Driving Simulator Performance Remains Impaired In Patients With Severe OSA after CPAP Treatment

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Study Objectives: To assess the effectiveness of CPAP treatment in improving 90-minute driving simulator performance in severe OSA patients compared to age/gender matched controls.

Design: Driving simulator performance was assessed at baseline and 3 months later, with OSA patients treated with CPAP during the interval.

Setting: University Teaching Hospital.

Participants: Patients with severe OSA (n = 11) and control subjects without OSA (n = 9).

Interventions: CPAP

Measurements and Results: Simulator driving parameters of steering deviation, braking reaction time and crashes were measured at baseline and ~3 months follow-up. At baseline, OSA subjects demonstrated significantly greater steering deviation compared to controls (mean [95% CI], OSA group, 49.9 cm [43.7 to 56.0 cm] vs control group, 34.9 cm [28.1 to 41.7 cm], p = 0.003). Following ~3 months of CPAP treatment (mean ± SD 6.0 ± 1.4 h/night), steering deviation in OSA subjects improved by an average of 3.1 cm (CI, 1.4 to 4.9), p < 0.001, while no significant steering changes were observed in the control group. Despite the improvement, steering deviation in

the OSA group remained significantly higher than in controls (OSA group, 46.7 cm [CI, 40.6 to 52.8 cm] vs control group, 36.1 cm [CI, 29.3 to 42.9 cm], p = 0.025).

Conclusions: While driving simulator performance improved after ~3 months of CPAP treatment with high adherence in patients with severe OSA, performance remained impaired compared to control subjects. These results add to the growing body of evidence that some neurobehavioral deficits in patients with severe OSA are not fully reversed by treatment. Further studies are needed to assess causes of residual driving simulator impairment and to determine whether this is associated with persistent elevated real-life accident risk.

Trial Registration: Data presented in this manuscript was collected as part of a clinical trial "Experimental Investigations of Driving Impairment in Obstructive Sleep Apnoea" ACTRN12610000009011, http://www.anzctr.org.au/trial_view.aspx?ID=334979

Keywords: OSA, CPAP, driving performance

Citation: Vakulin A; Baulk SD; Catcheside PG; Antic NA; van den Heuvel CJ; Dorrian J; McEvoy RD. Driving simulator performance remains impaired in patients with severe OSA after CPAP treatment. *J Clin Sleep Med* 2011;7(3):246-253.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Emerging evidence suggests that some neurobehavioral deficits associated with OSA may persist even in optimally treated patients. The present study examined the effectiveness of 3 months of CPAP treatment in improving driving simulator performance during prolonged 90 minute drive in patients with severe OSA compared to age/gender matched controls.

Study Impact: Three months of CPAP treatment improved driving simulator performance in patients with severe OSA, however, significant impairments in driving simulator performance persisted even in patients highly compliant with therapy. Clinicians should be aware that some patients who appear to be optimally treated with CPAP may have residual deficits that could impair driving.

methodological limitations. Short (20 min), divided attention driving simulator tasks were used,^{17,22} which may underestimate the driving risk of patients in more ecologically relevant situations such as highway or country road driving. Retrospective comparisons of driving accident rates pre- and post-OSA treat-

Obstructive sleep apnea (OSA) is linked to a 2- to 7-fold increased risk of motor vehicle accidents, particularly among patients with moderate to severe disease.¹⁻⁹ Community surveys have shown that OSA affects approximately 7% of the middle-aged population,¹⁰⁻¹² with as many as 80% of those affected being undiagnosed.¹³⁻¹⁵ Thus, OSA presents a serious public health concern with respect to road safety.

An important clinical question is to what extent treatment of OSA improves driving abnormalities and reduces the accident risk associated with OSA. Several studies and a recent meta-analysis¹⁶ support that continuous positive airway pressure (CPAP) treatment improves driving simulator performance¹⁷⁻²² and reduces accident risk.^{16,23-28} Two studies found that CPAP treatment of OSA patients returned driving simulator performance to the level of healthy control subjects,^{17,22} while another clinical observational study reported that CPAP therapy reduced motor vehicle accident rates to the background rate of the general population.²⁶ However, these studies suffered from several

ment¹⁶ do not control for other factors such as changes in driving exposure, changes in driver behavior by virtue of being in a study, and other medical treatments. The remaining driving simulator studies did not compare results in CPAP-treated patients with non-apneic control subjects, and thus do not address if CPAP treatment normalizes driving disturbance in OSA patients. Several recent studies suggest that CPAP treatment may be only partially effective in restoring cognitive function,²⁹⁻³³ cortical activation,^{31,34} and daytime somnolence^{35,36} even for subjects who comply optimally with therapy.³⁶

