Evaluation of laboratory-based tests for fitness to drive for patients with the obstructive sleep apnoea/hypopnoea syndrome

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DECLARATION

I declare that I have been the principle investigator in all the studies presented in this thesis and that the contents of this thesis are my own work. I have been assisted in aspects of these studies by members of the Department of Sleep Medicine whose contributions have been noted in the acknowledgement section.

This work was performed in the Edinburgh Sleep Centre within the Royal infirmary of Edinburgh, between 1999 and 2003.

Lynne Anderson
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For Martyn

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Glossary and Abbreviations

AHI – Apnoea/hypopnoea index

AI – Apnoea Index

ANP – Atrial natriuretic peptide

ASDA – American sleep disorder association

BMI – Body mass index

CNS – Central nervous system

CPAP – Continuous positive airway pressure

DADT – Divided attention driving task

EDF – European data file

EDS – Excessive daytime sleepiness

EEG – Electroencephalograph

EMG – Electromyograph

EOG – Electro-oculograph

ESS – Epworth sleepiness scale

FFT – Fast Fourier transformation

FOSQ – Functional outcome of sleepiness questionnaire

g – Eductive component of General intelligence

HRT – Hormone replacement therapy

IQ – Intelligence quotient

MAD – Mandibular advancement device

MCS – Mental components summary

Mins - Minutes

MMPI – Minnesota multiphasic personality inventory

MRS – Mandibular repositioning splint

MSLT – Multiple sleep latency test

MVA – Motor vehicle accident

MWT – Maintenance of wakefulness test

NART – National adult reading score

NHS – National health centre

NREM – Non-REM

OSA – Obstructive sleep apnoea

OSAH – Obstructive sleep apnoea/hypopnoea

OSAHS – Obstructive sleep apnoea/hypopnoea syndrome

PASAT – Paced auditory serial addition task

PC – Personal computer

PCS – Physical components summary

PSG – Polysomnography

PVT – Psychomotor vigilance task

QOL – Quality of life

RAM – Random access memory

RCT – Randomised control trial

RDI – Respiratory disturbance index

REM – Rapid eye movement

RSPM – Ravens standard progressive matrices

$Sa0_2$ – Arterial oxygen saturation

SDB – Sleep disordered breathing

SF36 – Short form 36

SOL – Sleep onset latency

SSS – Stanford sleepiness scale

TST – Total sleep time

UARS – Upper airway resistance syndrome

UPPP – Uvulopalotopharyngoplasty

Abstract of Thesis

Aims: This research project assessed the usefulness of a portable PC-administered driving performance task, the "AusEd" simulator, in assessing driving performance in patients with obstructive sleep apnoea/hypopnoea syndrome (OSAHS), a group known to be at increased risk of motor vehicle accidents.

Methods: The studies comprised a parallel-limb, randomised single blind, placebo-controlled trial of 4 weeks of CPAP therapy or an oral placebo and also a case-control study of AusEd performance. An array of secondary, sleep-specific outcomes were assessed in each of these trials including FOSQ, SF36, symptoms scale, IQ decrement and self-reported driving ability and 5-year accident history. EEG spectral density power and blink behaviour during AusEd trials were also assessed. Also conducted was a questionnaire-based study of self-reported driving ability and accident history in a larger cohort of patients and controls.

Participants: 45 OSAHS patients recruited for two testing sessions before and after 4 weeks' treatment with CPAP or a placebo [6 female, mean AHI 39 (22), Epworth sleepiness 14 (3), body mass index 33 (6.)]. Additionally, 19 healthy control subjects [3 female, Epworth sleepiness 5 (2), body mass index 26(4)kg/m2] matched to the CPAP treatment group by gender and age were assessed in a case control trial. 138 OSAHS CPAP treated (≥2years) patients [16 females, mean age 54 (8) mean AHI 55 (32)], 82 untreated OSAHS patients [(11 female, mean age 51 (9.) mean AHI 45 (27)] and 85 community-acquired controls [5 female, mean age 54 (11)] were recruited for the postal based driving ability questionnaire study.

Results: Symptom scores and two subscales of the SF36 and 3 subscales of the FOSQ were significantly improved in the CPAP treated group. However no differences in simulated driving performance were found with CPAP treatment. In the case-control trial median reaction time was significantly longer in the

untreated patients than controls in the AusEd performance, and this was abolished with CPAP treatment. EEG spectral density power showed increased sleepiness between baseline and the 20 seconds before a crash event recorded by the AusEd simulator. Time-on-task blink frequency during the driving task was not significantly different between treated and untreated patients and controls. In the driving based questionnaire study untreated OSAHS patients reported more accidents and near miss accidents than treated patients, however only sleep related incidents were commoner than in community acquired controls. Treated OSAHS patients also reported fewer accidents than the controls.

Conclusion: The PC based driving simulator did not distinguish driving performance between treated and untreated patients and only separated untreated OSAHS patients and controls by reaction time. Analyses of spectral density of EEG indicates cortical changes up to 20 second prior to crash and driving-off road events, but blink rate showed no indication of sleepiness. The questionnaire study suggests that a untreated OSAHS had more sleep related motor vehicle accidents (MVAs), but CPAP treated OSAHS patients pose no greater risk than healthy community dwelling volunteers for involvement in MVAs.

Chapter 1: Introducing the obstructive sleep apnoea/hypopnoea syndrome

1.1 Introduction

The obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is a common condition, which is estimated to affect between 1-2% of women and 2-4% of men between the ages of 30 to 60 (Young et al 1993).

At sleep onset the dilator muscles of the throat lose tone resulting in OSAHS patients in episodes of either complete (apnoea) or partial (hypopnoea) pharyngeal obstruction. During these periods of obstruction patients struggle in an attempt to breathe, and reversal of the obstruction usually requires a brief cortical arousal from sleep. Arousals allow the throat muscles to regain the required activity levels to clear the obstruction. In severe OSAHS patients the reoccurrence of sleep onset re-initiates upper airway muscle hypotonia and the cycle of obstruction and arousal recurs.

Therefore OSAHS is associated with multiple episodes of apnoea/hypopnoea, sleep fragmentation (as a consequence of arousal to clear the obstruction) and sometimes oxygen desaturation (as a consequence of limited or no airflow), resulting in predominant nocturnal features of heavy snoring and nocturnal choking. There are also waking consequences of the syndrome, including excessive daytime sleepiness, cognitive dysfunction, impaired mood and vigilance and an increase in reaction time. These features substantially reduce quality of life (Guilleminault 1976) and significantly impair performance on tasks requiring sustained attention.

This probably explains the increased risk of OSAHS patients having a motor vehicle accident (MVA). It is estimated that untreated OSAHS patients have between a 1.3-12 times greater chance of having a MVA as compared to healthy matched controls. (George et al 1999, Teran-Santos et al 1999, Hortsmann et al 2000). Such road accidents are one of the major risks associated with OSAHS, but there is no clarity

about precisely which patients are at risk. It would be highly desirable to have a laboratory-based test that could predict those at risk.
The research conducted for this thesis is based on the validation of a PC based driving simulator for fitness to drive in OSAHS patients. A review of the literature on OSAHS and driving can be found in chapter two.

A review of the obstructive sleep apnoea/hypopnoea syndrome follows.

1.2 History of the Recognition of OSAHS

Sleep medicine is still in its infancy compared with many other areas of medicine; in fact rapid eye movement (REM) sleep was only discovered around 50 years ago (Aserinsky and Kleitman 1953). Never the less there have been great developments in this area and the discovery of the obstructive sleep apnoea/hypopnoea syndrome is just one. OSAHS is not a new condition, merely a newly recognised one. There have been reports throughout history and literature of obese men who have suffered from excessive somnolence during the day. Perhaps the best known is Joe the fat boy, in Charles Dickens' 1830 novel 'The Posthumous Papers of the Pickwick Club'. Dickens was amongst the first to report the symptoms of somnolence and snoring and reported Joe's ability to fall asleep in a variety of situations including during meals and whilst talking, noting that his snoring was heavy and loud. He was also reported to suffer from right heart failure and due to his ruddy complexion he was suspected of suffering from polycythaemia. As more cases of patients with sleepiness, heart failure and polycythemia were identified, the name 'Pickwickian syndrome' was adopted (Burwell 1956)

In the mid 1960s both Gastaut (1966) and Jung (1965), independently of each other, provided polysomnographic evidence from nocturnal observations that breathing pauses occurred during sleep in Pickwickian syndrome patients.

Gastaut (1966) defined these breathing pauses as a cessation of airflow lasting at least 10 seconds and termed them apnoeas. He was able to show using the

polysomnographic signals that there were three types of breathing pauses. He termed them obstructive apnoeas, central apnoeas and mixed apnoeas.

All resulted in the cessation of airflow but from different mechanisms;
Obstructive apnoeas result from an obstruction of the upper airway with continued respiratory effort. These account for most events in sleep apnoea patients.
Central apnoeas result from the temporary loss of ventilatory effort, and are common in heart failure.
Complex apnoeas, commonly referred to as mixed apnoeas, as the name suggests, comprise a mixture with both a central and an obstructive component. Physiologically a mixed apnoea begins with a central apnoea, and as with a normal central apnoea there is a loss of respiratory effort. However on the resumption of this effort, airflow is still inhibited due to upper airway obstruction and the term mixed apnoea is used. These were the least recorded events by Gastaut.

As well as providing evidence regarding the physiological nature of apnoeas Gastaut (1966) and Jung (1965) provided evidence that arousals from sleep occurred at the end of an apnoea. Gastaut (1966) concluded that not only were these arousals a mechanism to end the apnoea, but were also the cause of the severe somnolence felt by apnoea sufferers during the day. He hypothesised that obesity was the main cause of these apnoeas, with the extra fat around the neck causing restriction in the upper airway, and that weight reduction was the obvious treatment.

The next ten years saw a rapid development in our understanding of the mechanisms, cause and effects of the condition. One of the most significant developments came when Guilleminault et al (1978) provided evidence to suggest that only a small proportion of "Pickwickian syndrome" patients suffered from right heart failure and polycythaemia, with most of the patients presenting only with daytime sleepiness and suffering from apnoeas. This new information signified a shift in the understanding of the condition and a new name was adopted for this syndrome, this being the 'sleep apnoea syndrome'.
The term obstructive sleep apnoea syndrome was then used to clarify that apnoeas in these patients were predominately obstructive in nature. Although obstructive and

central apnoeas are rarely seen in isolation it is worth noting that patients with predominately central apnoeas only account for between 4% (DeBacker 1995) and 10% of apnoea suffers (Rohers 1985) seen in sleep laboratory populations. Further support for making this distinction came when patients whose main complaint was somnolence were reported to suffer predominately from obstructive apnoeas (Sadoul 1972, Guilleminault 1974). Further developments came with the development of a treatment for OSAHS called continuous positive airway pressure (CPAP) (Sullivan 1981), which was found to alleviate nocturnal events and daytime symptoms from obstructive apnoeas. However some central events also respond to CPAP and may be due to reflex atonia of the inspiratory muscles following upper airway occlusion.

Apnoeas are not the only important nocturnal respiratory events. Gould et al (1988) reported that the same symptoms produced by apnoeas were also produced when airflow was reduced as opposed to completely stopped. This new breathing abnormality was termed hypopnoea. As with an apnoea respiratory effort is maintained, but unlike an apnoea there is still airflow although at a reduced level. Today there is still no consensus over the exact definition of hypopnoea (this will be discussed in a later section). Gould et al (1988) suggest that a hypopnoea occurs when continued respiratory effort is accompanied with a reduction of 50% in thoraco-abdominal movement in comparison with that during stable breathing in the 2 minutes preceding the event.

The recognition of the consequences of hypopnoeas caused a significant shift in the understanding of the syndrome; Gould et al (1988) suggested the syndrome should be re-named the sleep hypopnoea syndrome. They argued that an apnoea was a severe form of hypopnoea and so the new name would represent both. While this proposed term did not immediately take hold, nevertheless the importance of this new event was recognised and one common name now used for the syndrome is the 'obstructive sleep apnoea/hypopnoea syndrome', or OSAHS.

1.3 Defining the Obstructive Sleep Apnoea/Hypopnoea Syndrome.

Once it was recognised that apnoeas and the cortical arousals associated with their termination were the cause of many daytime symptoms it became necessary to establish criteria for what was clinically relevant.

Gastaut's (1965) definition of an apnoea as 'cessation of airflow for at least ten seconds' was widely accepted and is still the definition used. However, there was no consensus on the frequency of these events that constituted a clinically relevant syndrome.

The late 1970s and early 1980s saw a surge in recommendations for what should be used to establish an OSAHS diagnosis, with early definitions including:
30 apnoeas in 7 hours of sleep, (Guilleminualt et al 1976)
10 apnoeas per hour of sleep (Lavie 1983)
5 apnoeas per hour of sleep (Guilleminualt et al 1978)

However these criteria were largely arbitrary and none required the presence of symptoms to establish the diagnosis.

As the treatment for OSAHS was still primarily surgical in the 1970s and early 80s, it was vital that diagnostic criteria should be established to ensure only those who needed treatment should receive it.
Lugaresi et al (1983) aware of the need for describing less severe forms of OSAHS proposed that sleep apnoea was in fact a:

"Continuum of clinical conditions between trivial snoring and the severest form of obstructive sleep apnoea syndrome, all of which originate in hypnogenic stenosis of the upper airway"

He suggested that a system based on objective monitoring of respiratory behaviour during sleep and the tendency to daytime sleepiness could be used to characterise severity. Using this approach he divided this continuum into 4 stages. These were:
Pre-clinical: with sporadic apnoeas
Initial: apnoeas occurring during stage 1,2 and REM sleep
Overt: apnoeas throughout all stages of sleep
Complicated: alveolar hypoventilation persisting during wakefulness

They also divided daytime sleepiness into 4 stages but these stages did not match well to the nocturnal observations. Although this classification system did not take hold it was amongst the first to recognise the importance of milder forms of OSAHS and include the need for symptoms as part of a diagnosis.

Two common indices used to measure the frequency of respiratory events are the apnoea/hypopnoea index (AHI) and the respiratory disturbance index (RDI). These are defined as the combined number of apnoeas and hypopnoeas divided by the total sleep time in hours.

The best current working definition of OSAHS is 5 or more apnoeas + hypopnoeas per hour of sleep associated with at least two major symptoms out of those outlined in section 1.5 (ASDA 1999). This is supported by Young et al, who reported symptoms of OSAHS at this level of disturbance, and by Engleman et al (1999) who showed patients with an AHI of 5 to 15 per hr perceived benefits of treatment.

The American Sleep Disorders Association (ASDA) propose a two component model of OSAHS, these being severity of daytime sleepiness and the severity of breathing abnormality on nocturnal monitoring.

Daytime sleepiness is divided into mild, moderate and severe, depending on whether unwanted sleepiness or involuntary sleep produces minor, moderate or marked impairment of social or occupational function.

Sleep related obstructive breathing events (based on the AHI definition) are divided into-

Mild; 5 -15 events per hour
Moderate; 15 - 30 events per hour
Severe; 30 or more events per hour

The overall rating of clinical severity is based on the most severe component. Therefore, even if a patient is only classed as having moderate obstructive breathing events, they will still be classed as having severe OSAHS if they complain that their unwanted daytime sleepiness/involuntary sleep is severe.

The above definition is not universal, as many sleep centres use an AHI of 15 per hour as their clinical cut off and there is still not universal agreement on the definition of hypopnoea. Some centres require a 50% reduction in oro-nasal airflow rather than thoraco-abdominal movement, even although this is not truly quantitative (Gould 1988). Other centres require a 4% arterial desaturation accompanying both apnoeas and hypopnoeas.

One should also note that these definitions are based on polysomnographic evaluation, but some centres use limited sleep studies without EEG and others diagnose using oximetry alone and therefore the AHI and RDI indices cannot be used as they do not measure time asleep and their results are not directly comparable.

1.3.1 OSAHS as part of a disease continuum

As mentioned in the previous section OSAHS is part of a disease continuum. This spectrum ranges from partial airway collapse with increased upper airway resistance which manifests itself as snoring and hypopnoeas, to complete airway collapse with increased ventilatory effort which manifests itself with periods of snorts leading to apnoea (Young 1995). A common name for this continuum is sleep disordered breathing, with the breathing disturbance measured by AI, AHI or RDI, with or without a measure of oxyhaemoglobin desaturation.

Recently evidence has suggested that some patients, generally the less obese, experience increased upper airway resistance terminating in transient alpha EEG arousal, without the upper airway collapse or oxyhaemoglobin desaturation. These brief cortical arousals may cause sleep fragmentation and have been shown to increase daytime sleepiness objectively on the multiple sleep latency test (MSLT) (Guilleminault, 1993) and in turn produce excessive daytime sleepiness (Black 2000). As there is no occlusion of the upper airway this has been classified by some as a distinct syndrome from OSAHS called the 'upper airways resistance syndrome' (UARS) (Guilleminault 1993). However the existence of this syndrome is disputed (Douglas 2000).

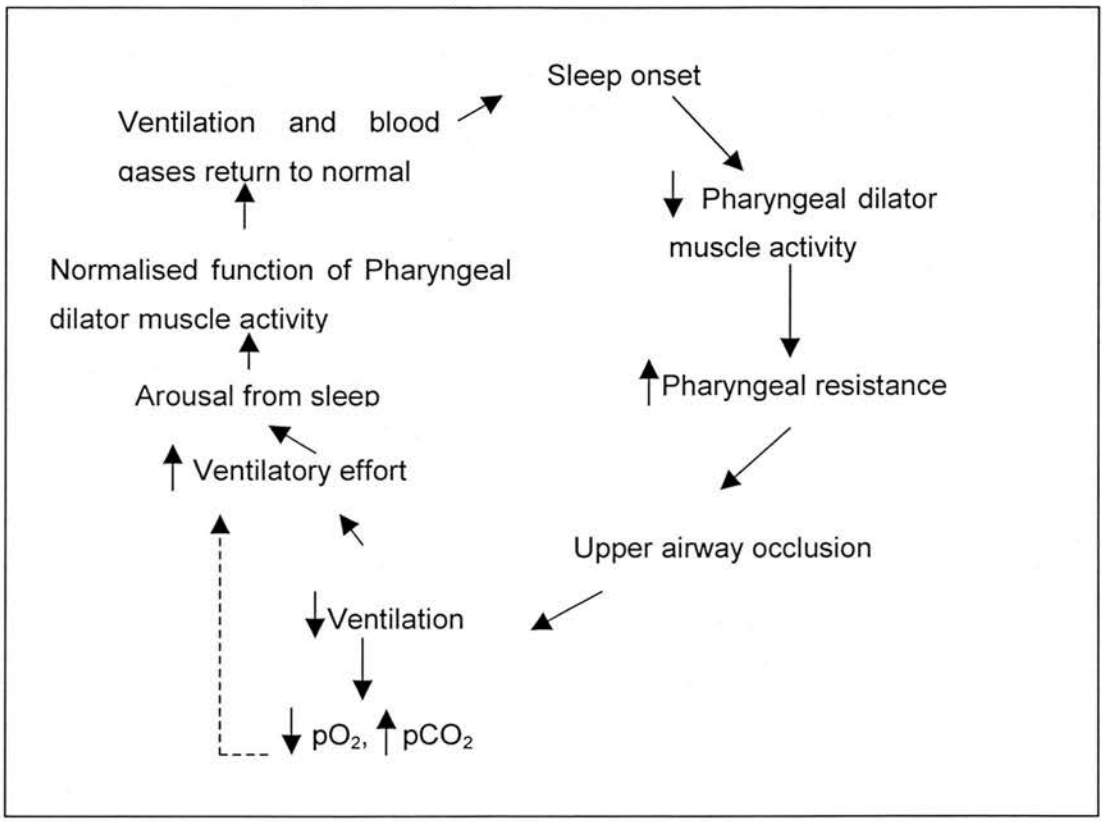
Guilleminault et al (2000) suggest that patients with OSAHS have an increased arousal threshold compared to UARS patients. Therefore, UARS patients are more sensitive to changes in internal respiratory load and this in turn leads to earlier detection of increased inspiratory effort and arousal before occlusion occurs. However, not all clinicians believe that UARS is a separate syndrome, and believe that it is in fact part of the disease continuum of SDB, between snoring and OSAHS. Douglas (2000) suggests that UARS highlights deficiencies in the definition of OSAHS rather than highlighting a new syndrome. Douglas also notes that the features attributed to UARS are not specific to that syndrome and that the major confusion in UARS may stem from confusion over the scoring of hypopnoeas, which may result from inadequate sensors in sleep studies, rather than detecting a distinct physiological event. The debate over UARS as a distinct syndrome continues.

