10±3	7±4	–1 [–3–1]	0.35
Non-REM sleep N2 % TST	49±8	49±7	46±10	49±7	4 [–3–10]	0.24
Non-REM sleep N3 % TST	25±6	26±7	24±7	24±4	–1 [–4–4]	0.80
REM sleep % TST	19±5	20±5	20±5	19±5	–2 [–6–2]	0.33
Wake after sleep onset min	71±33	65±51	87±56	53±32	–28 [–61–6]	0.10
Arousal index arousals·h ⁻¹	27±10	24±11	28±11	24±8	–1 [–8–6]	0.75
Supine % TST	48±28	52±31	49±28	46±28	–7 [–25–11]	0.43
Supine AHI events·h ⁻¹	38±28	32±21	46±24	37±23	–2 [–14–18]	0.82
Low arousal threshold AHI events·h ⁻¹ ⁺	23±12	20±11	21±11	16±10	–1 [–10–8]	0.82
Moderate arousal threshold AHI events·h ⁻¹ [§]	19±7	18±10	26±14	19±5	–6 [–16–3]	0.18
Respiratory event duration s	25±3	27±5	27±5	27±5	–2 [–6–1]	0.20
Mean SaO ₂ during sleep %	95±2	95±1	94±2	94±2	0 [–1–1]	0.93
Nadir SaO ₂ during sleep %	86±5	86±6	86±6	85±5	–1 [–4–3]	0.64

Data are presented as mean±SD or median (interquartile range), unless otherwise stated; the delta change column indicates the difference from baseline to night 30 between conditions (mean [95% CI] for normally distributed data and Hodge–Lehmann estimated median [95% CI] for nonnormally distributed data). REM: rapid eye movement; TST: total sleep time; AHI: apnoea-hypopnoea index; SaO₂: estimated arterial blood oxygen saturation (measured *via* pulse oximetry). [#]: n=16; [¶]: n=14; ⁺: for low arousal threshold (> -15 cmH₂O) AHI, n=9 in the placebo group and n=7 in the zopiclone group; [§]: for moderate arousal threshold (< -15 and > -25 cmH₂O) AHI, n=7 in the placebo and zopiclone groups. p-values refer to the difference from baseline to night 30 compared between placebo and zopiclone conditions.

TABLE 5 Placebo and zopiclone sleepiness/alertness and driving simulator performance data collected during the baseline and night 30 conditions

	Placebo [#]		Zopiclone [¶]		Delta change	p-value
	Baseline	Night 30	Baseline	Night 30		
ESS ⁺	5 (4–12)	6 (4–11)	8 (5–12)	7 (4–9)	–1 [–4–1]	0.55
FOSQ ⁺	101±11	101±12	101±8	103±11	3 [–2–7]	0.25
Leeds [§]	5±1	5±1	4±1	5±1	0 [–1–1]	0.62
KSS	6±2	6±2	6±1	6±2	0 [–1–1]	>0.99
AusEd driving simulator						
Deviation from median of lane cm	59±22	51±13	48±16	47±13	7 [–1–15]	0.10
Deviation from 60–80 km·h ^{–1} km·h ^{–1}	2±2	2±1	2±1	2±1	1 [0–1]	0.11
Braking reaction time ms ⁺	1016±233	1017±203	1034±312	957±206	–77 [–206–50]	0.22

Data are presented as mean±SD or median (interquartile range), unless otherwise stated; the delta change column indicates the difference from baseline to night 30 between conditions (mean [95% CI] for normally distributed data and Hodge–Lehmann estimated median [95% CI] for nonnormally distributed data). Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ) data were collected in the evening 1.5 h prior to sleep; Leeds Sleep Evaluation Questionnaire (Leeds), Karolinska Sleepiness Scale (KSS) and AusEd data were collected 30 min after awakening. [#]: n=16; [¶]: n=14; ⁺: for ESS, FOSQ and AusEd braking reaction time n=15 in the placebo group; [§]: for Leeds n=13 in the placebo group and n=11 in the zopiclone group. p-values refer to the difference from baseline to night 30 compared between placebo and zopiclone conditions.