The purpose of the present study was therefore to measure the effects of ~3 months of CPAP treatment on driving simulator performance in patients with severe, previously untreated OSA. OSA subject results were compared with those of healthy control subjects matched for age and gender. In contrast to previous driving simulator studies using short divided attention driving scenarios,¹⁷⁻²² we chose a relatively long simulated driving task, analogous to a monotonous country drive. We postulated that CPAP treatment would improve but not normalize driving performance in OSA subjects. The baseline OSA and control subject data reported in the present study are a subgroup of an earlier, larger report on the effects of alcohol and sleep restriction on simulator driving performance in OSA.³⁷

METHODS

The study was approved by the Human Research Ethics Committees of the Repatriation General Hospital, University of South Australia and University of Adelaide. Subjects were introduced to the study objectives and protocol during an introductory session, gave written informed consent, and were remunerated for their participation. This study was an investigator designed and conducted trial funded by the Australian National Health and Medical Research Council (grant 390400).

Study Design

This study was designed to test the effects of approximately 3 months of CPAP treatment on driving simulator performance in patients with severe OSA (apnea-hypopnea index > 45 events/h of sleep). Driving simulator sessions began at 14:00 in the laboratory, following a normal habitual nighttime sleep at home. Baseline driving performance measurements were collected in all subjects and repeated after approximately 3 months follow-up. During the follow-up period OSA subjects were treated with CPAP and control subjects continued their normal activities.

Subject Selection

Patients with severe OSA and healthy control subjects were a subgroup of participants recruited from an earlier study,³⁷ including patients who were willing to commence CPAP, and controls prepared to undertake repeat follow-up experiments and who consented to participation in the current study. The subjects included in this study were not statistically significantly different from the subjects from our previous study with respect to age, gender, BMI, sleep measures, or questionnaire results. OSA patients were recruited following diagnostic poly-

somnography. Neither they nor their referring physician had specific concerns about their driving. To minimize selection bias, patients were told the study was to investigate general neurocognitive performance and were unaware that the trial measured driving performance until after they agreed to attend an introduction session. Control subjects matched for age and gender were recruited from the general population through newspaper advertisements, which provided only a general description of the study and made no mention of driving performance measures.

Exclusion criteria were as follows: professional driver or shift worker; history of driving < 2 y or < 2 h per week; significant medical comorbidities (e.g., cardiac or respiratory failure), periodic limb movement disorder (periodic limb movement arousal index > 5/h), past head injury or depression; use of alertness altering prescription and non-prescription medications that may influence sleep and daytime behavioral function (e.g., antihistamines, opiates, antidepressants); and history of alcohol abuse or current use of recreational drugs. Control subjects were also excluded if they obtained higher than normal scores on sleep quality and daytime drowsiness questionnaires.

Subject Assessment

Prior to driving simulator assessment, all participants completed questionnaires assessing general health (medical conditions, medication, alcohol, caffeine, and drug use), sleep quality/habits and daytime drowsiness using the Pittsburgh Sleep Quality Index,³⁸ and the Epworth Sleepiness Scale.³⁹ One to 2 weeks prior to baseline experimental driving assessment, all participants had overnight standard diagnostic polysomnography with the following recordings: electroencephalography (C3/A2, C4/A1 lead placements), left and right electroculograms, submental electromyogram, nasal cannula to measure nasal pressure, limb movement sensors, inductive plethysmography for thoraco-abdominal motion, lead 2 electrocardiography, and arterial oxygen saturation (finger pulse oximetry). All signals were digitized and stored using a Compu-medics-E Series sleep system (Melbourne, Australia). Sleep and sleep arousals were scored using standardized methods.^{40,41} Apneas and hypopneas were scored according to internationally accepted "Chicago" criteria.^{41,42} The OSA severity cutoffs adopted by our laboratory were: normal (AHI < 15 events/h), mild OSA (AHI ≥ 15 events/h), moderate OSA (AHI ≥ 30 events/h), and severe OSA (AHI ≥ 45 events/h), bearing in mind that AHI cutoff values of 15 and 30 events/h using Chicago scoring criteria correspond to approximately 5 and 10 events/h, respectively, using the recent AASM "Recommended" scoring criteria.⁴² Diagnostic sleep study variables were calculated for the full night of polysomnogram. For the CPAP titration study, AHI, oxygen desaturation, and arousal indices were calculated over the period of sleep where the CPAP level was closest (± 1 cm H₂O) to that prescribed by the reporting physician in order to determine AHI under therapeutic pressure. All studies were scored by one staff member certified by the Board of Registered Polysomnographic Technicians. Anthropometric characteristics, sleep study results, caffeine and alcohol consumption, and medication use for all participants are shown in **Table 1**.