1.4 Obstructive Sleep Apnoea/Hypopnoea – Sequence of events

OSAHS is a result of narrowing of the upper airway during sleep. On falling asleep all striated muscles throughout the body become hypotonic including the muscles of the upper airway. Thus the negative pressure within the upper airway during inspiration is poorly resisted by the tone in the upper airway dilator muscles and upper airway narrows or even occludes during inspiration. As the apnoea continues, increasing levels of intrathoracic pressure are generated with each inspiratory effort until a critical level is reached and an arousal occurs signalling the end of the apnoea and allowing the

obstruction to be cleared (Remmers 1978). The arousal may be mediated by mechanoreceptors in the thorax or to central perception of hypoxaemia. On wakening the person resumes normal breathing and then returns to sleep and in severe cases of OSAHS an obstruction begins almost immediately and the cycle of occlusion/arousal continues.

Figure 1.1; Cycle of events in OSAHS



1.5 OSAHS Symptoms and Features

There are many reported symptoms of OSAHS but not every OSAHS patient experiences all of the symptoms. It is useful to note at this juncture that many of the nocturnal features associated with OSAHS (perhaps with the exception of nocturnal choking and nocturia), are reported not by the patient but by a family member, most typically the bed partner. It should also be noted that many of these features affect both the OSAHS sufferer and family members. A high degree of martial disharmony is often

reported, with one study finding that 46% of patients sleep in a separate room from their partner (Kales 1985a). For the purpose of this review features of OSAHS will be separated into those primarily affecting the patient and events affecting the partner.

1.5.1 Patient affected reports

Excessive Daytime Sleepiness (EDS)

Excessive daytime sleepiness reflects the propensity to falling asleep unintentionally during the day, especially in less motivating situations (Moldofsky 1992), and is the most common symptom associated with OSAHS. Sleepiness tends to be a significant problem in passive and monotonous situations such as watching television, listening to music, reading, operating a computer or driving on straight roads. However sleepiness can also intrude into situations not normally considered soporific, for example whilst lecturing or during sexual intercourse (Dement et al 1978). In many cases EDS is the main reason for referral to the sleep disorders clinic rather than the presence of other symptoms of OSAHS or narcolepsy (Roehrs et al 1983, Colt et al 1991).

One should not underestimate the problems that can occur with EDS, as these are more than a mere annoyance to the sufferer. In many cases these can produce deficits in performance due to non- or slow- response times. As well as this, EDS can cause progressive decrements in performance with time, by which the performance of the individual gradually deteriorates during the task (Melamed 2002). This may, in part, be responsible for the poor work performance often reported in these patients (Lavie 1983). As well as work-related issues it can also have a large impact on family and social life (Roth et al 1980). Many people suffering with EDS will alter their lifestyle to reduce the impact of sleepiness (Kryger 2000). By minimising contact with family and friends they take themselves out of social situations in which they may struggle to stay awake, i.e. going to the cinema or having friends around for supper.

It has been estimated that between 80–90% (Dement 1978, Douglas 2002 pg. 47) of OSAHS patients report EDS. However, this may not be an accurate reflection of the prevalence of sleepiness, as many patients who have been symptomatic for long

periods of time may have lost their frame of reference for what constitutes a normal level of sleepiness. Conversely, many people whose livelihoods depend on performing tasks which could be adversely affected by sleepiness, i.e. driving or operating dangerous machinery, may understate their level of sleepiness in an attempt to continue in their employment (Dement 1978). It should also be noted that many patients who do not report EDS on their initial consultation only realise how sleepy they were after they have been established on treatment. Nevertheless, the estimates for the prevalence of sleepiness for OSAHS patients is still markedly greater than estimates of sleepiness in the general population which have been placed between 0.3% and 13.3% (d'Alessandro et al 1995).

Unrefreshing nocturnal sleep

Many OSAHS patients will report that they feel unrefreshed upon waking in the morning (Whyte et al 1989). This is primarily due to the transient cortical arousal required to terminate apnoeas and hypopnoeas (Stepanski et al 1984). Although normally these arousals last only a few seconds the cyclical nature of the disorder means that the sufferer is woken several times an hour and in very severe patients, more than once a minute. Due to the briefness of these arousals most patients are unaware of them during the night and wake up perplexed by the residual sleepiness, despite what they believe has been an undisturbed period of sleep.

Difficulty concentrating

Many OSAHS patients also report problems in their ability to concentrate. This is probably a combination of the effects of both EDS and the reduction in the proficiency of short-term memory due to sleep fragmentation (Melamed 2002)

Decreased libido

Decreased libido or impotence is also reported (Whyte et al 1989) with suggestions that a third of OSAHS patients experience this symptom (Bassiri 2000 pg. 871) that may in turn place extra stress on the marital relationship.

Depression

Depression itself can cause sleepiness and therefore many patients presenting with depression and sleepiness may be misdiagnosed, especially if a detailed history of snoring etc is not taken. Nevertheless, depression is a common symptom reported by OSAHS patients (Cheshire et al 1992, Engleman et al 1994a).

Nocturnal choking

Many OSAHS patients (Kales et al 1985a, Whyte et al 1989) report choking on wakening. This can be a very frightening experience for people as yet undiagnosed with OSAHS, especially if they are unaware of any other OSAHS symptoms. Choking episodes are reported more frequently in people with milder OSAHS who have fewer events per hour, (Douglas 2002 pg. 49) which may suggest that more severe OSAHS sufferers have a blunted cortical arousal response.

Nocturia

Nocturia is a frequent problem for OSAHS patients (Koening et al 1988), and has been linked to elevated excretion of atrial natriuretic peptide (ANP) with resulting high urine output. It is a nightly inconvenience for these patents, many of which make multiple trips to the bathroom. As well as the annoyance factor it may also contribute to EDS by reducing the total sleep time available to these patients.

1.5.2 Partners Reports

Snoring

Snoring is a very common symptom of OSAHS and almost all partners of sufferers report it. In many cases there is a very long history of snoring, which is often into decades (Stradling 1995). It is a chronic symptom occurring on a nightly basis and is often reported during naps taken in the day. It is initially associated with lying in the supine position, however, severe OSAHS patients snore in all positions.

The noise generated by OSAHS patients when snoring has been suggested to equal that of a pneumatic drill (pneumatic drills register 130Db!) (Douglas 2002 pg. 50) and this can be a major disturbance to bed partners and to other occupants of the household. In many cases bed partners suffer from poor quality sleep (McArdle et al 2001a) and sleep fragmentation. This in part may be due the frequency and loudness of the snoring and this is the primary reason for many OSAHS patients and their partners sleeping in different rooms

Apnoeas

Most partners will have witnessed 'breathing pauses' (Davies 1992) and to them these events appear life threatening and are often a source of considerable anxiety. Characteristically loud snoring is interspersed with periods of silence (relating to the occurrence of apnoeas) and if left undisturbed the patient will eventually arouse from sleep, often accompanied by loud snorts. However if partners become aware of the lack of breathing noises only little, if any, movements of the chest, this leads the partner to take action, by shaking or nudging the patient to help induce breathing. This action is common and understandable, however patients are usually unaware of these apnoeic events and are less than happy to be shaken awake in the middle of the night!

Restlessness during sleep

McArdle et al (2001a) reported that partners of OSAHS patients complain of disturbance from their partner snoring, having apnoeas and restlessness. The partners also reported they themselves had reduced sleep quality and scored poorly on quality of life outcomes. Restlessness in OSAHS is probably related to apnoea termination. On arousing to clear the obstruction, many thrash around disturbing their bed partner, and on rare occasions causing physical injury to their partner by hitting them, unintentionally, with flailing limbs.

Other symptoms

There are a variety of other symptoms associated with OSAHS including drooling during sleep, enuresis, irritability and changes in mood/personality.

However the diagnosis of OSAHS cannot be based on symptomatology alone, Hillerdal et al (1991) demonstrated that simple snorers and OSAHS patients could not be distinguished on their symptoms alone.

1.6 Neuropsychological impairment

As well as the clinical symptoms and features of OSAHS, patients also have daytime neuropsychological impairments and these impairments can often be the reason OSAHS patients seek medical advice (Guilleminault 1978).

As mentioned in section 1.5.2 daytime sleepiness can have debilitating effects on OSAHS patients, but in addition to this some OSAHS patients also have cognitive deficits and impaired psychosocial well being. Greenberg et al (1987) were amongst the first to compare cognitive performance in OSAHS patients and healthy controls. They examined 14 OSAHS patients, 10 sleepy controls with EDS not attributed to OSAHS and 14 controls, matched for age, education and pre-morbid intelligence. They used a wide battery of tests including tests of IQ, visuo-motor skills, and memory scales, finding that the OSAHS patients had greater deficits on attention, verbal memory, visual memory and motor speed as well as of global neuropsychological impairment, than both the control groups.

Bedard et al (1991) compared 20 OSAHS patients (10 severe and 10 moderate) to 10 control subjects matched for age and sex, comparing their performances on the MSLT, a vigilance task and a variety of cognitive tasks. The moderate OSAHS patient group performed significantly worse on tests of manual dexterity, attention and executive function than the control group. The severe OSHAS group also had decrements in these areas (performing worse than the moderate apnoeics) and also showed

performance decrements on general intelligence, reaction time, planning, sequential thinking and constructional skill than controls. On analysis of these impairments the moderate OSAHS groups showed impairments of 1 to 2 standard deviations, while the severe group showed impairments of up to 3 standard deviations.

This study suggested that the cognitive impairment seen in OSAHS patients is dependent on disease severity, with lower, perceptuomotor cognitive functions affected first and worsening as the conditions worsens, and higher cognitive functions (executive functions) becoming impaired only in severe patients.

Naegele et al (1995) compared OSAHS patients to age, education and verbal IQ-matched controls on a battery of frontal lobe function tests. They found only one of three tests measuring attention was worse in the patient group. Overall patients were worse in the area of task learning, and showed small decrements in frontal lobe function tests. Analysis of the aspects of disease correlated with these deficits found that AHI was related to memory deficits, and nocturnal hypoxaemia related to tests of executive functions.

Cheshire et al (1992) also reported correlations between cognitive performance and nocturnal variables. Cheshire reported that poor cognitive performance on tests of attention and constructional skill correlated significantly with increasing severity of AHI, nocturnal hypoxaemia, and sleep disruption.

Redline et al (1997) recruited 52 community dwelling volunteers that were split into the case group (RDI 10-30 per hr) and control group (n=20) (RDI<5) following polysomnography and were matched by age, sex and intelligence. These two groups were tested on a battery of cognitive tests measuring attention, executive function and information processing. The groups were not significantly different in either subjective or objective sleepiness levels, and the case group performed significantly worse than the controls on only two tests of attention and working memory. There were no differences in the groups on tests of executive functions. As with the Bedard study, these results indicate that only small cognitive decrements may be found when RDI is low.

Thus these studies overall suggest that OSAHS patients have small decrements in cognitive function with mild OSAHS, which worsen as the severity of the condition worsens and that additional cognitive functions (executive functions), may become impaired only at severe levels of OSAHS.

As well as cognitive performance deficits OSAHS patients also show significant impairments in mood, anxiety and quality of life. Changes in personality and mood are estimated to occur in half of patients with severe OSAHS (Guilleminault 1978), with irritability reported by both patients and their families, (Whyte et al 1985) Depression has been frequently reported in OSAHS patients. Guilleminault (1977) using the MMPI (Minnesota multiphasic personality inventory), which assessed adult psychopathology, found 20-25% of OSAHS patients had high depression scores. Millman (1989), using the Zung self-rating depression scale, found 45% of patients showed signs of depression, and Cheshire (1992), using the hospital and anxiety depression scale, found 40% of their sample reported clinically significant levels of anxiety or depression.

However, Cassel (1993) using the Freiburger personality inventory found no evidence of depression in OSAHS patients. This inventory only has two questions relating to sleep whereas the Zung self-rating questionnaire asks sleep-specific questions regarding task performance and sleep disruption. Therefore scores on non-sleep disorder personality and depression scales that include sleep specific questions may be elevated in OSAHS as a result of the nocturnal effects of OSAHS.

OSAHS patients also seem to show decrements in quality of life (QOL) measures. Questionnaires assessing QOL measure well being, including physical and psychological factors. Generic quality of life questionnaires like the SF 36 (see section 3.9.2) contain 8 domains of health status including vitality, social functioning and physical functioning. Smith and Shneerson (1992) have shown that OSAHS patients 'requiring treatment' perceive themselves to have low health status, with patients scoring significantly lower on all domains except the general health sub scale, compared to normative samples, whereas simple snorers and mild OSAHS patients were not significantly different from the normal samples. After six months of CPAP treatment scores on all of the domains had significantly improved and several were no

longer different to the normal values, suggesting that OSAHS has a negative impact on many health status sub-scales as measured by the SF 36.

Questionnaires specific to disorders of sleepiness, measuring how sleepiness affects daily functioning and quality of life, have also shown that OSAHS patients can be discriminated from non-sleepy populations on the basis of how sleepiness pervades and disrupts their everyday lives (Weaver et al 1997a)
These studies indicate that OSAHS patients suffer from a wide range of psychological and psychosocial decrements that affect all areas of their lives. These daytime decrements in cognitive function and sleepiness can have severe consequences on a person's ability to safely control a vehicle, as will be discussed is chapters 2 and 6.

1.7 Epidemiology of OSAHS

Like any medical condition it is important to quantify its prevalence. This proves slightly difficult in OSAHS, as there is no consensus either on a diagnostic threshold for clinically significant respiratory disturbance or on symptom cut-offs. As mentioned in section 1.3, the ASDA suggest that an AHI of 5 or more is clinically relevant, but many physicians will only suggest conservative treatment until an AHI of 15 or more is present in association with significant symptoms. The definition of sleepiness is equally problematic.

Nevertheless a variety of epidemiological studies have been undertaken, most of these concentrated in Europe and North America, with the UK initially much slower to recognise the syndrome and its importance (Shapiro et al 1981)

Franchesci et al (1982), using unselected inpatients from a general hospital, estimated the prevalence rate of patients with both EDS and an AI of 10 or greater prevalence rate of around 1%. Lavie (1983) studying industrial workers also estimated the level of sleep apnoea at around 1.4%, when an AI of five or greater was accompanied by EDS. However neither of these studies included hypopnoeas as a measure of respiratory

disturbance, and employed an apnoea threshold of 10 per hour for their level of clinical significance. Therefore these studies may underestimate the true prevalence rate.

Cirignotta et al (1989) found 2.7% of their sample (males ages 30-69) had more than 10 apnoeas per hour of sleep, however when the presence of symptoms was included only 0.5% were symptomatic and therefore 'requiring treatment'.

Stradling and Crosby (1991) from a possible cohort of 1596 men used home oximetry on 900 men to screen for potential subjects to undergo polysomnography. Of these, 45 subjects (5%) had a >4% oxygen desaturation dip rate of more than five per hour, and of these 3 had severe, symptomatic sleep apnoea. Another 18 had supine-related sleep apnoea. This study gave prevalence rates of 0.3% for severe symptomatic sleep apnoea to 2% for milder sleep apnoea. Again these values may underestimate the true prevalence as it has been suggested that oximetry may produce false negative results in up to 1/3 of cases (Douglas 1992).

Young et al (1993) estimated that 9% of women and 24% of men (aged 30-60) had an AHI of five or greater without coexisting daytime sleepiness. When the presence of sleepiness was required to estimate OSAHS this reduced to 2% of women and 4% of men with an AHI of five or more per hour. This estimate was similar to that by Bearpark et al (1995) who found a prevalence rate of 24% in middle-aged Australian men who with a respiratory disturbance index of five or more per hour, however this was also reduced to 3% when the coexistence of daytime sleepiness was required.

Jennum et al (1992), using a randomly selected non-patient population found that from a sample of 748, RDI > 5 was present in 10.9% of men and 6.3% of females. Again when an RDI >5 and EDS were reported together reduced to the prevalence to 1.9% in men and 0.9% of females (1.4% of the sample).

Tishler et al (2003) analysed in-home sleep studies five years apart. All 286 participants had an AHI differing by less than 5/hr from the initial study. On re-test, 47 (16%) had an AHI of 10 or more, which the authors suggest is mild to moderate in OSAH severity. Twenty-nine (10%) had an AHI of 15 (severe) or greater; of this the authors suggest

that 2.5% may represent test-retest variability. Therefore they estimate the annual incidence to be 7.5% for severe and up to 16% for mild to moderate sleep disordered breathing. However the distinction between 10 and 15 apnoeas and hypopnoeas per hour as moderate to severe is not in line with the general view of under 15 an hour being mild and 30 or over being severe. Further the presence of sleepiness and symptoms is required for diagnosis of the obstructive sleep apnoea/hypopnoea syndrome and no measure of EDS this was obtained in this study, therefore the prevalence of OSAHS may be lower than that of sleep disordered breathing.

In summary these studies suggest that obstructive sleep apnoea/hypopnoea (OSAH) is a relatively common condition, and that many people in the general population may have the respiratory events of the condition despite a lack of symptoms. The obstructive sleep apnoea/hypopnoea syndrome (which requires the presence of symptoms) is less prevalent with estimates from these studies ranging from 0.5-4% of the populations studied.

However the prevalence estimates depend on the diagnostic criteria and methods of measurement implemented. A major issue in estimating the incidence of sleep apnoea concerns the need for patients to report features in addition to the observation of respiratory events. Several of the above studies require only the presence of sleep disturbed breathing to categorise OSAHS, rather than at least two symptoms including sleepiness as ASDA suggest (section 1.3).

Further reporting symptoms is dependent on subjective perception. Perhaps the two most common features, daytime sleepiness and snoring, may often be reported as absent when in fact they are present, and visa versa. This is not necessarily a case of the patients lying, as Stradling and Crosby (1991) found that if a bed partner was present during questioning regarding snoring, prevalence rose from 10% to 23%. Conversely, Bearpark (1995) found that 15% of people reporting snoring did not snore at all. Snoring is a subjective measure, and patients are dependent on witness reports to establish its occurrence, hence their reports of snoring will depend on what they have been told by others. EDS may also be denied if OSAHS sufferers have lost their frame

of reference for what constitutes a normal level of sleepiness (Dement 1978). If one is constantly sleepy over a long period of time, it may be perceived as normal.

1.8 Mortality in OSAHS

Untreated OSAHS may be associated with increased mortality. However all of the studies of survival with OSAHS are potentially flawed, and there are no randomised controlled trials proving cause and effect – neither are these likely ever to be performed for ethical reasons of withholding treatment of proven benefit.

Partinen et al (1988) conducted a five-year follow up on 198 patients and found 14 deaths. These all occurred in their conservatively treated patients (n=127), who had been advised to lose weight, compared to no deaths in the tracheotomised patients (n=71). On reviewing the cause of death, 8 were cardiovascular in origin and most occurred during sleep. He et al (1988) found that patients with an apnoea index >20 had a greater mortality than those with an apnoea index <20. Eight of the 98 patients treated with uvulopalatopharyngoplasty (UPPP) had died compared to zero in the group treated with either tracheotomy or CPAP. However mortality rates were most apparent in under those aged under 50.

Veale et al (2000) compared CPAP users who died (n=124) to age and sex matched patients who commenced CPAP at the same time (n=123), as well as to the general mortality rate of the French population. Overall the mortality rate was the same as the general French population, although by case control comparison, factors associated with subsequent death from past medical history were; cardiac arrhythmia, respiratory disorders, ischaemic events and neurological or psychiatric disorders. The authors report that a significant number of the deaths were cardiovascular in nature, but these patients may have had a history of cardiovascular conditions. Marti et al (2002) compared 444 patients diagnosed between 4 and 14 years earlier. The treatments employed were surgery (88), CPAP (124), weight loss (134) and 98 were not treated. Within the total cohort, 49 patients died. Treated patients had a lower mortality rate than non-treated patients, and mortality was higher in patients with a history of chronic

obstructive pulmonary disease. Compared to the general population, untreated patients adjusted for age and sex showed excessive mortality, but there was no significant difference in survival between treated OSAHS and the general population.

In summary these studies suggest that untreated patients have a higher mortality rate compared to both the general population and those treated by either CPAP or tracheotomy. The survival rate of those treated with UPPP seems to be slightly lower than CPAP. However, Keenan et al (1994) found no difference between the survival rate of OSAHS patients treated with CPAP and UPPP, therefore further comparison is needed to clarify.

Many of these studies are retrospective with relatively small numbers of cases and in most cases no adequate control group. Ideally a prospective study comparing survival rate of these treatments (as well as oral appliances) against untreated patients would clarify the situation much better then retrospective studies. However withholding treatment to analyse possible outcomes would be unethical.

As well as deaths caused by secondary medical conditions, OSAHS may also increase mortality in undiagnosed patients through their increased risk from driving and occupational accidents (Stradling 1989, Findlay et al 1991, Akerstedt, 2002).

1.9 Possible Predisposing Factors for Obstructive Sleep Apnoea

Numerous factors can increase the risk of developing OSAHS. Although not exhaustive this section outlines and lists a variety of these risks.