Effects of 1 month of nightly zopiclone on OSA severity

Despite no systematic change *versus* placebo, the 25% within-group reduction in AHI over 1 month from baseline with zopiclone is consistent with recent single-night proof-of-concept clinical studies with eszopiclone and trazodone in predominantly unselected patients (23% and 26%, respectively) [14, 19]. However, this contrasts with no change in AHI in two small physiology studies with zopiclone *versus* placebo and trazodone *versus* baseline [11, 19]. Unlike its stereoisomer eszopiclone, in which invariable reductions in AHI occurred in individuals with low arousal thresholds (~45% overall) [14], this was not the case with zopiclone in the current study. Rather, similar reductions in AHI were observed in individuals with low and moderate arousal thresholds. The exact reasons for the apparent disparity between the studies are unknown. However, the causes of OSA vary between patients [12, 24]. Thus, factors beyond the arousal threshold that were not measured in the current study, such as between-patient differences in upper airway collapsibility and muscle responsiveness, may have contributed. Although eszopiclone is considered to be pharmacologically equivalent to zopiclone, subtle differences between the two agents may have also contributed [27]. However, standard doses of eszopiclone (3 mg) and zopiclone increase the arousal threshold to a similar extent (~30%) [11, 14, 18]. Finally, only one participant with a low arousal threshold had an increase in AHI with zopiclone. While supine sleep was not systematically different from baseline to night 30 for the group, this individual had a >20% increase in supine sleep on night 30. Conversely, the participant with the greatest reduction in AHI with zopiclone had a >20% decrease in supine sleep on night 30. Thus, between-night changes in body position may be an important confounder at an individual level [28].

Another concern regarding hypnotic use in OSA is prolongation of respiratory event duration worsening blood gas disturbances. Indeed, previous studies indicate that certain hypnotics can worsen hypoxaemia, particularly at high doses or in obese individuals with very severe OSA [9, 11, 21]. Conversely, consistent with the current findings, several other hypnotic studies have shown no change in event duration or hypoxaemia in unselected patients and those selected on the basis of their baseline hypoxaemia [10, 11, 13, 14, 19, 20, 29–32].

Sleep parameters

Comparable to previous hypnotic studies [10, 11, 14, 30, 32], a standard dose of zopiclone tended to improve sleep efficiency by 7–8% compared with placebo in the individuals with OSA we studied. This was also reflected in the subjective sleep quality reports at the study conclusion. Increased sleep efficiency combined with changes in OSA severity without causing blood gas disturbances may be beneficial for the substantial proportion (~40%) of OSA patients who also experience sleep disruption and symptoms of insomnia [6, 7]. However, unlike the previous eszopiclone study where there was a significant shift from N1 to N2 sleep and reductions in the arousal index, which may have contributed to improvements in OSA severity [14], the proportion of time spent in non-REM and REM stages and the arousal index did not

significantly change with zopiclone in the current study. This may be due to a ceiling effect, as sleep stage proportions were within or close to the normal range at baseline in the current study of predominantly mild-moderate severe patients *versus* the more severe patients in the eszopiclone study [14, 33]. Thus, inclusion of patients with poorer baseline sleep quality may yield significant improvements in sleep parameters with zopiclone. Alternatively, a standard dose of zopiclone may not be pharmacologically equivalent to previous eszopiclone studies in OSA [14, 21]. Thus, while the potential for unwanted next-day side-effects may increase, a higher dose of zopiclone may be required to yield clinically relevant changes in sleep parameters, including AHI, in individuals with OSA.

Sleepiness and alertness

Hypnotics have generally been contraindicated in individuals with OSA due to concerns of harm relating to their central nervous system depressant properties, including the potential to exacerbate unwanted consequences such as next-day sleepiness and alertness. However, there are limited data on the effects of hypnotics on sleepiness and alertness in OSA. If hypnotics are to be considered as a therapeutic tool for certain individuals with OSA, it is crucial that they do not worsen next-day symptoms. The current study is the first to examine the effects of hypnotic use for an extended period on next-day sleepiness and alertness in individuals with OSA. Consistent with our previous single-night trial of a standard dose of zopiclone in unselected predominantly severe OSA patients, we found no change in next-day sleepiness as measured *via* the KSS [11]. Perceived sleepiness with the benzodiazepine nitrazepam [30] and next-day alertness and concentration with the melatonin receptor agonist ramelteon [34] also remained unchanged in acute single-night studies in individuals with OSA. In addition, none of the measures on the ESS, Leeds or FOSQ changed with zopiclone in the current study.