Table 1—Participant anthropometric characteristics, polysomnography results, and medication use

Groups	Control (n = 9)		OSA (n = 11)	
N Males/Females	7/2		10/1	
Age (y)	53.2 (9.6)		54.2 (13.0)	
Body mass index (BMI)	24.3 (2.6)		35.9 (9.6)*	
Polysomnography Results	Diagnostic PSG	CPAP Titration	Diagnostic PSG	CPAP Titration
Apnea hypopnea index (AHI: events/h)	6.6 (3.8)	-	69.1 (20.1)*	5.3 (5.7)#
% of sleep time with SpO ₂ < 90%	0 (0)	-	13.7 (17.8)*	0.1 (0.3)#
Average SpO ₂ desaturation	2.2 (0.4)	-	5.2 (2.8)*	2.0 (0.4)#
Respiratory arousal index (arousals/h)	1.6 (1.1)	-	25.9 (14.9)*	0.5 (0.8)##
Limb movement arousals (arousals/h)	4.1 (3.0)	-	3.9 (4.3)	1.8 (2.6)
Arousal index (arousals/h)	13.5 (5.8)	-	39.1 (16.3)*	11.6 (7.3)#
Total sleep time (min)	405 (32.5)	-	418 (35.0)	401 (45.0)
Sleep stage 1 (% of total sleep time)	8.7 (3.8)	-	19.6 (16.6)	7.5 (6.2)#
Sleep stage 2 (% of total sleep time)	54.3 (7.0)	-	49.2 (7.2)	50.9 (10.8)
Sleep stage 3 (% of total sleep time)	15.7 (7.5)	-	11.4 (6.4)	14.9 (6.4)
Sleep stage 4 (% of total sleep time)	2.3 (2.3)	-	3.7 (4.7)	6.2 (7.3)
REM sleep (% of total sleep time)	19.0 (4.5)	-	16.0 (6.8)	20.5 (6.9)
Sleep efficiency (%)	71.0 (15.6)	-	78.7 (11.3)	80.1 (11.0)
Actigraphy Estimated Sleep Time (min)	Baseline	3 month follow-up	Baseline	3 month follow-up
5 days prior to driving assessment	459 (66)	473 (51)	443 (59)	438 (65)
24 h prior to driving assessment	464 (74)	472 (52)	475 (93)	454 (91)
Epworth Sleepiness Scale	4.9 (2.6)	4.4 (2.2)	9.7 (5.6)*	7.0 (4.0)
Pittsburgh Sleep Quality Index	2.6 (0.9)		9.5 (6.0)*	
Driving history (kilometers/y)	11525 (4912)		18131 (4946)*	
Education (years completed)	13.4 (3.1)		11.4 (3.0)	
Caffeine consumption (cup or equivalent/day)	2.3 (1.1)		3.5 (1.6)	
Smoking (cigs/day)	0.0 (0.0)		2.1 (4.9)	
Habitual alcohol intake (std Drinks/week)	10.7 (4.5)		11.1 (14.6)	
Medication Use (# of people by condition)				
Hypertension	0		4	
Hyperlipidemia	0		1	
Diabetes	0		0	
Gastro-Esophageal Reflux Disease	0		2	
Arthritis	0		1	
Thyroid Disease	0		0	
Asthma	0		1	
Gout	0		1	
Hay fever	0		0	

Values are mean (SD), *between group, #within group $p < 0.05$.