1.9.1 Obesity/ Body Mass Index (BMI) /Neck Circumference

Obesity is an important risk factor for both snoring and OSAHS. Obesity can be measured by the body mass index scale (BMI) which is calculated as weight in kilograms divided by the square of height in meters (Khosla 1967). A BMI greater than 30 kg/m^2 is considered obese. However central obesity anthropometric measures such

as waist to hip ratio, or neck size, are better predictors of OSAHS severity (Katz et al 1990). Obesity is thought to affect upper airway dimensions through fat deposition within the soft tissue regions of the neck (Mortimore 1998) and this in turn may increase pressure on the upper airway, promoting collapse. Mortimore et al (1998) showed that even non-obese OSAHS patients have excess fat deposition in the areas anterolateral to the upper airway, when matched to control subjects by BMI and even neck circumference, which may represent a predisposition to the condition.

1.9.2 Age

Increasing age is also a risk factor for OSAHS. Although the syndrome occurs in all ages, most prevalence data exists for the middle aged, and the prevalence rate and the consequences of OSAHS are less clear in the elderly.

However OSAH is common in the over 65 group. Ancoli-Israel et al (1991) found that 65% of people in this age group had an RDI > 10 per hour, this was in keeping with an earlier study in which they found 70% and 40% of a nursing home population had an AHI of >5 and >15 respectively. Bixler et al (1998) also reported that prevalence rate in the 65-100 year age group was 2%, as compared to 1% under 44 and 5% between 45-66. These data would suggest that the elderly are also at risk from OSAHS. Clinical recognition within this age group may not occur due the acceptance of daytime sleepiness in the elderly and because snoring is more common in this age group. Further research on the prevalence of OSAHS and its effects on the elderly population are needed.

1.9.3 Gender

It is estimated that 85% of OSAHS patients are male, however discrepancies in the male-to-female ratio exist between community-based and clinic-based studies. These were highlighted in a study by Redline et al (1994) who, using an AHI of 15 or greater as indication of OSAHS, found a ratio of 8:1 (male to female) in a laboratory sample of patients (n=36) compared to a ratio of 2:1 in a community-based sample (n=65). They also reported differences between the females in both groups, with the laboratory group

being younger and significantly heavier than the males, whereas the community sample tended to be older than the males and were made up of a majority of postmenopausal women (75%) with no differences being observed in BMI of the males and females in the community sample.

Bixler (2001) found that the prevalence of OSAHS was higher in postmenopausal women (2.7%) as compared to premenopausal women (0.6%). However, the premenopausal women were both younger and more obese than the postmenopausal women. Postmenopausal women using hormone replacement therapy (HRT) had a similar prevalence rate (0.5%) to premenopausal women, suggesting female hormones, especially progesterone, may reduce the risk factor of OSAHS, and that conversely the menopause may be a risk factor in females for the development of OSAHS. Testosterone in males may encourage adipose tissue in the neck, and these hormonal differences may account for the differences in prevalence in younger male and female subjects, with the prevalence differences reducing in older subjects, although females of all ages have less severe OSAHS then males. These differences may also include an effect due to the differences in symptoms being reported by males and females, with females reporting depression (Young et al 1997), insomnia and difficulty maintaining sleep (Ambrogetti et al 1991), more commonly than males.

1.9.4 Familial and Genetic Risk

In 1978 Strohl reported a family in which a father and his two sons had OSAHS, with another sibling demonstrating upper airway occlusion during sleep, but reporting no symptoms. This was amongst the first reports that suggested the OSAHS might have a genetic component.

Further evidence for a genetic link came in 1992 when Redline et al compared 29 families with known OSHAS to 21 control families with no known history of OSAHS. Two hundred and seventy two subjects (first degree relatives and spouses) underwent polysomnography and provided information on sleep and respiratory symptoms. Redline et al (1992) reported that the odds ratio (adjusted for age, BMI, and sex) of habitual snoring, apnoeas, and EDS were 1.34 (95^{th}CI 1.10, 1.62), 1.45 (1.14,1.86) 1.42

(0.91, 1.39) for those with a relative with OSAHS. These increased to 2.38 (1.34, 4.23), 3.08 (1.46, 6.83) and 2.89 (0.75, 2.68) for habitual snoring, apnoeas and EDS respectively, with 3 affected relatives with OSAHS.

In a second study Redline et al (1995) found that 13% of OSAHS relatives compared to 6% of a control group had AHI>5 with one major symptom of OSAHS. They calculated the odds ratios (adjusted for age, sex, race, BMI) of having OSAHS as 1.58 (CI 1.02, 2.45) with one affected relative to 3.97 (1.07, 14.7) with three affected relatives. Relatives of OSAHS patients were significantly older than the control group and the initial group of OSAHS patients were obese, and as these two variables are know to increase the likelihood of OSAHS, interpretation of these results must be cautious.

Douglas et al (1993) assessed 40 first-degree relatives of 20 OSAHS patients. To reduce the influence of the known inheritability of obesity, the OSAHS patient group (n=20) all had a BMI of <30 and were therefore not obese. Of the 40 relatives who underwent polysomnography 10 (25%) had an AHI > 15/hr. These 10 relatives were older than the 30 with an AHI<15 but were not more obese. Eight of the 10 affected relatives were described as loud snorers and 8 of the 40 relatives also had more than five 4% desaturations/hr. Although no control group were recruited for this pilot study, Douglas et al (1993) compared their data to data published by Stradling et al (1991). Stradling found that of 893 randomly selected middle-aged men who underwent polysomnography 45 (5%) had more than five 4% desaturations/hr compared to 8 of the 40 (20%) in the Douglas et al study.

In a follow up study, Mathur and Douglas (1995) provide data to suggest a genetic component to OSAHS. Mathur and Douglas conducted polysomnography on 51 first-degree relatives of OSAHS patients and 51 age, sex, height and BMI matched controls. Results showed that significantly more OSAHS relatives complained of snoring (27 relatives to 7 controls, $p<0.001$) and EDS (28 relatives to 16 controls, $p<0.01$) than controls. OSAHS patients also had significantly more apnoeas and hypopnoeas than relatives (13/h relatives (CI 3, 82/h) to 4/hr controls (0, 53/h, $p<0.001$). Relatives also had significantly more arousals from sleep (30/h vs. 17/hr) as well as more 2%

desaturations/hr (6/h vs. 3/hr p=0.04) and more 3% desaturations/hr (4/h vs. 2/h p=0.04).

Mathur and Douglas also measured cephalometry in OSAHS relatives and controls. The OSAHS relatives differed from the control group by having retroposition of the maxillae and mandible. Guilleminault (1995) also found differences in cephalometry of OSAHS relatives (n=22) and a control group (n=6). Although the population size is small, nonparametric statistical tests found significant differences in 4 out of 5 craniofacial measurements taken, with the author reporting these differences indicate a heritable morphological component.

Pillar and Lavie (1995) conducted polysomnography in 105 offspring of 45 OSAHS-confirmed patients. From this Pillar found 49 (47%) of offspring (36 men) had OSAHS (AHI >5), and of these 14 had an AHI >20. Twenty three (22%) were classified as simple snorers (snoring with AHI <5). On analysis of age, 10 women and 22 men under 35 had AHI>5<20 and 5 men had an AHI>20. The authors argue that the prevalence of OSAHS in the general population is around 1-4% and these data suggest OSAHS has a genetic component, although this study lacks a matched control group.

1.9.5 Anatomical and congenital disorders

As well as genetic risk, anatomical factors may have a role to play in OSAHS. Attributes such as retrognathia, micrognathia, and acromegaly (Hudgel 1992) physically affect the size of the mandible and therefore reduce the size of the upper airway, restricting ventilation. The soft tissues of the pharynx also affect the size of the upper airway, therefore hypertrophy of the tonsils, tongue, uvular or adenoids can also reduce upper airway dimensions (Schwab 1995). Lateral narrowing, defined as 'the presence of bands of tissue impinging into the observable posterior pharyngeal space' also occur (Schellenberg et al pg. 742, 2000).

Some medical conditions such as the Prader-Willi syndrome and Downs syndrome, in which obesity is a common problem, may contribute to anatomical predisposition of the syndrome. In Down's syndrome, macroglossia is a contributant to reduced airway size.

1.10 Treatment for OSAHS

The most common treatments for OSAHS can be divided into three treatment types- conservative, surgical and non-surgical treatments.

1.10.1 Conservative

Conservative treatment for OSAHS includes weight loss, as obesity, BMI ($kg/m^{2)}$ and neck circumference are associated with OSAHS. Weight loss has shown to be effective in some cases, with a case-report of one OSAHS patient who reduced his weight from 111kg to 85kg, reducing his AI from 59.6 to 3.1, effectively from severe OSAHS to the normal range (Browman, 1984). Smith (1985) also reported a reduction in apnoea frequency with weight loss, with 15 severe OSAHS patients reducing their mean body weight from 106.2 kg to 96.6kg and in turn reducing the mean apnoea frequency form 55 to 29, and attenuating the level of desaturation associated with the remaining apnoeas. However the AI frequency did not return to normal – but then neither did the weights.

Other conservative regimens also include avoiding sleeping in the supine position (Oksenberg 1998), the avoidance of alcohol as this can decrease neuromuscular tone in upper airway dilator muscles (Issa and Sullivan 1984) especially evening alcohol before bed (Engleman 1993). However, these conservative treatments tend to only have short-term benefits.

1.10.2 Surgical Treatments

As obesity is a risk factor for OSAHS, surgery for weight loss has been advocated. Several different surgical approaches including gastric bypass surgery and vertical banded gastroplasty have been utilised with this aim. Peiser et al (1984) studied 15 morbidly obese OSAHS patients before and between 2- 4 months after gastric bypass surgery. Weight loss associated with this surgery was augmented by a reduction in apnoea frequency, and this was further reduced at revaluation 4-8 months after the

surgery. Charuzi et al (1985) also found that gastric bypass surgery improved the polyhypnographic recording of 13 obese OASHS patients, increasing the time spent in stages 3 and 4 and REM sleep and improving the quality of breathing during sleep.
However, the long-term outcome of these types of weight reduction surgery is not encouraging with significant weight gain reported in several studies, (Charuzi 1992, Wolfel 1994, Ramsey-Stewart 1995). Pillar et al (1994) followed up 14 OSAHS patients who underwent weight reduction surgery and found that although the groups' AHI of 40/hr (SD 28.8) and BMI of 45/kg/m^2 (7.2) had been significantly reduced to 11 (16.4)/hr and 33 (7.5)/kg/m^2 respectively at 4.5 months after surgery. However at 7.5 years after surgery, AHI had significantly increased to 24 (23)/hr even though the mean BMI had risen only to 35kg/m^2.
While weight reduction is in itself advisable, these studies suggest that at least some types of surgical intervention to reduce weight, as a precursor to alleviating OSAHS, may not offer long term benefits.

The original surgical intervention to directly treat OSAHS was tracheotomy, a procedure that bypasses the obstructed airway and is a very effective treatment for OSAHS (Guilleminault 1981). However, tracheotomy is a very intrusive procedure and requires long term postoperative care, both of which are less than acceptable to patients.

Uvulopalatopharyngoplasty (UPPP) is a surgical approach originally used as a treatment for snoring. It was first described in 1981 by Fujita et al as a treatment for OSAHS. This procedure involves the surgical removal of the uvula and part of the soft palate, and was a common procedure in the early 1980's. However, there are doubts over the efficacy of this treatment as a cure for OSAHS (He 1988, Larsson 1991, Larsson 1994, Miljeteig 1994) and the improvement in SDB may be less than with CPAP therapy (section 1.9.3.2), (Sher 1996, Douglas 1997). As this treatment removes pharyngeal and palatal tissue, it is effective in reducing snoring, but as people with 'simple' snoring often develop OSAHS with advancing age, UPPP may not be ideal as a cure for snoring either, as evidence suggests that after the UPPP surgery OSHAS patients tolerate CPAP poorly and use CPAP significantly less than matched controls (Mortimore et al 1996).

This surgical treatment may provide subjective improvement in snoring and EDS (Miljeteig 1994) and may provide benefits to certain individuals (simple snorers, mild OSHAS patients) but is no longer as widely used as a treatment in OSAHS due to evidence of poor objective efficacy of this surgery at follow-up. Follow-up studies suggest that only 50% of patients operated upon have benefit to apnoeas and hypopnoeas after one year.
However a review of literature (Brigman et al 1997) has highlighted many methodological issues related to UPPP as a treatment of OSAHS, hence further investigation would be required to determine the suitability of UPPP.

Other surgical procedures may be performed on OSAHS patients where distinct upper airway abnormalities occur. These can include the removal of tonsils, adenoids, and nasal polyps. Reconstruction surgery; straightening a deviated septum, or advancing the mandible (Bear 1980) or hyoid bone (Riley 1993) for patients with retrognathia may also be employed. However once any surgical procedure is undertaken, especially when tissue is being removed, there is often no way to reverse the procedure and as such any surgical treatment for OSAHS and snoring should be very carefully considered.

1.10.3 Non Surgical Treatments

1.10.3.1 Pharmacological Therapy

Various drug therapies have been used in the treatment of OSAHS, a sample of which include:

- **Progesterone** is a respiratory stimulant, and it was thought that it may increase respiratory drive and as such increase pharyngeal tone. However Hensley (1980) and Hudgel et al (1998) did not find any improvement over placebo.
- **Protryptyline** is a trycyclic anti depressant and as a function of this drug REM sleep is suppressed. As many apnoea and hypopnoeas are REM sleep related it was postulated it would remove the long respiratory disturbances found in REM. Some success was noted by Clark, (1979) and Conway (1982), but the effects of protryptyline were not reproduced by Whyte et al (1988).

- **Acetazolamide** (a carbonic anhydrase inhibitor) has been shown to significantly reduce the number apnoeas from pre-treatment levels, although these were mainly central in origin (White et al 1982). In a randomised controlled trial (Whyte et al 1988) acetazolamide reduced the number of apnoeas occurring as compared to a placebo but did not significantly reduce symptoms of OSAHS, and paraesthesia was a common side-effect.
- **Modafinil** (provigil) is a novel wake-promoting agent originally designed to reduce excessive sleepiness in narcolepsy. It acts selectively through the sleep/wake centres of the brain believed to regulate normal wakefulness, without generalised CNS activation (www.provigil.com). It does not have any specific effect on sleep apnoea mechanisms and could only affect sleepiness, not vascular risk.

Arnulf et al (1997) conducted a randomised double blind crossover study and found that in 6 patients modafinil reduced objective sleepiness, increased the duration of subjective daytime vigilance and improves long term memory, without adversely affecting night time sleep or respiratory events. Pack et al (2001) conducted a randomised double blind crossover study and also found that modafinil significantly improved both subjective and objective daytime sleepiness as compared to a baseline test, and significantly reduced subjective EDS compared to placebo, again with no alteration of night time events.

Although Kingshott et al (2001) found no improvement in quality of life measures, Epworth sleepiness score or sleep onset latency in the MSLT in their randomised double blind crossover study, they did find that modafinil significantly improved alertness as measured by the MWT when compared to placebo. They also found that CPAP use was reduced in the modafinil limb (6.3h/n) as compared to the placebo limb (6.5h/n). Both Pack (2001) and Kingshott (2001) used modafinil in conjunction with CPAP treatment, and although further RCTs (randomised controlled trials) are needed to ensure modafinil does not reduce CPAP use, it may be a beneficial, if pricey, adjunct therapy for OSAHS which has not fully responded to CPAP therapy.

1.10.3.2 Intra-oral Devices

Dental splints and other intra-oral devices are a useful treatment for OSAHS and snoring. These devices, worn whilst sleeping, generally either hold the tongue forward or reposition the mandible to increase the area of the upper airway and therefore reduce obstructive events. These devices are often referred to as mandibular advancement devices (MAD) or mandibular repositioning splints (MRS), amongst other names. They are usually cast and fitted by dental professionals. Reported side effects include tooth discomfort, excessive drooling while sleeping and temporo-mandibular joint discomfort (Fritsch, 2001). Although CPAP treatment is currently the treatment of choice in OSAHS (Engleman 2002) these devices may play a role in treating simple snorers, those with mild OSAHS and patients who are unable to tolerate CPAP.

Stradling et al (1998) performed 2 overnight sleep studies in 15 patients already established on a MAD, with one night while using the device and one without using the device (in randomised order) and found that snoring episodes were significantly fewer whilst wearing the MAD (20/hr) than without it (193/hr). They also found a reduction in respiratory effort, suggesting an enlargement of the upper airway.

Cohen et al (1998) initiated 25 OSAHS patients (10 mild to moderate OSAHS AHI<21, and 15 moderate to severe) on a dental splint. Treatment was regarded as successful if the AHI was <5 while using the dental device. After 2 weeks, polysomnography was once again performed and they found that 9 of the 10 mild –moderate patients and 9 of 15 moderate-severe patients had AHI<5. Both these studies were short term and had no control group, but may support dental splints as effective tools for treating snoring as well as mild and possibly even moderate and severe (Cohen 1998) OSAHS.

Randomised control trials using active and placebo (not protruding the mandible or tongue, hence no effect on OSAHS) devices, also suggest they may have a role to play in the treatment of OSHAS. Johnston et al (2002) found that AHI was significantly reduced in the active MRS period, although the OSAHS with severe OSHAS did not find them as effective. Gotsopoulos (2002) also used a placebo oral device as a control for active MRS and found that both the sleep onset latency of the MSLT and the

Epworth sleepiness score were significantly better than on the control limb. Again these studies suggest that MRS devices may not only help normalise AHI but are effective in treating daytime symptoms too. Mehta et al (2001) also used active and placebo dental devices and found that in 28 patients, 15 patients had a reduction in AHI frequency less than or equal to 50%, with the AHI remaining over 5, and nine had a reduction in AHI to less that 5/hr with the active MRS device.

Randerath (2002) in a randomised crossover trial of a dental splint and CPAP, found that initial use of both treatments reduced significantly reduced AHI and arousal frequency from their untreated baseline levels, but after six weeks of treatment only CPAP maintained these levels, although 30% of the dental splint group maintained their AHI < 10. Randerath also report that patients found the dental splint easier to use. Ferguson et al (1996) also conducted a randomised crossover trial comparing CPAP and a dental splint to investigate the efficacy of treatment and patient preference. Each treatment was used for 4 months and results showed that AHI was significantly lower in the CPAP limb as compared to the dental device (3.5 SD 1.6 and 9.7 SD 7.3). In the dental device limb 12 patients showed AHI <10 and 6 an AHI>10 while 6 did not use the treatment. In the CPAP limb 13 patients had AHI<10, 4 refused to wear CPAP after the dental splint limb, and 8 were compliance failures. Overall side effects were more common with CPAP and patients were more satisfied with the dental device.

These results may indicate that although CPAP seems to be more effective in reducing AHI long term, dental devices may be an effective tool for reducing AHI to less than 10/hr in a subset of device users, and so may be beneficial for mild OSAHS patients or those who will not tolerate CPAP.

However Engleman et al (2002) compared CPAP to an MRS device in an RCT and found that CPAP produced significantly better effects than MRS for AHI frequency, symptom score, subjective daytime sleepiness, as well as measures on the Functional Outcomes of Sleepiness Questionnaire (FOSQ) and the SF 36 questionnaire of health status. Patients also reported CPAP as a more effective treatment, but there was no difference in treatment preference. This held also for mild OSAHS (AHI<15).

These results imply that CPAP is more efficient long-term treatment for more patients with OSAHS. Engleman (2002), provided evidence that even mild OSAHS patients find CPAP more effective, although long term use in mild OSAHS patients may be poor (McArdle 1999). As such, dental devices may be best used as a first line treatment in simple snorers and patients opposed to using CPAP, and as a reserve treatment for those patients who cannot tolerate CPAP.

Further evidence is required, and more randomised trials are required to determine the long-term efficacy of dental appliances compared to both CPAP and conservatively treated patients, any future trials should investigate patients with all severity levels of OSAHS and include measurements of nocturnal events, and both objective and subjective daytime symptoms. One should note that there are a variety of different types of dental devices and positive results from studies involving one type of device that provide evidence that it is an effective treatment for OSAHS does not necessarily mean all dental devices will be effective.

1.10.3.3 Continuous Positive Airway Pressure (CPAP)

Maintaining optimal area in the pharyngeal lumen is dependent on balancing the negative pressure caused by narrowing forces, primarily inspiration, and the positive pressure caused by dilating forces, principally the pharyngeal muscles. As explained above, during obstructive events the equilibrium of this pressure balance is disrupted, probably due to the hypotonia of the pharyngeal muscles making them unable to counteract the negative pressure. This pressure imbalance causes the tongue and soft palate to be sucked towards the oropharyngeal wall and this can cause substantial area reduction (hypopnoea) or complete occlusion (apnoea) in the pharyngeal lumen. The continuous positive airway pressure (CPAP) machine is a flow generator that blows air into the upper airway via a well-fitted, leak free nasal or oro-nasal mask. At optimal pressure, which is different in each OSAHS patient, the positive pressure acts as a pneumatic splint by counteracting the negative pressure caused by inspiration; this restores the pressure equilibrium in the upper airway and abolishes airway collapse, snoring, apnoeas and hypopnoeas and the subsequent arousal they bring (Sullivan 1981).