Furthermore, none of the objective measures of alertness assessed using the 30-min AusEd driving simulator performance test changed with zopiclone during the 1-month trial. This is crucial from a safety perspective as untreated OSA patients are already up to six times more likely to be involved in a traffic accident [3]. A lack of impairment in driving simulator performance in the current study is in contrast to previous studies in healthy participants in which standard doses of the “z-drugs” zolpidem and zopiclone worsened on-road driving performance during an ~60-min task as well as next-day cognitive and psychomotor performance [35, 36]. It has been proposed that healthy individuals may have exaggerated acute residual effects of hypnotics, which are not present in long-term hypnotic users or in individuals with poor sleep quality such as insomniacs and individuals with OSA, as potential negative residual effects may be outweighed by improvements in sleep quality [37]. Indeed, on-road driving performance during an ~60-min driving task is not impaired in older insomniacs who use hypnotics frequently or infrequently after a standard dose of zopiclone [37]. Alternatively, as alertness declines with time during driving simulator tasks [38], it remains possible that driving impairment with zopiclone may occur beyond the 30-min period tested in the current study. Future studies that incorporate other objective alertness assessments throughout the day (*e.g.* the maintenance of wakefulness test) would provide additional insight. It is also important to note that the majority of the individuals in the current study population were not particularly sleepy at baseline, and were asked to avoid confounding factors such as inadequate sleep opportunity and alcohol during the trial. Thus, next-day sleepiness following hypnotic use may differ in sleepy patients and with other confounders.

Hypnotics and phenotyping

Our secondary findings of a modest reduction in AHI from baseline in the current 1-month trial with zopiclone raise the possibility that the drug may be helpful in some individuals with OSA and insomnia. However, this remains to be tested in this population as symptoms of insomnia before *versus* after the trial were not systematically assessed. Furthermore, the reductions in AHI from baseline were of insufficient magnitude to be a clinically relevant therapeutic option as monotherapy to treat OSA for most patients. This is in contrast to a single-night standard dose of eszopiclone which invariably reduced AHI (by ~45% overall) in patients with low arousal thresholds [14] and by ~45% when combined with oxygen in unselected OSA patients [21]. Consistent with the importance of the underlying pathophysiological causes of OSA, responders to eszopiclone and oxygen (defined as patients with >50% reduction in their AHI to <15 events·h⁻¹) had less collapsible upper airways, less severe OSA and greater upper airway muscle effectiveness [21]. These patients also tended to have low arousal thresholds [21]. Thus, these studies provide support for the potential use of hypnotics to reduce AHI to a therapeutic level when combined with other targeted supplementary therapies in patients who are carefully selected based on their underlying causes of OSA according to a phenotyping approach [23, 24]. However, further long-term studies with hypnotics that include additional phenotyping measures such as upper airway collapsibility are necessary to determine if AHI reductions are stable over time and apply to other clinically relevant targeted populations (*e.g.* sleepy patients and those aged >65 years in whom sleep disturbance is

common). Thus, for hypnotics to be implemented safely and effectively clinically, simplified tools which allow for accurate identification of underlying pathophysiological causes of OSA are essential [39]. In accordance with this objective, the use of a recently developed tool to estimate the baseline arousal threshold using readily available variables from a diagnostic PSG was highly accurate when combined with nadir saturation criteria to identify suitable candidates for safe use of zopiclone in *post hoc* analyses in the current study. These findings highlight the potential to correctly estimate the arousal threshold in patients with less severe OSA in whom a hypnotic may be considered. However, patients with severe OSA with AHI >30 events·h⁻¹ would benefit from a further PSG with a pressure catheter to accurately determine their arousal threshold prior to targeted treatment with hypnotics.

Summary and clinical implications

A standard dose of zopiclone taken nightly for 1 month does not worsen OSA severity, next-day sleepiness or alertness in selected OSA patients aged 18–65 years with low–moderate respiratory arousal thresholds without major hypoxaemia or sleepiness at baseline. In secondary analyses, there was also a tendency for zopiclone to reduce AHI by ~25% and increase sleep efficiency from baseline. The findings of this randomised clinical trial challenge previous assumptions regarding the effects of hypnotics in individuals with OSA. Indeed, the American Academy of Sleep Medicine guidelines for the treatment of primary insomnia caution hypnotic use in patients with signs or symptoms of OSA [40]. The current findings suggest that screening to rule out severe overnight hypoxaemia combined with the use of a recently validated clinical tool from PSG data to estimate the arousal threshold may be helpful to accurately identify individuals in whom zopiclone can be administered safely for mild–moderate OSA. In particular, this may be relevant for the large number of OSA patients who also have insomnia symptoms, or fail to comply with continuous positive airway pressure or other therapies. Conversely, hypnotics should be avoided in OSA patients who have high arousal thresholds, long respiratory events and/or severe hypoxaemia at baseline, as these patients potentially may experience prolonged event durations and consequently more hypoxaemia with hypnotic use. The novel findings of the current study highlight the need for further research on targeted use of different hypnotics of varying doses and when combined with other therapies in individuals with OSA.

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