Treatment Protocol

After the baseline experimental driving simulator sessions, subjects with severe OSA underwent laboratory-based CPAP titration polysomnography to establish the therapeutic CPAP setting. All OSA subjects were followed up by their referring physician and underwent CPAP education. The education session involved a clinical appointment with a qualified CPAP nurse, who provided clinical information regarding the purpose and effectiveness of CPAP therapy and provided comprehensive patient training to facilitate effective and adherent home use. In addition, all OSA subjects were fitted with a suit-

able mask and issued a fixed-setting CPAP machine (ResMed S8 Lightweight, NSW, Australia). OSA subjects were encouraged to use their CPAP machines as much as possible, and their compliance and clinical treatment were monitored by a CPAP nurse at 1 and ~3 months after commencement of treatment. The average daily compliance with CPAP therapy over ~3 months was downloaded from the inbuilt timer in each CPAP machine at each follow-up visit. To control for regression to the mean and possible practice effects, control subjects also had repeat driving simulator testing after approximately 3 months. Control subjects were not issued a CPAP or sham

CPAP, but were asked to continue their normal activities during this period.

Main Outcome Measures

All outcome measures were assessed at baseline and the ~3-month follow-up visit. Driving performance was assessed as previously described³⁷ using the AusEd driving simulator (Woolcock Institute for Medical Research, Sydney, Australia) which ran on a purpose-built Windows 2000 workstation (Microsoft, Redmond, Washington), 19-inch monitor (BenQ FP937s, Taipei, Taiwan), and MOMO steering wheel and pedals (Logitech, Fremont, California). The chosen simulated driving task was a 90-min country nighttime drive on a predominantly straight dual-lane road with bends occurring at 5-min intervals, each taking approximately 10 sec to negotiate. There was no oncoming traffic or traffic lights. The main outcome measures were the driving simulator performance parameters of lateral steering deviation, braking reaction time, and crash frequency.

Steering deviation was measured from the average deviation in centimeters from the driver's median lane position sampled at 30 Hz. Subjects were instructed to maintain speed within 60–80 km/h, but to apply the brakes as quickly as possible whenever a slow moving truck was presented ahead in the driving lane. Trucks appeared a total of 7 times during the drive, and the mean braking reaction time was computed for the 7 truck-ahead incidents. Crashes occurring throughout the driving task were defined as: car deviating from the road (all 4 wheels completely off the road), collision with a truck, or if the car was stationary for > 3 seconds. The main outcome measure for crashes was the number of controls and OSA subjects who experienced at least one crash incident.

Detailed Experimental Procedures

Subjects' sleep patterns and duration were monitored using sleep diaries and actigraphy monitors (Actiwatch, Mini-Mitter Co Inc, Model-AW64, Oregon, USA) worn from at least 5 days prior to beginning the experiments until study completion to estimate sleep/wake timing and ensure compliance with instructions in the 24 h prior to the experiments.⁴³ Subjects were instructed to abstain from alcohol and caffeinated beverages, not to nap for 24 h prior to each experimental session, and to consume breakfast before 09:00 on the day of the experiment. Participants were transported by taxi to and from the laboratory.

Upon arrival at the laboratory at 12:00, each subject's blood alcohol concentration was estimated using a calibrated breathalyzer (Dräger Alcotest 7410Plus), sleep diaries were collected and activity monitor data downloaded.

Subjects consumed a standardized lunch with a glass of water at 12:15 before electrode application for electroencephalographic monitoring (C3/A2, C4/A1, O1/A2, O2/A1 and EOG) of drowsiness throughout the driving test (data not reported).

Data Analysis and Statistics

Anthropometric characteristics, sleep study variables, driving experience, and habitual caffeine and alcohol consumption were compared between groups using unpaired Student *t*-tests. Paired *t*-tests were used to examine within-group differences between baseline versus follow-up evaluation. Steering deviation data, excluding the first minute of acceleration and initial

lane positioning, were divided and averaged into 18 intervals for the remaining 89 minutes of the drive. Eighteen intervals were chosen for consistency with our previous studies. To address the question of whether or not treatment normalized steering deviation in OSA patients following 3 months treatment, and to account for known time on task effects,³⁷ linear mixed model analysis was used to examine fixed effects of group (OSA vs. controls), time on task (18 intervals), follow-up period (baseline vs follow-up), and all possible interactions (SPSS Inc, Version 16.0, Chicago). Subject identity was specified as a random intercept term assumed constant across conditions and using an autoregressive covariance structure (AR1) to adjust for serial correlation across the 18 time points. The primary hypotheses were evaluated on the basis of main and interaction effects. In the case of statistically significant effects, custom post hoc contrasts were utilized adjusted for multiple comparisons using Bonferroni correction.