First developed by Sullivan et al (1981) in the early 1980s, CPAP has become widely used in the treatment of OSAHS. Studies conducted in sleep laboratories have provided evidence that after even only one night's use of this treatment, CPAP is effective in abolishing nocturnal events including: apnoeas and hypopnoeas, (Sanders 1984, Lamphere et al 1989) improving arterial oxygen saturation (McEvoy and Thornton, 1984, Bonsignore et al 1987), abolishing snoring (Berry and Block 1984), reducing EEG arousals (Sforza 1993, Fietze, 1997,) and restoring sleep architecture (Issa and Sullivan 1986, McArdle et al 2001b). There is a good body of evidence to support CPAP as a treatment that is able to alleviate the nocturnal features of OSAHS, and as such there is a general acceptance that CPAP is the treatment of choice for OSAHS.

However as previously indicated OSAHS patients have a range of symptoms and features associated with the condition. The ASDA (American Sleep Disorders Association) have recommended that diagnosis of the condition should be based on nocturnal events and daytime sleepiness (ASDA 1999). This is a significant point, a person is classed as having obstructive sleep apnoea/hypopnoea when nocturnal sleep is disturbed by respiratory events, but patients are only classed as having the obstructive sleep apnoea/hypopnoea syndrome if symptomatic. Therefore any treatment used for OSAHS should both eliminate nocturnal events and the daytime features of the condition, by reducing EDS and improving daytime performance and quality of life measurements.

Many studies have been conducted to investigate the potential of CPAP in alleviating the daytime features of the condition. Both Kribbs et al (1993a) and Sforza (1995) evaluated OSAHS patients after one year of CPAP use. Kribbs (1993a) found as well as a significant reduction in RDI (56.6 /hr to <5) to a level which was considered non-pathological that 15 OSAHS patients performed significantly better on both the MSLT and PVT after one year, and the subjective sleepiness score was also lower as compared to pre-treatment levels. At one year patients also underwent one night without using their CPAP therapy and there were significant increases in both AHI and MSLT and subjective daytime sleepiness. The reaction times recorded from the PVT also increased although not significantly. Sforza (1995) compared 30 OSAHS patients

(AHI 74.4 (SEM3.0) before and after 1 year of CPAP (mean CPAP use 6.2hrs/night), who as with the Kribbs (1993a) study, underwent one night using CPAP and one night without and completed the MSLT on each consecutive day. Again CPAP improved patients sleep architecture, sleep continuity and alleviated apnoeas. Pre-treatment MSLT mean sleep onset latency was 3.1minutes, at one year. Using CPAP this had significantly risen to 9.8 minutes, and in turn decreased significantly to 5.3 minutes after only one night without using CPAP. CPAP at one year had also improved subjective sleepiness. Sforza also compared patients whose MSLT score was still pathological (<10minutes) to those who were not (>10minutes) and found that those scoring >10minutes had a higher AHI at baseline, had a greater level of improvement of hypoxaemia and used CPAP more. This study confirms the results of Kribbs and reinforces that CPAP not only alleviates nocturnal features but daytime features also. As reported previously CPAP has been shown to have immediate effects on sleep quality after only one night of use, the Kribbs and Sforza studies however reinforce that CPAP is a therapy and not a cure, as reflected in the immediate reversal of many features, after only one night without use.

Investigation in to the time needed for CPAP to produce optimal effect was conducted by Lamphere et al (1989) looking at the effect of CPAP on sleep architecture, respiratory disturbance and MSLT at one day, 12 days and 42 days after commencing the therapy. Thirty-nine OSAHS patients with a mean age of 50.1 years (SD 11.6) underwent nocturnal PSG and 13 OSAHS patients were randomly assigned to each follow-up group. The three groups were not significantly different at baseline for any of the parameters measured.

Sleep architecture was restored (reduction in stage one and increase in all other stages) after only one night on CPAP and no further improvements were noted at 12 or 42 days. The mean respiratory effort index for the three groups at baseline was 73, falling to 22 after one night of CPAP, to 17 after 12 nights of CPAP and 7 after 42 nights of CPAP, which effectively changing the group status from severe OSAHS to no pathology whilst using CPAP. Baseline MSLT results were not significantly different in the three groups ranging from 3 to 4 minutes. After one night of CPAP the sleep latency were significantly improved to six minutes, and further improvement was found

at 14 days to 9.6 minutes. No further improvement was found 42 days. This early study provides evidence that CPAP is able to alleviate many symptoms of OSAHS after just one night; further benefits of the therapy are seen after a few weeks.

Kingshott et al (2000) incorporated all areas measured in the above studies by evaluating, sixty two patients' (mean age 51 SD11) baseline results of nocturnal variables, cognitive performance, quality of life and objective daytime sleepiness after 6 months of CPAP therapy. They found significant improvement in nocturnal variables including AHI (62 SD 33 to 9 SD7 $p<0.0001$), arousals (63 SD 30 to 21 SD12 $p<0.0001$), percentage of REM sleep (15 SD 8 to 26 SD 15 $p<0.0001$). Significant improvements (all at the level $p<0.01$) were found in the MWT (27 SD 13 to 32 SD 10), ESS (13 SD 5 to 6 SD 4), symptom score (24 SD 7 to 9 SD 7), digit symbol test (53 SD 11 to 56 SD 13), PASAT 2 sec (22 SD 11 to 37 SD 13), simple RT (0.32 SD 0.09 to 0.29 SD 0.04) as well as significant improvements in all 8 subscores of the SF-36. Kingshott et al provided intensive support for CPAP treatment by contacting patients on days 2 and 21 as well as seeing patients in an outpatient clinic at months 1, 3 and six, and the mean CPAP use for the six months was 4.8 (SD 2.4) per night.

These studies suggests that CPAP can alleviate both nocturnal and daytime features of OSAHS after only one night of treatment, that the optimal benefit of CPAP may only be found with continued use and that these benefits are still appreciable at six months to a year, however only one night without CPAP therapy can see deterioration on symptoms associated with OSAHS.

However none of these studies incorporated an adequate control group and the results of these studies may in part be influenced by placebo effects. As such these results should be interpreted with caution. Nevertheless they do indicate that improvements of symptoms are reported with CPAP even after relatively short periods of use.

Controlled trials are seen as a more robust design of investigation and several research groups have employed these in investigating CPAP and its effect on daytime function.

Engleman et al have produced several RCTs investigating the role of CPAP in cognitive and QOL outcomes. An early study (1993) comparing 21 CPAP treated OSAHS (mean AHI 57/hr) to 16 conservatively treated OSAHS patients (mean AHI 45/hr) in a parallel trial design. Engleman et al reported that moderate improvements in objective daytime sleepiness were recorded in the CPAP treated patients compared to the conservatively treated patients, all re-tested after three months. However both groups showed significant improvement in cognitive and QOL measures that were not significantly different from each other. This highlights the need for controlled trials. On looking at good compliers on CPAP (mean use of >4.5 hrs/night) as compared to the conservatively treated group, the CPAP group again showed decreased levels of objective sleepiness and an improvement in mood. However in other domains improvements were reported in a four-week cross over trial of CPAP and oral placebo Engleman et al (1994a). This reported that symptom complaint, objective and subjective daytime sleepiness and levels of snoring were significantly better at the end of the CPAP treatment limb than on placebo. Further, cognitive function, vigilance and general health and depression scores were also significantly better improved in the CPAP limb. Although several of these tests showed learning effects, the study used a randomised treatment order to control for these effects on treatment analysis. Some of these improvements seen with CPAP have also been reported in mild OSAHS (5-15 AHI/hr) (Engleman et al 1999). In a crossover trial of CPAP and oral placebo 34 patients, despite a relatively low mean usage of 2.8/h night (SD 2.1) CPAP significantly improved symptom score, subjective ESS, two of seven cognitive function tasks, depression scale and five of eight domains on the SF36 in 14 with and AHI <10/hr of the sample. However patient preference was higher for the oral placebo.

These studies using oral placebo or conservative control methods highlight improvement in mild to severe OSAHS patients in sleepiness (objective and subjective) and in a variety of cognitive tasks and QOL outcome measures.

Stradling et al (2000) compared the effect of CPAP and sub-therapeutic CPAP on daytime symptoms. Sub-therapeutic CPAP (also known as sham CPAP) is achieved by setting a CPAP machine to its lowest setting (<2 cmH_2O) and by increasing the number of holes on the CPAP mask. Hence the pressure received by the patients is not of a

level that can prevent apnoea and hypopnoea. Using a CPAP machine that does not have any therapeutic effect quantifies placebo effect (as patients are unaware that it is not an active treatment). Stradling et al, using a parallel study design compared both subjective (ESS) and objective (modified MWT) sleepiness and two outcome measures of the SF36 vitality and energy and the mental component summary score, pre-treatment and after 29 days of CPAP or sham CPAP. The authors report that the sham CPAP had no effect on nocturnal sleep apnoea activity. Both groups significantly improved in subjective sleepiness, and on both the SF36 factors, but the therapeutic CPAP produced a significantly greater improvement over the sham CPAP. Only the therapeutic CPAP group improved significantly on the objective measure of sleepiness.

Jenkinson et al (1999) used a similar study design to compare CPAP and sham CPAP effects on subjective (ESS) and objective sleepiness (MWT) as well as the SF36 questionnaire. The results obtained were similar to that of Stradling (1999), with the sham CPAP group showing small but significant changes in subjective sleepiness, and the therapeutic CPAP group reporting significantly improved ESS scored compared to their baseline and to the sham CPAP group post-treatment. The authors also report only the therapeutic CPAP group showing significant improvement in objective sleepiness. The SF36 results showed significant improvements in all 8 domains and the two summary scores in the therapeutic CPAP group. The sham CPAP group showed significant improvements in the mental health and vitality domains as well as in the mental and physical component summary scores.

Montserrat et al (2001) also used sham CPAP and CPAP to compare subjective measures of sleepiness (ESS), OSAHS symptoms and outcomes on the SF36 and FOSQ. Both groups showed significant improvement in subjective sleepiness, OSAHS related symptoms and sub-scores of both the SF36 and FOSQ questionnaires as compared to their baseline levels, however the therapeutic CPAP group showed significantly greater improvement in ESS score, OSAHS related symptoms and general productivity and vigilance scale on the FOSQ questionnaire. After a wash out period of 10 days the sham CPAP group were established on therapeutic CPAP and a greater improvement in ESS and OSAHS related symptoms was found than when using sham

CPAP, and these results were similar to those obtained from the original therapeutic CPAP group.

These studies suggest that CPAP is in fact a suitable treatment for alleviating objective and subjective daytime sleepiness as well as perceived health benefits. However they indicate that placebo effects may play a part in the perceived subjective improvement of symptoms associated with CPAP, and as such results from trials not adequately controlled, may inflate the subjective improvements in reported symptoms.

Other research groups conducting questionnaire-based studies have shown that CPAP produces subjective improvements on ESS (Engleman 1994a, Engleman 1999, Ballester 1999, Keily 1999) OSAHS related symptoms, (Ballester 1999, Engleman 1999), quality of life, (Jenkinson 1997, Weaver 1997a, Ballester 1999, Monasterio 2001) and daytime function (Ballester 1999, Engleman 1999). However some studies looking at objective daytime sleepiness and/or cognitive ability have found that although these may improve with CPAP many patients' scores do not return to normal levels. Bedard et al (1993) suggest that although CPAP significantly improves daytime vigilance some patients remain more somnolent by comparison to control groups, and some cognitive tests, especially those relating to executive functions and manual dexterity still show deficits. Bedard et al hypothesised that persistent cognitive deficits and daytime somnolence may be a result of long-term hypoxaemic effect on the brainstem, and as such would not necessarily be reversed the introduction of CPAP.

Valencia-Flores et al (1996) investigated cognitive function and daytime vigilance in OSAHS patients with varying degrees of hypoxaemia (as measured by oxygen desaturation levels during sleep without treatment). OSAHS patients were tested on a battery of cognitive tasks and a single sleep latency test before and after the commencement of CPAP. The authors grouped patients that showed increased alertness into baseline non-hypoxaemic and baseline hypoxaemic samples. They report that OSAHS patients who showed no signs of hypoxaemia at baseline showed greater improvement on some cognitive functions as compared to those OSAHS patients with hypoxaemia. Suggesting that OSAHS patients free from hypoxaemia performed poorer at baseline on the cognitive tests due to their hypersomnolence,

whereas the hypoxaemic groups deficits were thought to be a combination of both somnolence and hypoxaemia.

Both the Bedard and Valencia-Flores studies have limitations in that both used small patient samples and neither used control groups. The Valencia-Flores study was conducted after only two nights of CPAP therapy and the Bedard study after only six to ten months, hence one cannot rule out the reversal of these deficits after a longer period of treatment. However both do report that improvements are seen whilst using CPAP even if scores do not return to levels expected when no pathology exists.

It is important to note that in many of the studies mentioned not all of the daytime symptoms associated with OSAHS were improved to normal levels by CPAP. This may in part reflect the different study designs, level of sleep-disordered breathing in the patients, the test used to measure sleepiness, cognitive function and daytime function, or other confounding variables like hypoxaemia. Nevertheless these studies conducted into the efficacy of CPAP do consistently show that CPAP is effective in reducing levels of both objective and subjective daytime sleepiness and that subjective measures of quality of life are also improved.

One aspect that affects the effectiveness of CPAP is patient compliance. Compliance is a generalised term for patients' adherence to their medical practitioner's advice and prescription. Compliance can be measured in frequency terms as the proportion of patients who undertake the regime i.e. 40% of a sample, or on an individual basis as a proportion of the recommendation observed, i.e. patients take drugs only 70% of the time.

Compliance with CPAP can thus be defined as the percentage of OSAHS patients using their machine at the optimal level or as the average nightly use of a given period of time. This is possible as most CPAP machine have time clocks that can record the run time of the CPAP. Many of the newer models of CPAP also have the ability to record the time that the CPAP mask was worn, the time at optimal pressure. Prospective studies using both objective and subjective measure (with a range of CPAP use from 1month to 2 years), report levels of compliance ranging from a mean use of

2.5hrs/night to 6.5 hrs/night (Krieger 1988, Krieger 1992, Kribbs 1993b, Rauscher 1993, Engleman 1994b, Pieters 1996, Meislier 1998, Hui 2001, Lewis 2004).
The proportion of patients still using CPAP at 3-14 months issued with CPAP range from 60 to 80% of populations sampled (Waldhorn 1990, Kreiger 1992, Kribbs 1993b, Meslier 1998, Pepin 1999). The use of the CPAP machine in the first to third month is a good indicator of long term use (Kribbs 1993b, McArdle 1999) and good long term compliance has been associated with pre-treatment OSAHS symptomology (Meurice 1994), high pre-treatment AHI (Kreiger 1992), intensive support (Chervin 1997, Hoy 1999), living with a partner (Lewis 2004), and no or few side effects associated with CPAP in the first month (Lewis 2004). CPAP related 'side effects' can included mask discomfort, nasal congestion or dryness, as well as discomfort caused by wearing the mask straps to tight, mask leak and noise from the machine. Most of these problems are easily rectified and as such initial support from trained sleep specialist staff is recommended. It should be noted that subjective use of CPAP might be over reported (Kribbs 1993b, Rauscher et al 1993) and as such compliance rates may be more accurate when based on objective data.

Measures of compliance with CPAP are more easily audited than those with other treatments, for example pharmaceutical therapies. However, while suboptimal, CPAP use may not be substantially different from patients' use of other treatments. It is important to recognise that 40 to 50% of patients do not use medications as prescribed (Ley et al 1998). 70% of patients with obstructive lung disease did not adhere to their drug regime (Rand et al 1992) and anti-epileptic medication was used correctly in only 39% (3248 days) of days observed in other studies (Cramer et al 1989).
In recent years CPAP technology has advanced and new auto titration machines are now available. These machines do not give a fixed pressure but are able to provide variable positive pressure to the upper airway in response to apnoeas, hypopnoeas and snoring. Fixed pressure machines are set at the highest pressure required to eliminate the majority of events but low enough not to cause mask leak and irritation. The auto titrating machines detect each episode of airflow limitation and this is counteracted with the optimal level of pressure, which can vary from episode to episode. This means during periods of no airflow limitation that the pressure can be reduced to a minimum and can ramp up when required.

Comparisons of patients treated with fixed pressure and variable pressure CPAP machine have found that there are no significant differences in the AHI, snoring, sleep fragmentation, subjective sleepiness, or compliance between the two treatments (Ficker 1998, Ayas 2004, Hussain 2004, Noseda 2004). Some studies also suggest that mean or median pressure is lower and nightly hours usage of the variable machine is higher than fixed CPAP (Hudgel 2000, Teshler 2000, Massie et al 2003). As the cost of variable CPAP is currently substantially higher than fixed pressure CPAP, its usage may be most cost effective for using for CPAP titration, research and in patients who have severe difficulty in tolerating fixed pressure.

The efficacy of CPAP has been questioned in an early systematic review (Wright 1997). However since this publication several adequately controlled trials have demonstrated that CPAP can alleviate both the nocturnal and daytime features of OSAHS. Recent systematic reviews (Cochrane review 2001, SIGN guidelines 2003) have shown a growing evidence base that CPAP improves nocturnal and daytime features of OSAHS. Evidence exists that the effects of CPAP can be immediate, and failure to use the treatment can see the symptoms of OSAHS return quickly. It has been shown to reduce mortality compared to non-treated patients (Partinen 1988, He 1988, Marti 2002) and overall compliance with this treatment is good and as such there is justification for CPAP as the treatment of choice for OSAHS.

CPAP and its effects on driving ability are discussed in chapter two and six.

1.11 Discussion

OSAHS is a multi-factorial condition with both nocturnal and daytime features. It is a common condition with wide reaching implications physiologically psychologically and socially and it's impact and on these is not completely understood. Treatment for the condition is primarily CPAP although some surgical procedures and intra-oral devices may be more acceptable for patients with simple snoring or mild OSAHS. CPAP is an effective treatment, however with 10-16% of patients refusing it after their CPAP titration (Waldhorn 1990, Krieger 1992), and its ambiguous use in mild OSAHS patients further research must be conducted to find a better treatment that is acceptable to all OSAHS, and ideally finding a cure would be desirable in the long term.

Chapter 2: OSAHS and driving ability

2.1 Introduction to OSAHS and driving

Patients with OSAHS have high rates of motor vehicle accidents (MVAs) (Findley et al, 1988, George et al 1999) and impaired driving performance (George et al, 1987). This section aims to both review data on real life and simulated driving performance, and discuss the need for objective fitness-to-drive tests. This review covers literature and published data to 1999, when the current study was designed.

2.2 Aspects of OSAHS impairing driving

OSAHS patients suffer from a wide range of daytime problems, such as sleepiness and impaired concentration, which may affect their ability to perform tasks necessary to daily life. These problems include; attention and visuo-motor performance (Greenberg 1987), memory (Berry et al 1986), intellectual performance (Telavaki et al 1986), impaired executive functions (Naegele et al 1995), impairments in tracking and reaction times (George et al 1996b), time-on-task deficits (Dinges and Kribbs 1991) and difficulty in concentrating (Greenberg 1987).

It is not yet clear whether these deficits are the product of the sleep fragmentation, hypoxaemia, or both of these. It is most likely a combination of the two. Studies have shown that disturbing sleep with noise induced arousals can produce sleepiness and deficits in daytime performance, even after only one night (Martin et al 1996). However, daytime function correlates better (although still relatively weakly) with the degree of nocturnal hypoxaemia, rather than the frequency of arousals (Bennett 1999, Kingshott et al1998).

Regardless of the actual mechanisms causing these performance deficits, it may be the interaction of impaired daytime abilities and severe sleepiness that increases the risk of motor vehicle accidents in OSAHS sufferers. The safe operation of a motor vehicle requires alertness, accurate perception, and the ability to judge and react rapidly and

effectively to external factors. OSAHS patients suffer from both excessive daytime sleepiness and perform poorly in neuropsychological tests, especially those requiring a high degree of vigilance and concentration (Bonnet 1985). Therefore, they might be expected to be at an increased risk of involvement in motor vehicle accidents and have more near-miss accidents.

2.3 Driving impairment due to sleepiness

OSAHS patients have poor driving abilities, with an increased number of motor vehicle accidents and, reports of feeling sleepy and falling asleep at the wheel. Several studies have shown that sleepiness is a major factor in Motor Vehicle Accidents (MVAs) that occur in the general population.

