Online Supplement for manuscript titled:

Effects of 1-month of zopiclone on OSA severity & symptoms: A randomised controlled trial

Authors: Sophie G. Carter[1]
Jayne C. Carberry[1]
Garry Cho[2]
Lauren P. Fisher[1]
Charlotte M. Rollo[1]
David J. Stevens[2]
Angela L. D'Rozario[2,3]
David K. McKenzie[4]
Ronald R. Grunstein[2,5]
Danny J. Eckert[1]

Affiliations:

1. Neuroscience Research Australia (NeuRA), Sydney, NSW, Australia
2. The Woolcock Institute of Medical Research, Sydney, NSW, Australia
3. School of Psychology, Faculty of Science, Brain and Mind Centre and Charles Perkins Centre, The University of Sydney, NSW, Australia
4. Prince of Wales Hospital, Sydney, NSW, Australia
5. Royal Prince Alfred Hospital and Sydney Local Heath District, Camperdown, NSW, Australia

Corresponding author: Sophie G. Carter, B.Sc. (Hons)
Neuroscience Research Australia (NeuRA)
PO Box 1165, Randwick, NSW, 2031
s.carter@neura.edu.au
Ph. + 61 2 9399 1069

Results

Anthropometric characteristics

Anthropometric characteristics at baseline, night 1 and night 30 for both conditions are summarised in Table E1. These characteristics were well matched at baseline and there were no changes in any of these measures at night 1 or night 30 in either the placebo or zopiclone group.

Respiratory events and sleep parameters

Polysomnography (PSG) data at baseline, night 1 and night 30 during both conditions is summarised in Table E2. The mean reduction in the apnoea-hypopnoea index (AHI) on night 1 and night 30 from baseline with zopiclone was similar on both nights (-5.3±12.8 and -5.9±10.2 events/h respectively). Conversely, there was little change in AHI on night 1 or night 30 from baseline in the placebo group (-1.1±8.2 and -2.4±5.5 events/h respectively). The change in sleep efficiency from baseline to night 1 was significantly greater with zopiclone compared to placebo (8.8±0.1 vs. 1.2±0.1%, p=0.02). A comparable increase of 6.9±0.1% in sleep efficiency from baseline to night 30 with zopiclone occurred but did not reach statistical significance (p=0.06). Total sleep time reflected these changes with a significant increase on night 1 but not night 30 with zopiclone compared to placebo. The amount of wake after sleep onset was reduced from baseline to night 1 with zopiclone versus placebo (-41±45 vs. -8±38 minutes, p=0.004) but not compared to night 30. There were no between condition differences in the majority of the other sleep parameters on night 1 or night 30, including: sleep onset latency; percent total sleep time (TST) spent in non-rapid eye movement (NREM) or rapid eye movement (REM) sleep, arousal index, percent TST in the supine position, supine AHI, obstructive, hypopnoea and central apnoea index, low and moderate arousal threshold participants AHI, or respiratory event duration. Mean arterial

blood oxygen saturation (SaO_2) during sleep at baseline was ~1% lower in the zopiclone group (p=0.03). However, zopiclone did not alter mean SaO_2 or nadir SaO_2.

Sleepiness and alertness

Sleepiness and alertness data from baseline to night 1 and night 30 for placebo and zopiclone conditions is summarised in Table E3. Apart from an increase in the standard deviation from the median of the lane position during the AusEd driving simulator task with zopiclone on night 1 compared to placebo (6.7±8.4 vs. -5.4±12.1cm, p=0.004), measures of alertness and sleepiness on night 1 and night 30 were not different between conditions.

	Placebo			Zopiclone		
	Baseline	Night 1	Night 30	Baseline	Night 1	Night 30
BMI (kg/m^2)	29±4	28±4	29±4	28±4	28±4	27±4
Neck circumference (cm)	40±3	39±3	40±3	39±3	39±3	39±3
Waist circumference (cm)	101±11	104±14	101±14	97±13	96±11	96±12
Systolic blood pressure (mmHg)	125±23	121±14	126±16	121±11	127±17	120±9
Diastolic blood pressure (mmHg)	74±10	79±9	77±8	78±11	78±10	75±15

Table E1. Participant anthropometric characteristics

Group anthropometric characteristics at baseline, night 1 and night 30. N=16 in placebo group and n=14 in zopiclone group. Values are mean ± standard deviation. BMI = body mass index.