RESULTS

Eleven subjects with severe OSA and 9 control subjects were studied and their characteristics are presented in **Table 1**. It was not possible to precisely schedule 3 months follow-up for each subject. Mean follow-up time was 103 (range 76–129) days after CPAP treatment was initiated in the patient group and 113 (94–152) days after baseline assessments in the control group. All subjects exhibited a blood alcohol concentration of 0.0 g/dL upon arrival to the laboratory. Participant BMI did not change significantly between baseline and follow-up evaluation. Mean $\pm$ SD CPAP compliance over the 3-month follow-up period in the patient group was high at 6.0 ± 1.4 h/night. Average CPAP compliance in the 3 days prior to driving simulator assessment was also high at 7.0 ± 1.2 h/night.

Driving Simulator Performance

Steering Deviation

Steering deviation in control and OSA subjects at baseline and follow-up evaluations is shown in **Figure 1**. Linear mixed model analysis revealed significant main effects of group ($F_{1,18} = 8.8$; $p = 0.008$), time ($F_{[17,342]} = 3.7$; $p < 0.001$), and a group by treatment interaction ($F_{1,190} = 10.8$; $p = 0.001$). At baseline evaluation, untreated OSA subjects demonstrated statistically significantly greater steering deviation than controls (Mean [95% CI], OSA group, 49.9 cm [43.7 to 56.0 cm] vs control group, 34.9 cm [28.1 to 41.7 cm], $p = 0.003$). At follow-up evaluation, CPAP-treated OSA subjects demonstrated a small but statistically significant improvement in steering deviation (mean decrease calculated over the full drive, 3.1 cm [CI, 1.4 to 4.9], baseline vs follow-up, $p < 0.001$), while no significant change was observed in the control group. Despite improvement, steering deviation remained significantly greater in treated OSA subjects than controls (averaged across the whole drive, OSA group, 46.7 cm [CI, 40.6 to 52.8 cm] vs control group, 36.1 cm [CI, 29.3 to 42.9 cm], $p = 0.025$).

Braking Reaction Time and Crashes

Braking reaction time was not statistically significantly different between groups, conditions, or treatments, and there

Figure 1

(A) Mean (SEM) steering deviation throughout the 90 minute simulator drive in OSA and control groups at baseline evaluation and 3 months follow-up. (B) Mean (SEM) steering deviation collapsed across time in OSA and control groups at baseline evaluation and 3 months follow-up. BL, baseline; FU, follow-up. Symbols indicate significant difference, $p < 0.05$: *OSA different from controls within the same evaluation, #baseline different from follow-up.

were no significant interaction effects. There were no simulator crashes recorded for the control group, while 2 OSA patients had a crash at baseline and 2 at follow-up. Due to the small number of crashes, meaningful statistical analyses could not be performed.

DISCUSSION

Similar to previous reports,^{1,4,5,37} this study demonstrates that driving simulator performance is impaired in untreated subjects with severe OSA compared to healthy control participants. The important new findings of this study are that while driving simulator steering performance among OSA subjects improved marginally after ~3 months of CPAP treatment, driving ability remained significantly impaired compared with age- and gender-matched healthy controls. There were no significant group, condition, or treatment-dependent changes in braking reaction time, which may reflect the small number of reaction time measurements collected during the drive (7 truck presentations in 90 min). Alternatively, the lack of differences in reaction time may suggest that controls and OSA subjects were similarly able to relatively rapidly activate critical cortical areas needed for alerting responses when suddenly presented with novel stimuli (e.g., truck ahead). Due to their rare occurrence, simulator crashes could not be meaningfully compared between groups or pre- versus post-treatment, but two OSA patients had a crash at baseline and also at follow-up, while no crashes occurred in the control group.

Our study is the first to directly compare prolonged (90 min) driving simulator performance in CPAP-treated OSA patients