McCarrt (1996) conducted random telephone interviews, enquiring about sleepiness and MVAs, with 1000 New York residents. Twenty three percent reported that they had at some point fallen asleep whilst driving, while 2.8% reported a MVA that was a direct consequence of having fallen asleep. This was similar to the results of Maycock (1997) who reported that, of 4621 males that responded to a questionnaire survey in England, 29% admitted to falling asleep at the wheel in the last year. He also reported that 17% of this population admitted to having a MVA, and tiredness was a contributory factor in 20%, 14% and 7% of accidents occurring on motorways, rural roads and roads in built up areas, respectively.

In studies, the proportion of accidents attributed to sleepiness has ranged from 1-27%. For example, Maycock (1997) estimated that tiredness accounted for between 9-10% of all accidents reported whereas Parsons (1986) reviewed 223 unexplained MVAs and concluded that 27% of these were sleep-related. Parsons also noted that falling asleep at the wheel caused 83% of those deaths attributable to trauma.

Further evidence comes from Horne et al (1995). They conducted two studies assessing whether accidents had been caused by the driver falling asleep. From the first study, which included one motorway and several major and minor roads, they

found that 606 sleep-related accidents accounted for 16% of all accidents reported in a 5-year period. In their second study (1995), police attending the scene of accidents completed a short structured sleep questionnaire, regardless of whether the officer believed sleep was a contributory factor in the accident. On analysis they found that 73 accidents were sleep-related, which accounted for 23% of all the accidents to which the police were called.

It has been suggested that accidents caused by sleepiness account for between 1-3% of MVAs in the USA (Pack 1995, Lyzniki 1998). Unfortunately, these sleep-related accidents seem to be more serious and more often result in high casualty rates. Pack (1995) estimated that 3-4% of all fatal accidents are sleep-related. This is similar to the estimate of Summala and Mikkola (1994) who reported that 7% of all fatal accidents in Finland were due to the driver having fallen asleep, and 3% were due to driver fatigue. Mitler et al (1988) estimated this rate to be even higher in the USA, at 13%.

Further, Benbadis et al (1999) examined subjective sleepiness levels in a driving population in the USA. Using the Epworth sleepiness score (ESS) they found that of 526 drivers, with a mean age of 37 (SD 15), 26% had an ESS score over 10, and 2.5% had an ESS greater than 15. This suggests that a quarter of this driver population reported subjective sleepiness that could be considered pathological in terms of being well above the 95th centile of Epworth Score (Johns 1991,1993). These studies examined sleepiness as a predictor of accidents, but did not separate sleepiness from likely OSAHS when assessing overall accident rates.

2.4 Characteristics of crashes caused by sleepiness

Accidents caused by falling asleep at the wheel are associated with a high mortality (Pack 1995). This high fatality rate in sleep-related accidents is not surprising given that drivers who have fallen asleep will be unable to brake before an impact or before leaving the road, and so will crash at a greater speed (Horne 1992). Investigators at accident sites can often attribute these fatal crashes to sleepiness by the lack of skid

marks at the crash site (Pack 1995), although antilock braking systems complicate this interpretation.

It has also been suggested that as a consequence of falling asleep, a driver is more likely to cross the edge of the lane onto the verge rather than veer into the path of oncoming cars. This theory is supported by Sagberg (1999) who found that over 40% of sleep-related accidents resulted in deviation off the road while 15% resulted in crossing the centre line. Both Pack (1995) and Garder (1995) also support this suggestion. Pack found that in accidents related to sleepiness most were drive-off-the-road type (78%), and Garder (1995) found that 62% of a random sample of motorists and student drivers reported that on occasions when they fell asleep while driving, they had at least one pair of wheels off their lane on waking, with the majority of these being the offside wheels.

Where sleep is involved, these driving-off-road events are probably more common than other types of crash due to the typical transverse section characteristics of most roads, which incorporate a camber. This design is used for water drainage and, therefore, the elevation is higher at the centre line of the road and lower at both edges. Hence, a car travelling at speed will follow the natural incline of the road and veer towards the edge if no steering correction is applied (Sagberg 1999)

Although these studies were not specifically investigating driving accidents in OSAHS sufferers, they are important. They clearly implicate sleepiness as a major cause of MVAs in the general population, and as sleepiness is often a major symptom in OSAHS patients, it suggests that sleepiness plays a large part in MVAs in OSAHS patients.

2.5 Evidence of driving impairment in OSAHS.

In an early study using self-report, Guilleminault et al (1978) found that most of their sample of 50 OSAHS patients reported falling asleep whilst driving, while 54% admitted to having an accident due to falling asleep at the wheel. This study was amongst the first to create awareness among doctors and researchers that these road accidents could be a potential source of morbidity and mortality in OSAHS patients. However, as

this study did not use a control group it is impossible to say with confidence that the levels of sleepiness and accidents were elevated.

George et al (1987) used objective accident data obtained from the regional department of motor vehicles to compare the MVA rates of 27 OSAHS patients and 270 age and sex matched controls, randomly chosen from the database. They found that 54% of the controls compared to 93% of the patients had at least one accident and the mean number of accidents was 2.63 for OSAHS patients, twice that of the control (1.28). Unfortunately, in their letter to the Lancet, the authors do not report the period of time covered by the motor vehicle records. Additionally, seven of the patients had not had their diagnosis of OSAHS polygraphically confirmed, but were included in the analysis on the basis of symptoms alone. In fact, the authors' note that if these patients did have another sleep disorder then the results would lose significance.

Findley et al 1988 found that OSAHS patients (AHI >5) had a rate of MVAs seven times greater than patients attending the sleep centre who did not have OSAHS (AHI <5). Specifically, 0.41 accidents per driver per five years in the OSAHS group compared to 0.06 in the control group. Findley et al also found that the rate of accidents in which the driver was at fault was significantly higher in the OSAHS group (0.24 /driver/ 5 years) than the control group (0.03 /driver /5 years). Further examination of the distribution of accidents showed more OSAHS patients (31%) had at least one MVA in the five-year period compared to the controls (6%). This suggests that it was not merely a small sub-sample of the OSAHS patients who were having a large number of accidents.

Findley et al were also able to compare the accident rates of these two groups to those of the 3.7 million drivers in the state of Virginia. Again they found the OSAHS group had a significantly higher MVA rate than the normal population in a five-year period (0.41 compared to 0.16 per driver). However, the non-OSAHS patient control group had significantly fewer accidents than the licensed drivers of Virginia.

A further control group (n=30) was obtained and matched to the OSAHS patients for age and sex. The OSAHS group reported significantly higher frequencies of falling asleep at the wheel than all three of the other groups. 67% of the OSAHS patients admitted falling asleep at least once when driving, whereas only 38% of patients without

sleep apnoea and 30% of the age and sex matched control group reported this. More striking was the difference in the number of OSAHS patients admitting to falling asleep at least once a week when driving (24%) as compared to the patients without sleep apnoea (3%) and the control group (0%).

In an extension to this study Findley et al (1989a), still using objective accident data, recruited 44 patients with OSAHS, who were classified as having mild (n=16), moderate (n=17) and severe (n=13) OSAHS on the basis of the severity of their nocturnal hypoxaemia. They compared the MVA rate of these three groups to that of all licensed drivers in the state of Virginia and found that all three groups of OSAHS patients showed at least a two-fold rise in motor vehicles accidents compared to normal controls. However, only the severe OSAHS group had a statistically significantly higher rate of MVAs than the Virginia drivers (0.46 vs. 0.16 accident/driver/5 years). The authors suggest that patients with severe OSAHS are at particular risk. Although this study did use objective measures of MVA the small number of OSAHS patients and the lack of a dose response across the severity groups weaken the support for this conclusion.

Aldrich (1989) and Cassel et al (1990) add further support to the proposition that patients with more severe OSAHS may be at increased risk of MVAs. Aldrich (1989) compared reports of sleep-related accidents in patients with an AHI of less than 60 an hour to those with more than 60 an hour. The more severe patients were twice as likely to have had a sleep-related MVA (30% for men and 20% for women in the severe group) as the moderate group (15% for men and 12% for women).

Cassel et al (1990), using a questionnaire administered prior to diagnoses of OSAHS, found that patients with severe OSAHS, defined as an apnoea index (AI) greater than 20 (n=31) and moderate OSAHS (AI 5-10, n= 31) reported fatigue while driving significantly more often than patients without OSAHS (AI 0-5, n=10). Although there were no significant differences in the average mileage of the three groups, those patients with an AI greater than 5 also reported falling asleep at the wheel at least once a week more than non-OSAHS patients. In addition, the non-OSAHS group reported only three accidents and none of these were attributed to EDS whereas patients with an

AI greater than 5 reported 14 accidents; 11 of which were attributed to EDS. When asked whether they had reduced the amount they drove in the preceding few years, and the associated reason, none of the OSAHS patients gave EDS as a reason for driving less. In fact, the mean distance driven by the three groups, 23,200 km/year was higher than the German average at that time (15,000 km/year), and the severe OSAHS group reported driving a mean of 26,400 km/year.

Although there are large differences in the thresholds for sleep-disordered breathing events used to define OSAHS in these studies, they complement each other as they report increased driving problems as the severity of the condition increases.

In a larger study conducted by George and Smiley (1999) driving records of OSAHS patients were compared to those of age and sex matched controls, randomly selected from the Ministry of Transportation of Ontario (MTO). Four hundred and sixty OSAHS patients, all confirmed by polysomnography, were divided into three groups; AHI 10-25, AHI 26-40 and AHI>40, and were compared to 581 controls extracted from the MTO database. On analysis of the accident rate, 155 of the OSAHS patients and 150 of the controls had one or more accidents in the preceding five years, giving an accident/year for the preceding five years as 0.09 compared to 0.07 for the control group. However, this small yet significant difference was accounted for entirely by the accident rate in the AHI>40 group (0.11 MVA/year) as the accident rate in the AHI 10-25 group (0.06 MVA/year) and AHI group 26-40 (0.08 MVA/year) did not differ significantly from that in the control group.

The number of driving related citations for both OSAHS patients and controls was also analysed. Citations were given for a variety of reasons including speeding, unsafe driving, failure to stop, improper turns and driving whilst intoxicated. Two hundred and seventy two OSAHS patients had one or more citations as compared to 240 of the controls (x^2 =32.7, $p<0.001$), and OSAHS patients had twice as many citations (1.74 SD 3.13 vs. 0.86 SD 1.43 $p<0.001$) as the control group.

Although this study estimates a slightly smaller accident rate than their previous study, George and Smiley did use polysomnography to define the severity of these patients.

The results are thus comparable with those of Findley et al (1989a) and Aldrich (1989) who indicated higher accident rates in OSAHS. It also suggests that the higher MVA rate seen in OSAHS patients may mainly arise in the more severe patients. Additionally, the greater number of citations in the patient group also lends support to the hypothesis that OSAHS patients have poorer driving performance than controls- even when the measure is not solely accident rate.

Teran-Santos et al (1999) conducted a case-control study to investigate the relationship between sleep apnoea and MVA risk. They found that drivers in accidents sufficiently severe that they received emergency treatment at hospitals in Burgos or Santander, Spain were more likely to have sleep apnoea than a control group recruited via primary health-care centres, matched for sex and age. The adjusted odds ratio of having an MVA was 11.1 (CI 4.0-30.5) 7.2 (CI 2.4 – 21.8) and 8.1(CI 2.4-26.5) when AHI was greater than 5, 10 and 15, respectively. They also noted that patients who reported feeling drowsy just before their accident had a mean AHI of 24 (SD 25) as compared to drivers who reported being alert just prior to the accident, who had a mean AHI of 13.8 (12). Further interpretation of these results must be cautious as the confidence intervals (CI) for the odds ratios were wide making it difficult to pinpoint the real impact OSAHS may have played in these MVAs.

Barbe et al (1998) also investigated MVAs in an OSAHS population. MVA rates for a period of three years were obtained from subjective reports and insurance companies for 60 OSAHS patients (47 SD 1years, mean AI 58 SD 3) and 60 age and sex matched controls (free from OSAHS as determined by previous medical history). The control group had significantly lower BMI (27 SEM 0.8 versus 33 SEM 0.8 $P<0.001$), ESS (3 SEM 0.3 versus 12 SEM 1 $p<0.001$) and had consumed significantly less alcohol at weekends (13 SEM 3 versus 31 SEM 6 g/d, $p<0.05$) than the OSAHS patient group. There were no differences between the groups in the amount of drugs ingested that could influence driving. The percentage of patients with OSAHS reporting one accident in the three year period was higher than the control group, and the OSAHS group also reported a higher mean number of accidents in the same three year period (0.53 SEM 0.1 versus 0.22 SEM 0.06, $p<0.05$). The OSAHS group reported driving more kilometres per year (27,305 SEM 2,905 versus 15,695 SEM 1,580 km/yr $p<0.01$) and,

after adjusting for this, the odds ratio for having an MVA was OR 2.3; 95th CI 0.97 to 5.33 p=0.06.

Data obtained from these studies show that despite some methodological issues, both self-reported and objective MVA risk seems to be greater in OSAHS patients, and may be greatest in those with the highest apnoea/hypopnoea frequency. However, it has been suggested that some patients with sleep apnoea may under-report symptoms related to OSAHS, especially sleepiness, either because they lack a normal frame of reference, or because making such an admission might lead to negative outcomes (Dement et al 1978).

In order to assess whether this may commonly happen, Engleman et al (1997) questioned patients (AHI >5) about their subjective level of sleepiness (ESS) and driving impairment by asking if they had 'had' or nearly had an accident because of falling asleep. These questions were asked twice, once on initial presentation to the sleep clinic, before diagnosis, and again after starting CPAP therapy, to retrospectively assess their pre-treatment impairment. The median ESS scores for pre-treatment rose significantly from 12 (range 0-24), when assessed at the time of diagnosis, to 14 (5-24) when reported retrospectively. Driving impairment was initially reported by 23% (n=19) of the sample, rising to 37% (n=31) after treatment use.

This study confirms that patients underreport these symptoms at the time of initial presentation, suggesting that the prevalence rate of sleepiness and sleep-related MVAs estimated in the self-report studies mentioned previously may be artificially low. The changes in admitted impairment level seen in the study may be due to active treatment which would allow patients to feel the difference in their daily levels of sleepiness before and after treatment. Alternatively, it could reflect deliberate under-reporting of symptoms in an attempt not to risk losing a driving licence. However as patients in the UK are normally allowed to continue to drive once established on CPAP treatment, any fear of licence withdrawal would no longer exist, possibly making patients feel more comfortable about answering these questions accurately.

Young et al (1997) used participants in an ongoing population study of sleep disordered breathing to estimate MVA rate. A cohort of 913 (542 men) aged between 30-60 underwent polysomnography to determine their sleep-disordered breathing status (SDB), and MVA rate was obtained from a state-wide database holding information of traffic violations and road accidents. Controlling for age and miles driven per year, Young et al estimate that men with an AHI between 5-15 are four times more likely to have a MVA in a five year period (OR 4.2,95th CI 1.6-11.3) than those without SDB. Men with an AHI>15 were three times more likely (OR 3.4 CI 1.4-8.0) to have MVAs than those without SDB. However, no statistically significant differences were found in females with SDB. Compared to the male sample without SDB, men with an AHI>15 were 12 times more likely to be involved in multiple MVAs in the five year period (OR 11.9 1.1->25). When both sexes were analysed together (controlled for age, miles driven per year and gender) they found that an AHI>5 was associated with a 4.6 times greater risk of multiple MVA.

This study is free from clinic selection bias, employs objective methods for both quantifying SDB status and MVA rate and indicates that men with even mild OSAHS are at a higher risk of being involved in at least one MVA. However, as with the Teran-Santos (1997) study, the confidence intervals are wide, mainly due to the small number of participants having accidents (167), with only 24 of these having multiple MVAs. If the true value lies at the lower end of the CI then the real impact of SDB on MVAs may be small. Conversely, if the true value lies at the higher end, it would suggest that OSAHS has a greater impact on MVAs than previously speculated.

2.6 Effect of OSAHS treatment on driving

George et al (1995) interviewed 124 untreated OSAHS patients, 35% of whom reported experiencing sleepiness whilst driving and all of whom reported that the sleepiness was present during long drives (>60 minutes). Only 17 reported feeling sleepy during city driving, adding support to those who suggest that monotonous roads, such as motorways, induce sleepiness. Only one of the 124 patients (0.9%) admitted to having either an accident or a near-miss accident. In a second part of the study, George et al

contacted 100 OSAHS patients using CPAP treatment. Of the 65 questionnaires returned, 72% reported trouble staying awake while 28% admitted to having an accident due to sleepiness. 97% of these patients reported that their daytime sleepiness was 'some' or 'a lot better' than before CPAP therapy, and 33% reported they could and did drive longer without problems. However, as the two groups were not matched, it should be noted that this could account for the dramatic differences between the levels of reported sleepiness and accidents.

Further support for an increased accident rate in OSAHS patients comes from Krieger et al (1997) who compared retrospectively self-reported accidents including MVAs before commencement of CPAP therapy, and recent accidents at 6 and 12 months after the start of CPAP therapy. The questionnaire enquired about vehicle, domestic, work and other unspecified accidents asking for the number of actual and near-miss accidents that had happened in each time period, and how many of these were related to sleepiness, fatigue or reduced vigilance. Although they do not report the statistical differences between each subtype of accident, the authors note that the average number of actual accidents per patient decreased after treatment ($p<0.01$) as did near-miss accidents ($p<0.01$). The number of real MVAs fell from 46 (49% of all accidents reported) to 14 (34%) and the number of near miss accidents fell from 505 (75%) to 39 (66%). All near-miss accidents, both before and after CPAP, were related to a lack of vigilance, while 53% and 33% of the actual accidents were attributed to lack of vigilance before and after CPAP, respectively (These are expressed as a percentage of all accidents reported). Although this study employs self-reports, which may be error prone (Engleman 1997), the statistically significant reduction of all types of accidents before and after CPAP allows speculation that CPAP may reduce MVAs. This in turn, may suggest an elevated MVA rate in these patients as a consequence of OSAHS.

Minemura et al (1993) also found a reduction in reported MVA rates after CPAP, in a very small study: prior to treatment. Initially 42% of the 14 patient group had reported having at least one accident in the previous 3 years whereas during a year of CPAP treatment, none of the patients reported any MVAs. The small sample size and lack of control group again limit conclusions that can be drawn from this study. Engleman et al (1996) also reported a statistically significant reduction in near-miss accidents when

comparing the period five years before treatment and the time since starting CPAP. They also reported that 77% of their 204 sample reported improvement in their ability to drive long distances safely after CPAP. However, they did not find significant differences in actual accident rate.

These studies suggest that OSAHS patients have higher MVA rates than control populations. Interpretation of many of these studies is difficult due to methodological problems, particularly small sample size and/or lack of a control group. Additionally, many studies have not adjusted MVA rate for the average mileage driven per year, which is a risk factor for driving accidents. However, while these studies have shown that many OSAHS patients have MVAs, it should be noted that many drivers with sleep apnoea have not had accidents. Therefore, there is an issue as to whether it is reasonable to prevent all people with OSAHS from driving. As there is still no consensus regarding which consequences of the condition cause these MVAs it may be problematic to prevent driving based on one aspect of the condition alone i.e. AHI severity.

Currently in the UK, any person diagnosed with OSAHS who is sleepy when driving, and holds only a non-commercial driving licence, must inform the Department of Vehicles and Licensing Authority and should be advised by their clinician that they must not drive if they feel sleepy. HGV (Heavy good vehicle) and PCV (passenger carrying vehicle) licence holders must stop driving commercially until treatment has been established. However, as previously mentioned, many patients under-report their sleepiness levels. If this is due to an inability to recognise internal cues of sleepiness then advising patients not to drive while sleepy may not be preventative. In addition, patients with OSAHS may not be aware of the effect the condition has on their driving ability. Indeed, most studies suggest that only a small number of OSAHS patients have MVAs compared to controls. A method of screening potentially sleepy people for fitness-to drive is thus clearly desirable.

2.7 Current methods to assess fitness to drive.

In the UK, drivers may continue to drive once established on CPAP treatment, although in some individual cases the Driver and Vehicle Licensing Agency (DVLA) requires objective evidence of a person's fitness to drive, especially if they hold a commercial driving licence. Currently, the Maintenance of Wakefulness Test (MWT) is used in some centres to establish patients' ability to remain awake during four forty-minute tests conducted over the day at two-hour intervals starting at 10am. This test assesses polysomnographically the ability of an individual to remain awake in a soporific situation. If patients cannot remain awake for 20-40 minute periods when motivated in the test situation, one may argue that their ability to remain fully vigilant whilst driving may be impaired. But the MWT test itself does not and cannot assess one's ability to safely control a vehicle. Staying awake for forty minutes on four separate occasions does not necessarily mean one could safely handle a motor vehicle for a prolonged period of time. Indeed, many OSAHS patients can remain awake for these four tests before being established on treatment, begging the question as to whether they might be unimpaired. In addition to the fact that the MWT does not directly assess driving fitness, the test is both time-consuming and expensive to run - during each of the four forty minute tests, the polysomnographic trace must be monitored constantly by an experienced sleep technician so that the test can be stopped if the individual falls asleep.