	Placebo			Zopiclone		
	Baseline	Night 1	Night 30	Baseline	Night 1	Night 30
Sleep onset latency (min)	10 (6 to 13)	7 (5 to 31)	6 (2 to 15)	9 (5 to 26)	12 (7 to 20)	16 (10 to 32)
Sleep efficiency (% sleep)	84±7	82±10	85±10	79±13	88±5*	86±6
Total sleep time (mins)	415±34	414±56	424±45	386±61	442±33*	427±27
NREM N1 (% total sleep time)	10±3	7±3	7±4	7±4	6±3	5±3
NREM N2 (% total sleep time)	49±8	48±10	49±7	46±10	50±4	49±7
NREM N3 (% total sleep time)	25±6	26±7	26±7	24±7	26±6	24±4
REM sleep (% total sleep time)	19±5	20±5	20±5	20±5	17±3	19±5
Wake after sleep onset (minutes)	71±33	80±44	65±51	87±56	47±25*	53±32
Arousal index (arousals/h sleep)	27±10	26±12	24±11	28±11	28±15	24±8
% supine (% total sleep time)	48±28	50±27	52±31	49±28	40±25	46±28
Supine AHI (#events/h)	38±28	32±21	32±21	46±24	36±22	37±23
Apnoea-hypopnoea index (AHI)	21±10	20±11	19±10	23±12	18±10	17±8
Obstructive apnoea index (#events/h)	3±4	3±3	3±4	4±10	2±2	2±1

Hypopnoea index (#events/h)	17±9	17±10	16±8	19±9	16±9	16±7
Central apnoea index (#events/h)	0.2±0.5	0.2±0.5	0.1±0.4	0.1±0.2	0.1±0.1	0.1±0.1
Low arousal threshold AHI (#events/h)	23±12	23±10	20±11	21±11	16±13	16±10
Moderate arousal threshold AHI (#events/h)	19±7	17±12	18±10	26±14	20±7	19±5
Respiratory event duration (s)	25±3	26±4	27±5	27±5	28±4	27±5
Mean SaO_2 during sleep (%)	95±2	95±1	95±1	94±2	94±2	94±2
Nadir SaO_2 during sleep (%)	86±5	85±6	86±6	86±6	85±5	85±5

Table E2. Polysomnography sleep parameters

Placebo and zopiclone polysomnography data for the 8-h overnight sleep studies during baseline, night 1 and night 30 conditions. Values are mean ± standard deviations. N=16 in placebo group and n=14 in zopiclone group. There were n=9 in the placebo and n=7 in zopiclone group who had a low respiratory arousal threshold (>-15cmH_2O) and n=7 in the placebo and n=7 in zopiclone group who had a moderate respiratory arousal threshold (<-15 and >-25cmH_2O). AHI = apnoea-hypopnoea index (the average number of apnoeas and hypopnoeas per hour of sleep), NREM = non-rapid eye movement sleep, REM = rapid eye movement sleep, SaO_2 = blood oxygen saturation measured via pulse oximetry. * indicates a significant difference in the delta change from baseline between conditions

		Placebo			Zopiclone		
		Baseline	Night 1	Night 30	Baseline	Night 1	Night 30
Epworth Sleepiness Scale (ESS)		5 (4 to 12)	8 (3 to 10)	6 (4 to 11)	8 (5 to 12)	6 (5 to 11)	7 (4 to 9)
Evening Karolinska Sleepiness Scale (EKSS)		4±2	5±2	5±2	5±2	5±2	6±2
Functional Outcomes of Sleep Questionnaire (FOSQ)		101±11	100±13	101±12	101±8	101±9	103±10
Leeds Sleep Evaluation Questionnaire (Leeds)		5±1	4±1	5±1	4±1	5±1	5±1
Morning Karolinska Sleepiness Scale (MKSS)		6±2	5±2	6±2	6±1	6±1	6±2
AusEd	Deviation from median of lane (cm)	59±22	53±16	51±13	48±16	54±16*	47±13
	Deviation from 60–80 km/h (km/h)	2 (1 to 3)	1 (1 to 2)	1 (1 to 3)	2 (1 to 2)	2 (1 to 3)	2 (1-3)
	Braking reaction time (ms)	1016±233	987±257	1017±203	1034±312	1036±323	957±206

Table E3. Sleepiness and alertness questionnaires and driving simulator Performance

ESS, EKSS and FOSQ data were collected in the evening 1.5h prior to sleep. Leeds, MKSS and AusEd data were collected 30 minutes after wake. Data are mean ± standard deviations or median and interquartile range in parentheses as appropriate. N=16 in placebo group and n=14 in zopiclone group for all parameters except: ESS and AusEd braking reaction time where data was available in n=15 for placebo; n=14 for EKSS

for placebo and n=13 for zopiclone. AusED = AusED driving simulator. * indicates a significant difference in the delta change from baseline between conditions.