with age- and gender-matched control subjects. However, in discussing the results of active versus sham CPAP treatment in OSA patients, Hack et al.¹⁸ noted that driving performance in the actively treated group (mean CPAP use 5.6 h/night) did not quite fall to figures obtained previously in the same laboratory in a matched control group using the same simulator.⁴ Also, several other studies have shown only partial recovery of daytime sleepiness and no significant improvements in neurophysiological function following treatment of OSA,^{29-31,33-36,44} potentially contributing to persistent driving impairment. One study³⁶ demonstrated that approximately 60% of OSA subjects had persistent daytime sleepiness (multiple sleep latency test sleep onset time < 7.5 min) despite 3 months of optimal (> 6 h/night) CPAP treatment. There are several other driving simulator studies that have shown improvements in driving performance in OSA subjects days to months after initiation of CPAP therapy.¹⁷⁻²² However, all but two of these studies^{17,22} failed to include a healthy control comparator group, making it difficult to know whether driving simulator performance was normalized by CPAP treatment. One of the simulator studies that did include a healthy control group showed that after a mean of 9.2 months of CPAP treatment, lane position variability during a 20-min driving task was the same in OSA subjects as in healthy controls.¹⁷ Results from another study that used another 20-min divided attention driving simulator task and included a healthy control group also demonstrated normalization of driving simulator performance in OSA subjects who were treated for 3 months.²² An important methodological difference that could explain contrasting results with the current study is that we assessed primary vehicle control (steering deviation) during

a 90-min simulation of monotonous country driving, in contrast to the 20-min divided attention oriented driving simulator tasks used by George et al.¹⁷ and Mazza et al.²² The authors of the latter study acknowledged that although deficits in driving simulator performance normalized after treatment on a 20-min divided attention task, this may not take into account the effects of cumulative soporific factors associated with longer distance driving, where impairments may become more severe. Indeed, we have previously demonstrated that steering deviation continues to deteriorate throughout a 90-min monotonous driving test, beyond what is evident within the first 30 minutes.³⁷ Therefore, shorter driving tests may miss driving impairment occurring later during a long drive in untreated OSA subjects. In addition, residual driving difficulties following CPAP treatment may be masked by alerting effects of divided attention tasks.⁴⁵ Furthermore, normalization in driving performance reported by George et al.¹⁷ was observed in mildly sleepy OSA subjects (mean multiple sleep latency of 7.2 min before treatment) and was partly explained by an improvement in objective sleepiness in treated subjects. However, the driving performance deficits and improvements with CPAP observed by Mazza et al.²² were in OSA subjects who were not objectively sleepy on the Oxford sleep resistance test (OsleR). Although objective sleepiness was not assessed in the present study, subjective sleepiness prior to treatment was within normal limits in our OSA subjects (mean ESS of 9) prior to treatment, highlighting that residual driving simulator impairment occurs in non-sleepy OSA subjects.

There are several possible explanations for residual driving simulator performance abnormalities observed among OSA subjects after CPAP treatment in our study. OSA may produce some persistent effects on neurocognitive function or genetic factors that simultaneously influence OSA propensity and sensorimotor systems involved in driving. Alternative explanations include that the treatment period may have been too short, CPAP levels or CPAP compliance inadequate to show full benefits, or there may be effects of comorbidities or perhaps obesity *per se* in OSA compared with control participants. One small uncontrolled study found that residual sleepiness after 7 weeks of CPAP treatment was not evident when affected subjects were re-studied ~4 years later⁴⁶; however, most studies show that improvements in sleepiness occur very early in the course of treatment and do not accumulate over time.^{29,47,48} Suboptimal CPAP treatment levels also appear unlikely, given that the AHI of OSA subjects during CPAP titration was not different from the AHI of control subjects without CPAP. Six or more hours of CPAP use per night also likely represents maximal or near maximal treatment, as previous studies show that improvements in objective (mean multiple sleep latency) sleepiness scores plateau at adherence rates of 6h/night.³⁶ Some evidence suggests that obesity without OSA is associated with excessive daytime sleepiness,⁴⁹ but we are not aware of any data suggesting that obesity *per se* or the types of comorbidities present in our OSA subjects, or their treatments, affect driving performance. We were careful to exclude patients with comorbidities and medications known to affect driving such as anti-depressants and opioids. Some studies show that hypoxia may play an important role in causing persistent cognitive performance impairments in treated OSA patients independent of sleepiness.^{30,50} This is further supported by recent studies that have shown structural

changes in central nervous system white and gray matter among OSA subjects,^{51,52} suggesting that some persistent neurocognitive deficits observed in OSA subjects may be irreversible by the time of diagnosis. While these mechanistic questions remain unresolved, we believe, based on current clinical research experience,^{36,53} that the average CPAP adherence of 6h/night achieved by subjects in the present study is relatively high, and likely the most that can be expected in this patient group given the current state of CPAP technology and practices. Therefore, our data showing residual driving impairment after 3 months of CPAP is highly pertinent to practitioners in this field. Nevertheless, further studies are needed to confirm these findings and establish mechanisms.