Therefore, as a method for assessing fitness to drive, this test not only lacks face validity, but also lacks the validation of what level of sleepiness corresponds with the inability to safely operate a vehicle. These issues, as well as the fact that most health boards would not be in a financial position to use the MWT to test the increasing numbers of patients being diagnosed with OSAHS, inhibits this sleep resistance test as being a widely used, valid or reliable test for fitness to-drive.

2.8 Do patients with OSAHS need to be assessed for fitness to drive?

As previously mentioned in section 2.4, research supports the suggestion that patients with OSAHS are at an increased risk of MVA, reporting more incidents of feeling sleepy and falling asleep while behind the wheel. Estimation of the increased likelihood of OSAHS patients, compared to non-sufferers, having an MVA ranges from twice (George et al 1987) to seven times (Findley et al 1988). As the condition becomes more widely recognised in both the medical profession and by the general public, the numbers of people presenting to sleep centres, and being diagnosed with OSAHS increases each year. This in turn increases the potential number of accidents that may be attributed to OSAHS. However, it is still very likely that many people with OSAHS are not being diagnosed, and it may be likely that some of the MVAs that occur on our roads each year are a result of this condition, but are attributed to other factors.
Sleep-related accidents are often fatal, and a method for screening patients with OSAHS seems desirable to reduce loss of life, associated injuries and the cost of the accidents.

The number of patients attending sleep centres increases annually (BTS/SIGN guideline 2003), as treated patients are followed up and new patients diagnosed and added to the follow-up list. However, for most NHS based centres funding does not match the increase in attending numbers and, as a result, waiting times for both diagnosis and treatment are also increasing. This has several implications:

Firstly, there are thousands of people awaiting diagnosis who are still able to continue driving, most of whom may not be aware of the dangers associated with the condition. Secondly, there are patients who have been diagnosed with OSAHS but are still awaiting treatment. In many cases patients are advised not to drive if they report feeling sleepy, but are otherwise allowed to continue to drive. This is not an ideal situation.

Although there is evidence to suggest that, once established on CPAP for OSAHS driving ability (as measured by number of MVA's, near misses and sleepy spells behind

the wheel) returns to a normal level, there is still no evidence that this level of ability is maintained over years of treatment. Also, one must not forget the consequences for patients who are unable to use or tolerate CPAP treatment, and hence are often untreated.

Taking all these factors into account it would be highly desirable that a tool which is objective, reliable, re-usable (on potentially several occasions), and can accurately measure the main aspects of driving (tracking and visual searching) is developed and employed to try to identify those patients with OSAHS who are at risk when driving.

2.9 What aspects of driving need to be analysed for fitness to drive?

As mentioned in section 2.2 people with OSAHS perform poorly on most aspects of cognitive testing, showing reduced abilities in vigilance, thinking, perception, memory and perceiving new information. This, coupled with evidence that they also perform poorly in psychomotor tests that require high levels of sustained attention and concentration (Kales et al 1985b, Findley et al, 1986), and the diurnal hypersomnolence that patients often experience, adds support to the hypothesis that OSAHS patients could be impaired in their ability to safely control a motor vehicle.

However it is still not evident which aspects of the condition, (sleep disruption or hypoxaemia) cause these driving impairments, and it is not known whether each OSAHS patient's driving is impaired. It is not ideal to assess each of these cognitive areas in isolation to determine a person's fitness to drive, as all of these abilities are required to safely operate a motor vehicle. Therefore, it would be advantageous to assess actual driving performance. This can be done by splitting driving into its component tasks;

Tracking: this involves the person's ability to accurately perceive the road in front of them and manoeuvre the vehicle appropriately. To do this they must be aware of the contour of the road and any upcoming changes in road layout i.e. from straight to corner to chicane, and be able to apply the correct amount of steering correction.

Visual search: this involves a person's ability to search each area around the vehicle i.e. red lights, people stepping out from the kerb, cars behind speeding. This component involves reaction time, as many of these incidents are unpredictable and require immediate and effective action.

Speed control: this involves a person's ability to maintain the speed of the vehicle as regulated by both speed limit and road conditions.

However, one aspect often attributed to actual MVAs and near miss accidents is sleepiness, both of feeling sleepy and actually falling asleep at the wheel. This cannot be assessed directly in terms of a component of driving but is measured through presence or absence of sleep spells as reported by the driver or actually measured sleep episodes while driving. The ability of drivers to acknowledge sleepiness was supported by a study comparing driving ability on a car simulator with driving performance after a nap, caffeine drink, or placebo caffeine drink. Horne and Reyner, (1996) found that normal subjects who were drivers were always aware of the presence of sleepiness whilst driving and concluded that it would not be possible to fall asleep at the wheel without noticing this.

However, this study was conducted on non-OSAHS subjects, and, due to the fact that many OSAHS patients under report their levels of sleepiness, (perhaps because of the loss of a normal frame of reference following years of sleepiness), this may not be applicable to OSAHS patients. A more practical way might be to compare subjective sleepiness before and after a drive with the use of a state questionnaire like the Karolinska sleepiness scale (Åkersdedt and Gillberg, 1989). Alternatively, one could take a subjective measurement of sleepiness during a driving performance as Horne and Reyner did (1996). However, as this requires the subject to internalise how they feel and then scale their sleepiness level by verbal statements, it may in turn act as a stimulus and as such may cause sleepiness to be under-reported. Although it has limited practicality, the Road Transport Research Laboratory has monitored EEG during a driving task. Again, this represents a data rich research resource, but is an expensive, labour-intensive and time consuming option, as well as inhibitory for the driver. There is also a subjective element when deciding which aspects of the EEG are

significant. Therefore, the methodology of fitness to drive tests will essentially be determined by which aspects can be measured.

2.10 Objective methods of fitness to drive

2.10.1 Real life driving tests

One method of screening OSAHS patients would be to test them in real life driving situations. However this method has several limitations, not least of which is the cost; large patient numbers, numerous re-tests for each patient, employee costs maintenance of suitable cars and insurance are almost sufficient to exclude this as a viable tool to assess fitness to drive in OSAHS patients, at least at the current time.

There is also the issue of who should be directly assessing these patients. It may require several disciplines including sleep physicians, technicians, psychologists and DVLA trained testers. There would have to be several places in the country that would be able to provide these services, as a central agency would necessarily involve more travelling for patients in outlying areas. Although ethical guidelines of acceptable practice would have to be drawn up, real life driving would not give a rigorously controlled assessment, and any such test could face potential legal and financial challenges.

The natural testing of a person's reaction to their surroundings (for example by incorporating a test of reaction time and/or possible dangerous situation) would also be difficult without placing the tester and patient in danger. It would not be reasonable on safety grounds to ask testers to allow a potentially dangerous situation to progress before they intervened (by applying steering correction, or braking).
However, the main factor inhibiting real car driving as a tool for assessing fitness to drive is the difficulty inherent in objectively and validly assessing tracking and visual search, the two components of driving. Establishing whether the subject is accurately performing a visual search of the surroundings is not easy to quantify, despite EEG and tracking/steering data from highly equipped vehicles, driving on empty roads.

Therefore, it is unlikely that real time driving would be the first choice to assess fitness to drive.

2.10.2 Driving simulators as a method to assess fitness to drive.

Driving simulators might provide a safer and more reliable way to objectively measure the two main aspects of driving performance – tracking and visual search - as well as being able to assess sleepiness as a factor in MVAs. The two main advantages that driving simulators have over other testing methods is that they are safe and can be specifically designed to incorporate the aspects one wishes to analyse.

Many studies measuring driving ability on patients with OSAHS also include data from patients diagnosed with narcolepsy, another sleep disorder which produces diurnal hypersomnolence. As this thesis is designed around the validation of driving simulator in OSAHS patients and does not include narcolepsy patients, results concerning this other sleep disorder will not be mentioned unless the data also incorporates results from OSAHS patients.

One of the initial "driving simulators" used to assess driving performance in patients with OSAHS is the Steer Clear test (Findley et 1989b). This is a PC based vigilance task - not a true simulator at all - which depicts a bird's eye view of a two-lane road, a car and intermittent obstacles (cattle or American Steers- hence the name). As part of the simulation, the car progresses down the lane (going from the bottom of the lane towards the top). Steers appear on both lanes of the highway at irregular intervals of between 2 seconds and 2 minutes. The obstacle free period of up to 2 minutes increases the monotony of the test. Subjects must move the car to the other lane when a steer appears in their lane. Subjects alternate the position of the lane by pressing the space bar on a standard computer keyboard. If the subject is unsuccessful in changing lanes in time they hit the steer and they are automatically placed back at the beginning of the left hand lane. They also return to the beginning of the left hand lane if they successfully travel to the top of either lane without hitting any steers. Patients are generally given a one-minute practice run before commencing a 30-minute drive in a darkened room.

Several studies have utilised the Steer Clear test and found significant differences in the performance of OSAHS patients and matched controls, as well as evidence to support changes in performance after CPAP treatment.

Findley et al (1989b) compared 12 OSAHS patients (nine men) with a mean age of 50 years (SD 14) and a mean apnoea Index of 55 (SD 32)/hr to 12 age and sex matched controls (mean age 45 years SD 15) with no history of OSAHS. As suspected the OSAHS patients hit significantly more obstacles than the control group (44 SD 52 and 9 SD 7 respectfully). Findley et al also compared six patients with pre-treatment desaturations of 61 SD 33/hour of sleep, on SteerClear after treatment. The paper does not state the length of time patients received CPAP treatment. They found that post-treatment desaturations were reduced to 3 SD 2 per hour of sleep on CPAP and again found significant differences in the number of steers hit, falling from 29 SD 19 to 13 SD 8. The normative data established from a later study by Findley (see below) (1995), brings these six patients from the category of poor to normal score range.

This change in performance by treatment was reproduced in a later abstract by Findley et al (1992). Twelve patients, with a mean oxyhaemoglobin desaturation index of 64 SD 8 per hr of sleep before treatment, hit 3.7 SD 0.6% of obstacles on the steer clear test. After 3 to 5 months of CPAP treatment patients' oxyhaemoglobin desaturation levels dropped to 2 SD 1 per hour of sleep, and they hit significantly fewer obstacles on steer clear (1.4 SD 0.3%) than before treatment.

In a further study Findley et al (1995) compared 62 (53 men) OSAHS patients, as defined as an AHI >5 (with a mean AHI of 51 SEM 4), with a group of 12 age and sex matched non-OSAHS patients who had been referred to their sleep centre for symptoms of OSAHS, but who had an AHI <5. A group of ten volunteers, who showed no symptoms of hypersomnolence, were also matched to the OSAHS group. There were no differences in age between the three groups, with the mean age of the OSAHS patients being 51(SEM 1). Normative data was assimilated from age and sex matched controls (free from any sleep disorder) in this study. A normal score was reported as < 1.8% obstacles hit, a poor score as >1.8% but $\leq$ 4.5 % obstacles hit, and a very poor score as > 4.5% obstacles hit.

The OSAHS patient group hit significantly more steers (4.4% SEM 0.6%) than both the non-OSAHS patients (1.4 SEM 0.3%) and the volunteer group (1.2 SEM 0.3%). When the OSAHS patient group were split into mild (n=41) moderate (n=13) and severe (n=8) cases (based on oxyhaemoglobin desaturation rates), the severe group hit significantly more steers than the other groups.

Interestingly, Findley also found significant mild to moderate correlations between performance on Steer Clear and the percentage of steers hit and desaturation index ($r=0.55$, $p<0.01$); oxyhaemoglobin desaturations per hour ($r=0.50$, $p< 0.01$) and AHI per hour of sleep ($r=0.29$, $p<0.01$), however, it is notable that these relationships only explain a maximum of 30% of the variance in performance. These relationships add some support to the belief that SteerClear might be measuring vigilance.

The study also included data from ten untreated patients with narcolepsy (3 males), who were age and sex matched with 10 patients who were not diagnosed with narcolepsy, but who had been referred to the authors' sleep centre with symptoms of daytime sleepiness. Both groups had AHI<5. There was also a third volunteer group matched to the narcolepsy patients for age and sex, who had no previous symptoms of excessive daytime sleepiness. These three groups performed Steer Clear and the narcolepsy group hit significantly more obstacles than the non-narcolepsy patients and the volunteers (7.7 SEM 3.2%, 1.2 SEM 0.3% and 0.9 SEM 0.3% respectively).

Patient groups (OSAHS (n= 62) and narcolepsy (n=10)) were categorised into normal (n=22), poor (n=26) and very poor (n= 22) performance groups (see above for cut of values). The authors were able to obtain driving records for 21 of the normal performance group who had 1 accident in 5 years (0.05 acc/driver/ 5yr). These were compared with driving records for 25 of the poor performance group who had 5 accidents in 5 years (0.02 acc/driver/5yr) and 21 of the records for the very poor performance group who had 8 accidents in 5 years (0.38 acc/driver /5yr). Thus, the very poor performance group not only hit significantly more obstacles during the steer clear task, but they had a significantly higher MVA rate than the normal performing group.

Although these results are hard to interpret, as both sleep disorder groups are analysed together, they serve to show that SteerClear does seem to differentiate between sleep disordered patient groups known to have high incidences of excessive daytime sleepiness, and control groups. It further differentiates between people with good driving abilities in real life (few accidents) and those with poorer abilities (a higher number of accidents).

Barbe et al (1998) looked at MVA rate subjective sleepiness and vigilance as measured by SteerClear and a PVT (see section 2.5 for participant details). Not only did they find that the OSAHS group had significantly more MVAs in a three year period than the control group, but that the group performed significantly poorer on both SteerClear (2 SEM 0.5 versus 0.4 SEM 0.1 % hit, $P<0.01$) and the PVT (measuring reaction fatigue) - 0.04 SEM 0.007 versus –0.03 SEM 0.004 $p<0.07$. Although they did not find any correlation between SteerClear and the number of MVAs reported, this is one of the first studies to report performance decrements in both simulated and actual MVAs in a case controlled study.

Other studies have also shown that SteerClear is sensitive to change in performance after treatment (Findley et al 1991, Engleman et al 1994a, Findley et al 1999) showed that performance on the SteerClear simulator can deteriorate with time on task in narcoleptic patients, with a trend towards this in OSAHS patients.

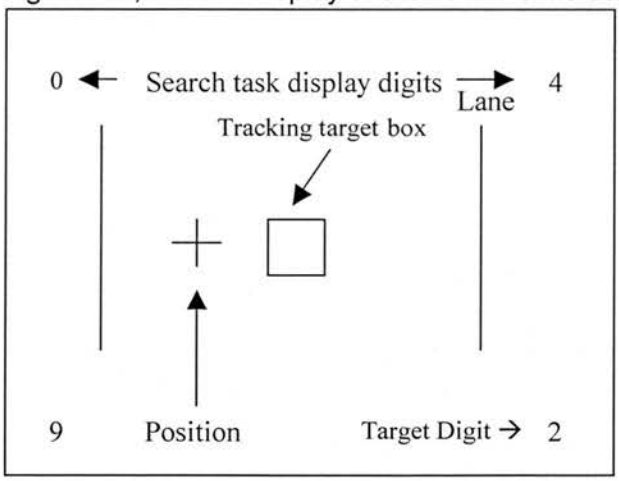
SteerClear does seem to show performance differences between untreated OSAHS patients and healthy non-OSAHS matched controls, and this performance deficit does seem to be reduced once treatment for OSAHS is established.

However, this test is not a driving simulator, but would more accurately be described as a vigilance test. It does not test reaction time and it requires only one action to be performed- very different to the actual experience of driving. Driving requires multiple tasks to be performed in tandem and, as such, any driving simulator trying to emulate real life driving, with the aim of providing a method by which to assess fitness to drive, must incorporate a divided attention task. SteerClear also lacks face validity for a driving simulator. It does not incorporate any features of real driving and it lacks a

steering wheel and foot pedals. More basically, the test is performed with a bird's eye view on a continually straight road that does not allow for any tracking or any real visual search. As such it would be hard to justify to patients why their driving licence was being suspended on the basis of this task. Nevertheless, SteerClear is an important tool for measuring vigilance, and is widely used. However, although vigilance does play a major role in ability to safely control a vehicle, it is not the only psychocognitive factor involved and to test fitness to drive one must test the other areas of psychocognitive and psychomotor skills required.

A second driving simulator designed by George et al (1993) is the Divided Attention Driving Test (DADT). This simulator consists of a PC screen that is connected to a steering wheel with mounted buttons, which is in turn interfaced with the computer. A screen display taken form the George et al (1997) paper is shown in figure 2.1 below.

Figure 2.1; Screen display of the DADT simulator



The DADT requires subjects to divide their attention between two tasks.

The visual task requires subjects to monitor the single digits displayed in the four corners of the screen. The digits from 0-9 are programmed to change in a randomly appearing pattern around the four corners. At the beginning of the simulation the subjects are given a target number, which the authors standardised as the number '2'.

This target number is displayed for anything between 5 and 15 seconds. When it appears in one of the four corners subjects must react by pressing a button mounted on the steering wheel. Four buttons, corresponding to the four digits on the screen, are mounted on the steering wheel roughly at the 10 o'clock and 2 o'clock positions so that the thumbs can easily reach them.

The tracking task used in the DADT requires the subject to keep the cross hair position indicator within the area of the tracking box. The cross hair, which represents a car, travels at a constant forward speed. However, to increase the difficulty of this task, the DADT employs a subcritical tracking task. In a subcritical tracking task subjects control an unstable element that, in the case of the DADT, is represented by pseudo-randomly appearing gusts of side winds. This results in the lateral shifting of the cross hair, and requires a steering correction by the subject to maintain their position in the tracking target box. If no steering wheel movement has been detected for 30 seconds, the subject is assumed to have fallen asleep and a buzzer sounds. Neither accelerator nor brake is required for the DADT task.

The DADT task is initially tested on subjects in six five-minute blocks with a period of 2 to five minute intervals in between each run. This allows a practice period for the subjects, but also allows for the establishment of a learning curve.

To determine if the DADT is sensitive to driving impairment, George et al (1996b) compared driving performance in ten (8 males) healthy sleep disorder free subjects (mean age 45 SD 6yrs) under control (normal drive) and intoxicated (drunk) drive.

Alcohol was used as a comparative impairment agent to sleepiness, as there is a blood alcohol level over which driving ability is impaired and driving illegal. Subjects were tested twice each day, morning and afternoon, and conditions were counterbalanced to reduce any order effect. On the control days subjects drank 300ml of grapefruit juice over a thirty minute period and then performed the DADT one hour after completion of the drink.

On days when the subjects received alcohol they were given 0.75g/kg of alcohol mixed through with grapefruit juice, which again was drunk over a thirty min period and testing commenced on the DADT one hour after it was finished. For the afternoon trial, subjects' alcohol dose was adjusted according to the first blood alcohol level and the authors aimed for a blood of 80 to 100mg/dl. The mean blood alcohol level for the subjects was 95 SD 25 mg/dl. Hence, not all subjects were legally impaired; the current legal limit in the UK being 80 mg/dl.

There were significant differences between the normal and alcohol conditions in both the tracking error (p, 0.001) and the visual task (p, 0.05), with both tasks impaired following alcohol. Out of bound events increased from 0.5 SD 0.7 times under normal conditions to 15 SD 22 times following alcohol. Although the authors do not report the values, they do note that there was an increase in missed and incorrect responses for the visual task from the control to alcohol condition.

Having shown that the DADT could detect impaired driving performance George et al (1996a) compared the performance of 21 OSAHS patients (AHI 73 SD 29) with 21 age, sex and driving experience matched controls (AHI 3 SD 6). The OSAHS groups showed significantly greater tracking error. The mean tracking error for the OSAHS groups was 228 SD 145cm compared to the controls which was 71 SD 31cm($p=1x10^{-9}$), with over half of OSAHS patients doing worse on the tracking task than the worst control subject. The OSAHS patients' even performed more poorly on the tracking task than the original alcohol impaired controls (228 cm vs. 161 SD 11 cm). The control group maintained a steady performance in the tracking task over the 20 minute task, while the OSAHS patients (as a group) were consistently worse than the controls at all times within any given 20 minute run, regardless of time of day the test was done.

With the visual task element, average response times for digit recognition were significantly quicker in the control group (2.9 SD 0.8) than the OSAHS group (3.3 SD 0.8), and the control group (38 SD 2.5) responded to the target digit correctly significantly more times than OSAHS patients (36 SD 4.2). There was much more of an overlap in these two groups with the visual task than the tracking task. The authors do not report how the OSHAS patients compared to the original alcohol impaired controls.

Out of bound events are recorded when the position indicator crosses a lane boundary. The OSAHS group recorded significantly more (12.6 SD 20) out of bounds events than the controls (0.1 SD 0.3). Further, due to a lack of steering correction for 30 seconds, three subjects in the OSAHS group were assumed to have fallen asleep. This occurred twice in one patient, thrice in another and six times with the worst patient, which may have resulted in the subject sleeping through 15% of the driving simulation.

Interestingly, the authors note that while over half of the OSAHS patients performed significantly worse than the control subjects, a number of them did as well as or even better, than the control subjects. This is encouraging in that the simulator appears to be measuring an actual element required in real life driving. Many of the previous studies in section 2.4 confirm that it may only be a sub-sample of OSAHS patients who are at increased risk of MVA's.

In an extension of this study, George et al (1997) re-tested 17 of the OSAHS patients on overnight polysomnography, MSLT and the DADT. Eighteen of the control subjects were also re-tested on the MSLT and the DADT. As these patients were OSAHS free and were still free from any associated symptoms, it was assumed that overnight polysomnography would not have been statistically different on a second night of testing. Patients underwent their polysomnography night and subsequent day of testing between 1-12 months after establishment on CPAP (Mean 9.2 SD 4.2). The control group underwent the MSLT and DADT between 2-12 months (mean 8.4 SD 3.4) after initial testing.

Before CPAP treatment, OSAHS patients had significantly more micro-arousal's, awakenings, and had a greater AHI than the original control polysomnography studies. After commencement of CPAP there were no significant differences in the overnight sleep measures between the CPAP-OSAHS group and the control group.

This trend was followed with the MSLT changes. Before CPAP treatment OSAHS patients had a mean MSL of 7.2 (SE 0.8) minutes compared to the control group, which had a mean of 12.3 (SE 0.9) minutes, whereas post CPAP patients mean MSL increased to 13.2(SE 0.8) minutes and was not significantly different from the controls.

There was no significant change in the MSLT results for the re-test of the MSLT in the control group (Mean 12.9 SE 0.8) minutes.

Both groups were given practice trials on the DADT (six 5-minute tests) on each testing day. There were no differences in the performance of control subjects on either the tracking or visual search task, for both within-test learning and practice trials (from initial trial to re-test). There was also no difference in the OSAHS group for both within-test learning and practice trials, although the magnitude of tracking error was significantly higher ($p<0.001$)-pre CPAP treatment. The OSAHS patients learned at the same rate as the controls on both test tasks. This provides evidence that there is little learning effect in DADT test and, as such, shows a good level of test–retest reliability.

The authors compared changes in performance of the two groups. They calculated this by subtracting the mean outcome values of test one from two (i.e. retest score of controls minus initial score of controls) for both groups, and then analysed the difference in changes between groups. The control group showed no significant changes in either of the DADT test tasks, or in the number of out of bound events.
The OSAHS patients showed significant improvements in performance relating to tracking error (mean difference 106 (95th CI 75-135cm)). In fact only one post CPAP OSAHS patient did not improve to the control range for tracking error. Also observed were significant improvements in the number of correct responses (1.2 CI 0.4-1.9), number of missed responses (1.7 CI 0.9-2.3) and number of out of bounds (10 CI 7.9-13.6). However, reaction time did not improve (0.1 CI 0.3-0.2s).

It should be noted that the authors did not enquire about real MVA's and near misses in the two groups, and so it is not possible to determine if the improvement in simulated performance was mirrored in real driving, or in fact if the OSAHS group prior to treatment had an increased level of the MVA's/near misses as compared to the control group.

The DADT has shown that it is sensitive to changes in driving performance, as is shown by the changes in the controls from normal to intoxicated and in OSAHS patient's pre and post CPAP treatment. It seems sensitive to the differences in driving performance

between control subjects without sleep disorders and untreated OSAHS patients. It also seems to show an improved driving ability in OSAHS patients on CPAP treatment who, by measurement of nocturnal sleep measures, are similar to that of non-OSAHS sufferers. As it is PC based and the equipment required to use the machine (steering wheel) can be easily purchased and adapted, it is does appear to be functional, affordable and reliable for re-test situations.

However, much like the Steer Clear Simulator, it lacks face validity with its bird's eye view and screen layout. Although the tracking task does seem to be sensitive to impairment in driving ability, it does not simulate real driving in that the subject does not need to correct steering as a function of the oncoming road layout, but instead as a function of lateral movement caused by the "side wind". Of course positioning oneself laterally in a safe area of the driving lane is essential for safety, but so is the ability to maintain this safe position while controlling the speed at which one travels forward, and it is not possible to measure this ability with the DADT. Also, the DADT does not incorporate any chicane or changing element in oncoming road layout. This also reduces its face validity as a measure of real life driving, as most roads, other than possibly motorways, will not be so regular in layout.

Additionally, the visual search element of the DADT, requires the subject to react when a number appears in the corner of the screen, and is therefore more a test of vigilance and reaction time, as commonly monitored by other psychomotor tests like the psychomotor vigilance test - it does not reflect real life driving. The type of visual search required when actually operating a motor vehicle is much more complex, requiring the person to be constantly checking other items such as their speed, looking for pedestrians, traffic lights and the manoeuvres of cars in front. Therefore, the DADT visual task may be too simplistic to actually measure one's ability to perform the visual task required when driving.

In summary, the visual presentation on the DADT does not resemble a real life road layout, it lacks foot pedals to control speed and it does not represent a realistic visual search task. The suspension of patients' driving licences on this basis might be questioned.

The DADT appears to be a good tool to measure changes in certain aspects of one's fitness to drive, and it showed promise for research to assess CPAP related performance improvements. However, it does not seem to be an ideal tool to use, especially as the main goal of a driving simulator is to assess fitness to drive- and conversely to suspend driving if performance is poor.

In Sweden, Haraldsson et al (1990) created a computerised driving program to be used in conjunction with the advanced Swedish Road and Traffic Research Institute's simulator. This driving simulator is state of the art technology and is based in the front of the cabin of a SAAB 900 car. The shell of this car is mounted on a moving base that allows the whole car to move laterally and the nose of the car to raise and lower. It is fully interactive with every action performed by the driver, which simultaneously feeds into a computer. This in turn updates the visual representation and causes momentum in the steering wheel. The simulator is surrounded by three colour TV projectors, which give a wide-angle view, showing a real life view of a two-lane road. It is also equipped with a sound system which emulates engine and wind noises.

Haraldsson et al developed a monotonous driving task in which subjects drive the vehicle at 55mph in a one lane, narrow (3.5m) curving road at simulated twilight. Subjects also had to respond to flickering quadratic shapes that appeared in the front view TV in one of six equally distributed positions along the top of the screen. The stimuli either appeared as red/green requiring the subject to brake immediately (this is used to calculate reaction time) or yellow/black (not used to calculate reaction time) when the subjects had to press a signal button as fast as possible. The yellow/black stimuli appeared four times more often during the 90minute drive than the red/green. The quadratic stimuli (regardless of colour) appeared in intervals of 1- to 81 seconds at an average of 40 seconds. This design was the basic driving task. A second protocol was developed in which an additional signal button was triggered when steering wheel movement was smaller than 1° for two seconds.

Fifteen male OSAHS patients and ten male control subjects of similar age (OSAHS patients mean age 54 vs. controls mean age 55years, with regular driving experience of average miles per years 28,000 vs. 21000km) were recruited for the study. The authors

do not report any respiratory disturbance index. However, the patient group complained of symptoms of heavy snoring sleep disturbance, excessive daytime sleepiness and hypersomnia while driving, recurring almost always or often. The control group were free of these symptoms although some did report some snoring.

Ten patients and 6 controls were tested on the basic drive, while 5 patients and 4 controls drove on the second driving protocol. All subjects were given a 15 minute practice session on the simulator before being served lunch, and then were given another 10 minute practice immediately before the actual drive.

Overall, the OSAHS patients' performance was poorer than the controls' regardless of which program they drove on. Although both patients and controls were asked to drive for 90 minutes, three of the patients gave up within an hour due to sleepiness and, therefore, the average test period was shorter for the patients (77 minutes) than for the controls (87 minutes). The driving programs allowed analysis of lateral position deviation (LPD) which is the deviation of the car from the straight road line (tracking) and break reaction time (BRT), which is the time it takes to press the break when the appropriate stimuli appear visual search. It also recorded the number of times they drove off road. The LPD was sampled twice per second and the standard deviation was calculated every 5 minutes. The number of "off road" episodes was also recorded.

The OSAHS patient group performed significantly more poorly on all three-outcome measures, regardless of which driving program was used. Eight of the OSAHS drivers had off road episodes with the total number of off road events being 101, where as only one control subject went off road twice. Overall the OSAHS group had significantly increased reaction times (1.89 SD 0.57 seconds) and deviated more from the straight line (LPD 0.39 SD 0.10) than the controls (1.31 SD 0.2, 0.29 SD 0.05, for reaction time and LPD respectively). This was also the case when the groups are split into the two different driving programs. The average 90th centile of the BRT of patients was 1.2 seconds longer than the control patients. This would mean that in real life, when driving at 55mph, they would take an extra 30 meters to stop.

Haraldsson et al (1991) re-tested two of the patients and five controls and reported no change in performance on the outcome measures. This suggests the simulator has test–retest reliability. They then re-tested the 15 patients three months after under going the UPPP surgery for treatment. Significant group improvements were found for LPD, BRT and the number of drive-off-road events (all $p<0.05$). The average improvement of the 90th percentile BRT corresponded to a reduction of stopping distance of around 20m driving at 55mph (although three patients were classed as treatment failures due to their subjective feelings of non-improvement of symptoms. patients showed no improvement in any of the driving outcomes on their postoperative drive). Nevertheless, as a group there were no significant differences between the postoperative driving outcomes for the patient and control groups for BRT and LPD (for both mean and 90th percentile). In a further continuation of the study (Haraldsson et al 1995a), 13 of the patients and the five controls were then re-tested an average of 45 months (range 35-49months) after the UPPP. All thirteen patients subjectively reported reductions in the number of sleepy spells occurring while driving and that they felt more vigilant whilst driving. In addition, their level of EDS had significantly reduced (measured on a visual analogue scale). The improvement of performance on the LPD, BRT and the number of drive off the road events were still maintained at 45 months postoperatively, with the control and patient group showing no significant differences between performances.

These studies had small sample size, the presence of OSAHS was based on daytime PSG with the AI not reported by the authors at the 45-month mark, and UPPP is no longer considered a first choice of treatment for OSAHS. Nevertheless, these studies highlight that the simulator is sensitive to the differences in driving performance between untreated OSAHS patients and OSAHS free controls, as well as being sensitive to treatment interventions. Although they do not report any objective improvement in real life driving (i.e. reductions in actual number of accidents etc), they do support the hypothesis that simulators may be sensitive to driving impairment in untreated OSAHS patients and as such, could provide an effective tool in measuring fitness to drive.

This true simulator has obvious advantages over both SteerClear and the DADT. With the far superior design of the car mechanism and the visual display it would be hard to improve on the look and feel of the simulator. Furthermore, it is sensitive to the differences between the two groups in terms of lateral performance and brake reaction time. However, even this simulator is not a practical tool for assessing fitness to drive. This Swedish simulator has good face validity, but it still employs a visual search task - a flickering quadratic shape that does not relate to normal driving. This simulator may have improved characteristics over the DADT, as the response to these stimuli is to depress the brake pedal rather than a signal button. A more realistic target in the path of the car could also improve its realism.

The most negative aspect of this simulator as a widely used, realistic and objective tool for the assessment of fitness to drive is the fact it is so high tech and expensive. The simulator is the property of the Swedish Road and Traffic Research Institute, which uses the simulator for multiple tasks including training of drivers, research into road and traffic solutions, and assessing young drivers. Just like real world driving tests, it would be prohibitively expensive to run and maintain, and staff would have to be specially trained to test on it. Also, as a tool to assess driving ability, there would need to be many such simulators based around the country, indeed possibly several per site, to ensure that the waiting list for tests is short enough that is does not mirror the waiting lists for diagnosis or treatment. Thus this advanced simulator would also have limitations in a clinical laboratory setting for the assessment of fitness to drive in OSAHS patients.

Results from each of these simulators have helped inform the research community about what aspects of driving need to be assessed and, indeed, the DADT and the Swedish driving simulator have both tapped into some of the requirements. Therefore, the ideal driving simulator might incorporate some of these features, as well as adding or refining certain tasks.

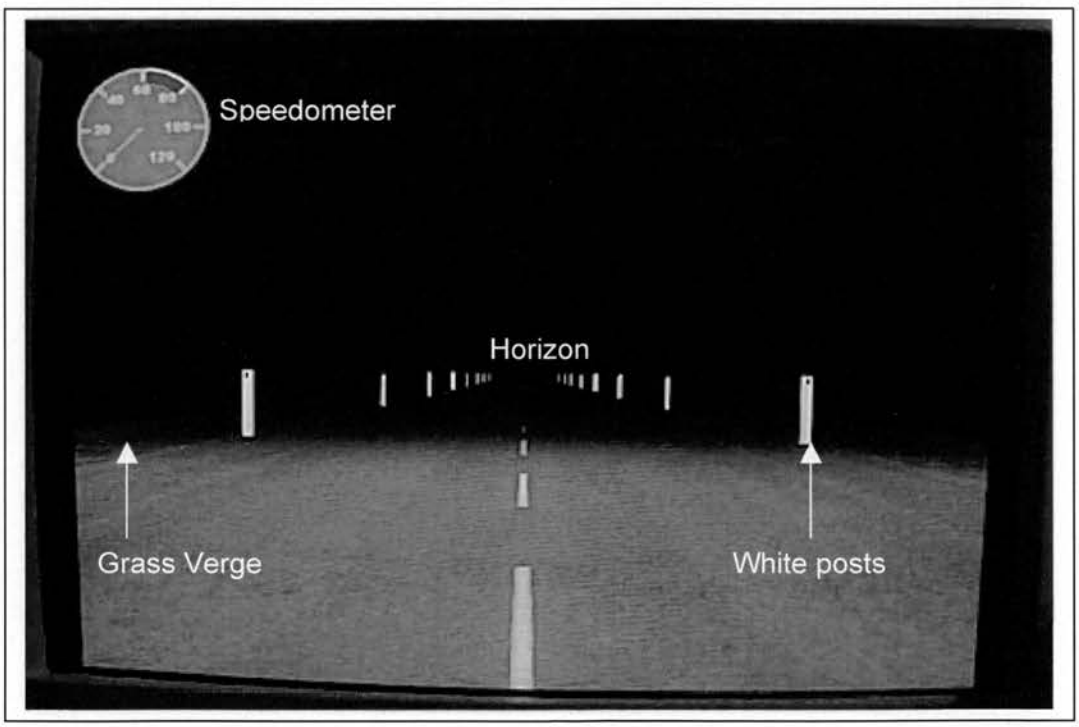
2.11 Development of the AusEd driving simulator

The AusEd driving simulator was designed as a laboratory based tool to assess fitness to drive in patients with the obstructive sleep apnoea/hypopnoea syndrome. The simulator was designed in collaboration between the Royal Prince Albert Hospital Australia (Aus) and the Department of Sleep Medicine (Ed) Edinburgh, Scotland.

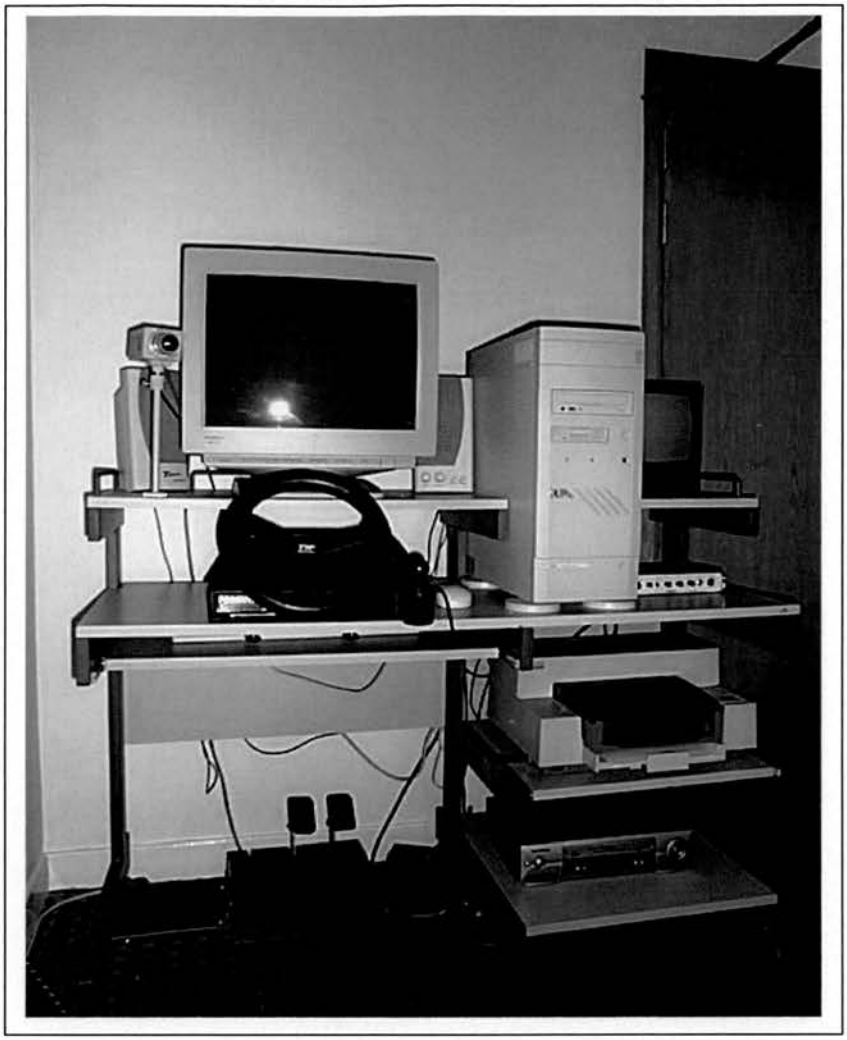
The simulator is PC based and incorporates a steering wheel and, an accelerator, and brake pedals. It requires a 19-inch computer screen, on which a two-lane road, with road marking posts and side verges, is visible. A speedometer is also situated on the top left-hand side of the screen. The simulator was designed to be non-stimulating to increase the likelihood of attention lapses or brief sleeps. It simulates a night time drive; hence, the sky and horizon are pitch black.

The AusEd simulator has advantages over the views of the Steer Clear and DADT tests as it incorporates a first person perspective view of the road layout. There is no car representation on the screen.

Picture 2.1: Patient view of AusEd screen



Picture 2.2: AusEd computer set-up



For the AusEd tracking task, subjects must keep their position in the middle of the left-hand lane. The road layout changes between monotonous periods of straight road (five minute blocks) and the more demanding chicane (two minute blocks) layout. This mimics real life driving, as the subject must be aware of the upcoming changes in road layout to be able to adjust steering correction and remain in the lane. Unlike the DADT and the Swedish Road and Traffic Research Institute simulator the AusEd simulator does alert the driver if no steering correction is applied. As one outcome of the simulator was to measure the number of driving-off-road events and crashes, a buzzer or alerting device sounding after a period of inactivity may alert a driver on the cusp of inattention. This stimulus may be enough to allow them to regain control of the vehicle and prevent and off-road event from happening. In real life driving (except cars with in-car attention devices), there is no beeping or buzzing if no steering correction is applied. In the AusEd driving task, if no steering correction is applied the simulator is designed to drift towards the left-hand edge of the screen. When this hits the perimeter of the screen the simulation temporarily stops, the word crash appears on the screen, and a loud buzzing sound is heard. Only after a crash event does the AusEd simulator alert the driver.

The visual task element of the AusEd task requires drivers to bring the vehicle to an immediate stop when a truck appears in the distance in front of them. This corresponds to vehicles coming into sight whilst driving and is more like the type of visual task that one must carry out in real life driving. Reaction time is taken from the time of the truck appearing to the time the brake pedal is 90% depressed. If no braking occurs the car will travel on until it crashes into the back of the truck. If this happens, the word crash appears and a loud buzzer sounds. If the car is stopped for more than 10 seconds the crash screen also appears.

The task also requires the driver to keep their speed within the range of 60-80Km; the speedometer is located on the top left corner of the screen and is out of the line of sight for the road. If they speed over this range they must apply the brake to reduce speed to the required level.

Hence, the AusEd simulator incorporates three main aspects of driving; tracking, visual search and speed control.

A sub program created in-house (see acknowledgements) calculated the outcome measures. These outcome measures of AusEd include;

- Mean area of deviation from the lane centre (cm)
- Mean area of deviation from required speed (km/h),
- Numbers of crashes, which are categorised as driving-off-road crash, stop crash or truck crash.
- Number of driving-off-road incidents (where the person drives along the grass verge before returning to the lane)
- Number of trucks presented (held constant at ten for each person and 30 minute drive), the reaction time for each individual presentation and mean RT value, (AusEd samples the road position and speed 12 times per second).