Several epidemiological studies recently reviewed in a comprehensive meta-analysis¹⁶ have reported reduced motor vehicle accident rates among CPAP treated OSA subjects by comparing accident rates before and after treatment.²³⁻²⁸ Only two of these studies included a concurrently assessed control population^{23,26} to allow an assessment of the degree of normalization of accident rates in CPAP-treated subjects. These studies reached somewhat different conclusions: one study²⁶ showed accident rates reduced among CPAP treated patients to the level of controls, while the other²³ observed accident rate reductions in both treated patients and re-evaluated controls. The authors of the latter study²³ concluded that a period of CPAP treatment was associated with reduced accidents in the OSA group, but that this could not necessarily be attributed to CPAP *per se*. OSA subjects may modify their driving or other behaviors by virtue of being in a clinical study examining accident risk (i.e., the Hawthorne effect),¹⁶ and this confounding factor is shared by all retrospective epidemiological studies. Thus, these clinical epidemiological studies suggest that CPAP is associated with a significant reduction in accident risk but whether this is the result of CPAP therapy *per se* or other treatments or behavioral changes associated with OSA diagnosis and management is not known. Whether there remains an increased accident risk after CPAP therapy particularly in situations conducive to fall asleep accidents also remains unknown.

Study Limitations

There are some limitations that need to be considered when interpreting the findings of this study. The sample size was relatively small but was nevertheless sufficient to detect residual between group differences at follow-up with the repeated-measures design. However, a larger sample would be required to assess relationships between various clinical factors such as self-reported sleepiness and medical comorbidities versus residual driving performance impairment after CPAP treatment.

Some caution needs to be exercised in extrapolating the findings of this driving simulation study to on-road driving. Driving simulators measure the main aspects of real driving, including visual tracking and coordination, attention, reaction, and vigilance.^{54,55} In direct comparison studies, while tending to overestimate some driving abnormalities, simulator results correlate well with on-road driving performance.^{54,56-58} It is difficult to know if the AusEd simulator is able to predict real world motor vehicle accident risk, and further studies are required to address this question. However, the AusEd driving simulator is not fundamentally different from other research driving

simulators and has been previously validated and shown to be sensitive to fatigue and alerting/sedating substances (e.g., caffeine, alcohol, and benzodiazepines) in a range of experimental settings.^{37,59-63} Ours is the first study in OSA to use such a lengthy driving simulator task. It is possible therefore that our results may have been due to poor subject motivation or cooperation in completing the 90-min monotonous driving simulator task, but we found no evidence of this. Patients appeared to cooperate fully with the procedures, and none requested the task be terminated early because of boredom, fatigue, motion sickness, or other factors. Simulators offer the advantage of assessing driving performance in a safe and well-controlled environment particularly in studies such as this where the effects of excessive daytime sleepiness are unpredictable and potentially severe (i.e., fall asleep crash). Furthermore, we believe that prolonged monotonous driving tasks that simulate country driving are likely to be more relevant when assessing crash risk in OSA than relatively short divided attention tasks.

Clinical and Public Health Implications

Most studies, including our own, conclude that CPAP treatment of OSA results in an improvement in driving performance and potentially reduction in accident risk. Taken together with other studies showing persistent sleepiness and neurocognitive deficits after several months of apparently optimal CPAP treatment, the findings of this driving simulator study suggest that driving impairment during long drives persists in severe OSA patients optimally treated with CPAP. Further controlled studies are needed using larger patient samples to confirm these findings and to explore whether persistent driving simulator abnormalities in CPAP-treated OSA patients are associated with increased on-road motor vehicle accident risk.

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ACKNOWLEDGMENTS

The authors wish to thank the National Health & Medical Research Council of Australia (grant #390400). The authors would also like thank the developers of the AusEd driving simulator, and all technical, research and nursing staff from the Adelaide Institute for Sleep Health for their valuable contribution to this project.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication January, 2011

Submitted in final revised form January, 2011

Accepted for publication February, 2011

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DISCLOSURE STATEMENT

This was not an industry supported study. Drs. McEvoy and Antic are involved in a trial funded by Philips Respironics with equipment provisions by ResMed and Fisher & Paykel. Dr. McEvoy has participated in speaking engagement sponsored by Philips Respironics. Dr. Catcheside is an investigator on an industry funded trial (APNEX) and has received an equipment loan from Philips Respironics for research purposes. The other authors indicated no financial conflict of interest.