The analysis program can provide the mean values for these outcome measures for;

- The full 30 minutes drive,
- Four quarters of 7.5-minutes (consisting of 5 minutes of straight road and 2.5 minutes of chicane road)
- Mean values for four 5-minute blocks of straight road and five 2-minute blocks of chicane.

The AusEd driving simulator has a good level of face validity as it incorporates the first person perspective from the driver's seat of a car. It utilises a steering wheel and foot pedals, both of which are essential to mimic a real driving situation and also includes tracking and visual tasks that mirror those required in real life driving. Additionally, the speed control mimics lower and upper safe levels of a speed limit.

2.12 Discussion

Due to economic and mass-screening demands, a cost-effective, portable simulator appeared to serve a clinical need, and the AusEd-driving simulator was designed to incorporate aspects of those mentioned previously as well as including aspects that were missing in these simulators which inhibited them form being used an effective tool.

Chapters four to seven in this thesis incorporate data from the validation of the AusEd-driving simulator as a laboratory based task for fitness to drive.

Chapter 3: Methods of measurement

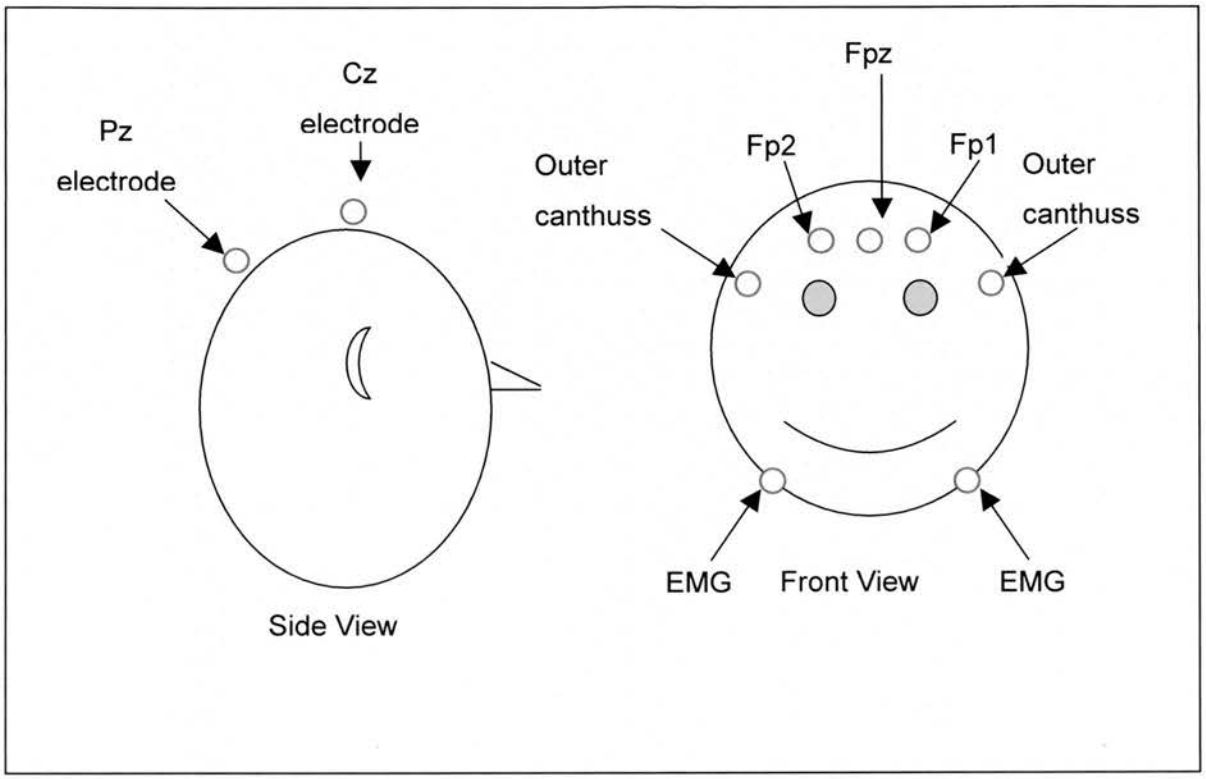
The laboratory research conducted for this thesis was undertaken to validate the AusEd PC based driving simulator program as a potential test of fitness to drive. All research included within this thesis was completed in the Edinburgh Sleep Centre between February 2000 and December 2002.

3.1 Nocturnal Polysomnography

Polysomnography (PSG) the most sensitive and specific test of sleep disordered breathing currently available, was the main diagnostic procedure in patients and its merits and validity for use in OSAHS patients are well-established (Gould et al 1988, Douglas et al 1992).

All studies were performed in the same sound-proofed and electrically screened bedroom in the hospital-based Edinburgh Sleep Centre.
Sleep states were monitored using electroencephalography (EEG), electro-oculography (EOG), and electromyography (EMG) recorded from bipolar montages from silver chloride surface electrodes. To measure and score sleep quality and quantity, a modified Rechtschaffen and Kales (1968) method was employed. EEG was recorded from two vertex scalp sites (CZ/PZ) of the international 10/20-electrode placement system (Jasper 1958). Eye movements were monitored from frontal electrodes (placed at sites Fp1 and Fp2) and referred to an electrode at the contralateral outer canthus of each eye, allowing eye movements to be recorded in all directions. 'Mixed' channels were recorded using EEG/EOG signals (Cz/Fp1 and Cz/Fp2) resolve frontal EEG. Sub-mental EMG was recorded from two electrodes placed under the chin on the belly of the genioglossial muscles. A grounding electrode was also place at site Fpz.

Figure 3.1; Electrode placement



Respiratory monitoring in the PSG comprised –

- Thoracic and abdominal movements using inductive plethysmography,
- Airflow from oro-nasal thermistry,
- Arterial oxygen saturation from pulse oximetery (Ohmeda Biox 3700).

All signals were subject to 50Hz notch filtering and high and low band pass filtering to reduce artefact an were recorded on a 16 channel computerised polysomnography system (Compumedics S, Australia).

Other PSG channels included leg EMG recorded from electrodes placed on the right and left anterior tibialis, body position recorded using a mercury tilt switch, heart rate from electroencephalogram (ECG) chest electrodes placed on the left and right of the thorax, and snoring from a discrete microphone on the headboard.

3.2 Scoring Of Nocturnal Variables

3.2.1 Sleep Scoring

Sleep was staged from EEG, EOG and EMG using modified criteria of Rechtschaffen and Kales (R&K 1968). Staging of sleep was performed on an epoch-to-epoch basis, with 30-second epochs. Each 30-second page is assessed as a whole and scored as sleep when 15 seconds or more of sleep (regardless of stage) occupies the page, rather than by looking at changes on a second to second basis. Thus R&K scoring rules are very much time based rather than event based, regardless of whether an event indicative of a stage of sleep is seen, it must be within the context of 15 seconds of sleep before the stage can be scored.

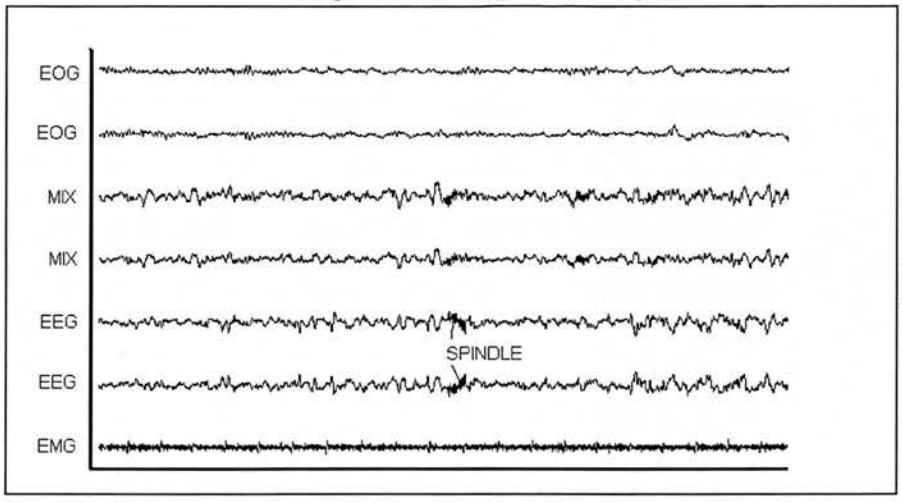
R&K (1968) defined seven stages.

Stage wake: Wakefulness is defined when EEG frequencies are in the alpha (8-13HZ) or sigma (>13HZ) range. This stage is characterised by high EMG tone and eye blinks on the EEG.

Stage 1: Sees intrusions of theta EEG frequency (4-7Hz). It is characterised by vertex sharp waves, a reduction of amplitude on the EMG and rolling eye movements on the EOG.

Stage 2: Again EEG is predominately of theta frequency (4-7Hz), with stage two characterised by the presence anywhere on the page of either a sleep spindle (fast burst of activity, 0.5-2sec in the frequency of 12-15Hz) or K complex (a negative deflection in the EEG followed by a positive one).

Figure 3.2; Stage 2 with spindle

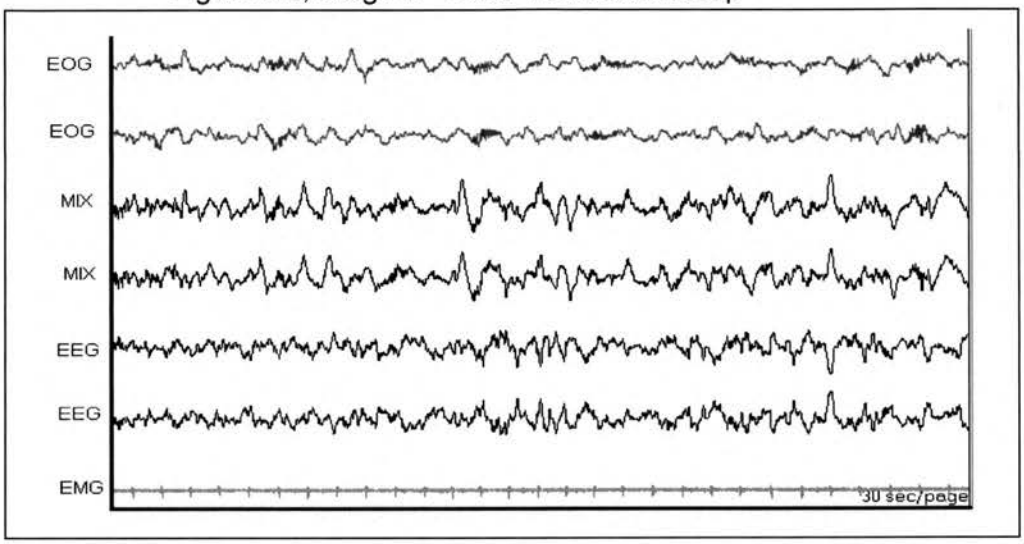


Rechtschaffen and Kales (1968) suggest that stage one should be scored after a page of wake before stage two can be re-scored. However OSAHS sufferers can often arouse briefly and regularly due to the termination of apnoeas and then return directly into stage two. Due to this, an in-house scoring technique subsequently recommended by Carskadon and Rechtshaffen (2000) and Thorpy (1992) has been implemented. If an epoch has either characteristics of stage two (sleep spindle, K complex) it is scored as this rather than stage one as R&K guidelines suggest.

Stage 3: EEG frequency of slow wave delta frequency 1-3Hz. This is a transitional stage scored when delta activity occupies between 20-50% (6-15 seconds) and amplitude reaches at least 75μV.

Stage 4: This is scored when 50% or more of the epoch is occupied by slow wave delta EEG activity.

Figure 3.3; Stage 4 – Slow wave/delta sleep

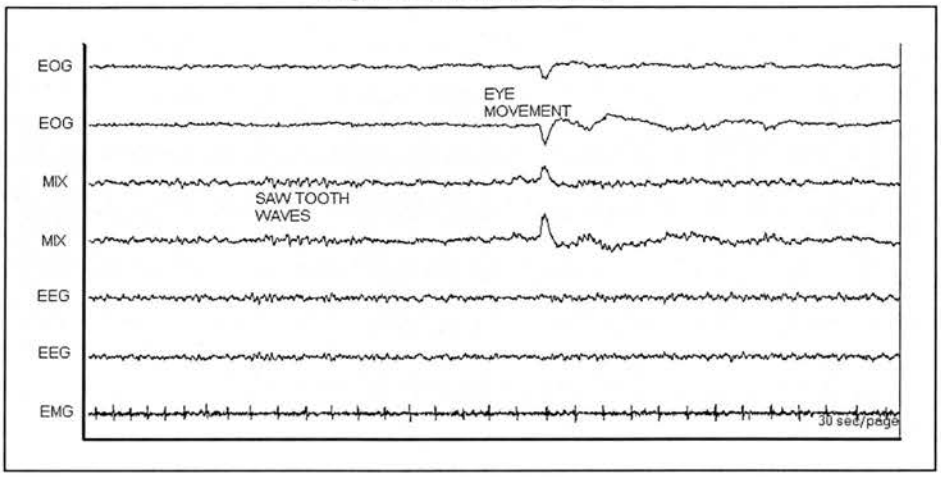


Slow wave sleep: Stages three and four are often collectively known as Slow Wave Sleep (SWS) or Delta sleep. Due to the frequency of arousals that are associated with OSAHS, patients often can not pass from the lighter stages of one and two down to stage three and four before another arousal.

Stages one through four are collectively known as Non-REM sleep; In adults (60 years and under) NREM accounts for 75-80% of night-time sleep, with slow wave sleep mainly occurring in the first third of the night.

Stage REM: EEG frequency similar to that of stage one with waves resembling saw teeth on the EEG channels. The EMG tone is at its lowest during REM except for bursts of phasic twitches. Rapid eye movements are seen on the EOG, giving this stage of sleep its name. These characteristic eye movements are not always seen on each epoch, and R&K criteria allow three minutes (six epochs) without an eye movement. This stage of sleep occupies between 20-35% of night time sleep and REM periods last longer in the last third of the night.

Figure 3.4; REM sleep



In adults free from sleep disorders non-REM and REM sleep periods tend to follow a 90-minute cycle (William, Karacan and Hursch 1974)

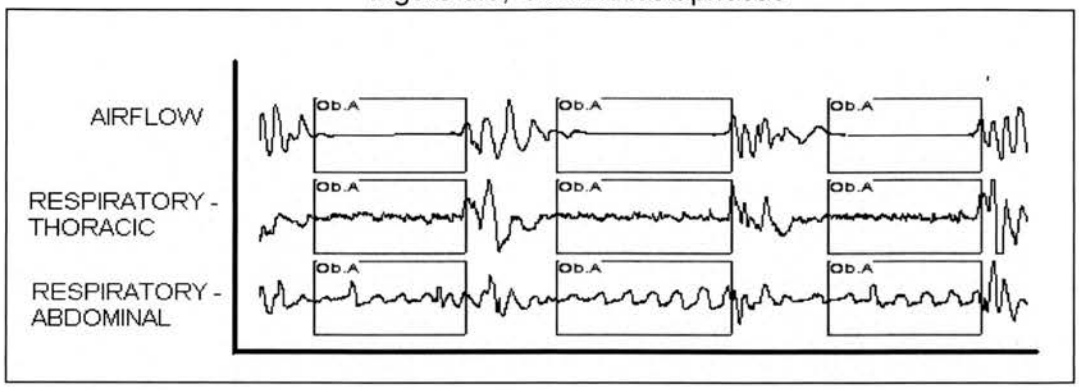
Movement time: This is scored when either amplifier blocking or movement artefact obscures more than 15 seconds of the EEG and EOG channels. This does not include muscle activity seen with an arousal when the patient is waking up.

3.2.2 Respiratory Scoring

There are two types of respiratory event routinely scored in the sleep apnoea/hypopnoea syndrome.

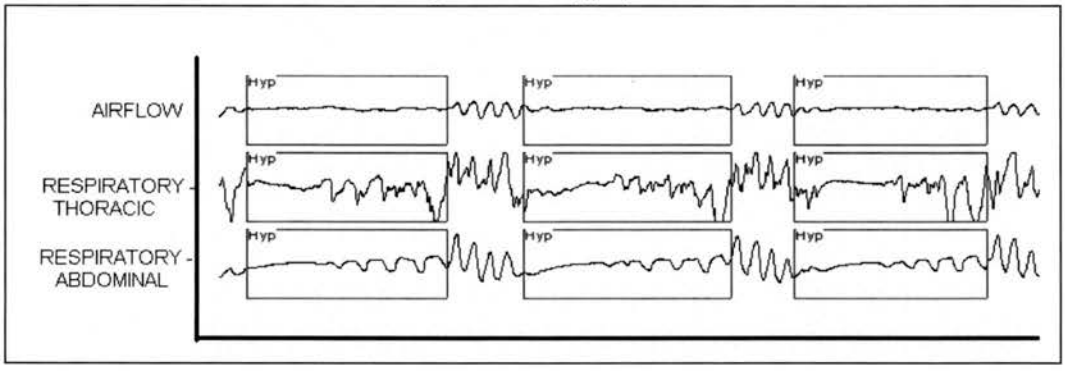
Apnoea: This is defined as a complete cessation of airflow for at least ten seconds but associated with continued thoraco-abdominal effort (Guilleminault et al 1978). These events can produce oxygen desaturation and are usually terminated with an arousal from sleep. However not all events terminate with a visible arousal on the EEG (Dingli et al 2002).

Figure 3.5; Obstructive apnoeas



Hypopnoea: Was defined as a reduction in airflow of 50% for at least ten seconds (Gould et al 1988; AASM 1999), and did not require either oxygen desaturation or arousal from sleep as in some scoring systems.

Figure 3.6; Hypopnoeas



3.2.3 Arousal Scoring

Epoch based R&K scoring cannot resolve arousals shorter than 15 seconds. However as mentioned earlier due to the termination of apnoeas and hypopnoeas sufferers of OSAHS tend to have brief arousals from sleep lasting for less than 15 seconds. These 'micro-arousals' are an important aspect of the condition, as they can inhibit slow wave sleep. PSGs were scored for in house Cheshire arousals (Cheshire et al 1992) subsequently validated by Martin et al (1997). Cheshire arousals were defined as a

return to alpha or theta rhythm for at least one and a half seconds with an increase on the EMG, however short.

The total number of arousals is divided by the total sleep time (TST), which gives the number of arousals per hour of sleep.

3.3 Reproducibility of Polysomnography Scoring

Although all sleep scoring was conducted using the above guidelines, there is an element of subjectivity involved. To ensure that scoring of the studies within this thesis are reliable 13 of the 45 nocturnal polysomnography studies were re-scored by me, blind to subject name or previous score.

The results of these intra-rater scoring assessment are shown in table 3.1.

Table 3.1; Intra-rater reproducibility Means ± SD and correlation values of sleep variables (LA)

Sleep Variable	First Score Mean & Standard deviation (SD)	Second Score Mean (SD)	R value *	Difference First score – second score
Total sleep time (minutes)	370.6 61.0	374.9 62.0	0.998	-4.2
Sleep efficiency (%)	78.12 13.2	79.1 13.4	0.998	-0.9
Arousals per hour	32.5 12.16	31.3 13.4	0.944	1.2
AHI per hour	41.3 16.7	41.8 16.5	0.993	-0.5

* All significant at P= 0.01 level

Small differences are not unusual when re-scoring. These differences can result from the both apnoeas/hypopnoeas and epochs of sleep being marginal, for example when an apnoea is just ten seconds long, when an arousal lasts around 15 seconds or when the person is drifting in and out of sleep. It is these "is it -isn't it?" events, which call upon the scorer to make a judgement call which inevitably will vary from time to time and person to person. This unfortunately, is a limitation of manual scoring of polysomnographic recordings and many believe an automated program would be more

advantageous. However a high level of correlation is found within the present study, in all variables the means and standard deviations of both scores were very close indicating high reproducibility.

3.4 Measure of Objective Daytime Sleepiness

Excessive daytime sleepiness (EDS) is a major consequence of the OSAHS and is thought to play a major role as a determinant of driving ability, and therefore was studied using a range of subjective and objective instruments.

There are many subjective methods of measuring a person's sleepiness level. Many examine 'state' sleepiness by asking for a verbal description or numeric score of how a person is feeling (Stanford Sleepiness Scale, Hoddes et al 1973, Karolinska sleepiness scale Åkersdedt and Gillberg, 1989). Others like the Epworth Sleepiness Scale (ESS) (Johns et al 1991) assess longer term general levels of sleepiness by asking about sleepiness levels in a variety of different situations. There are also questionnaires like the Functional Outcomes of Sleepiness Questionnaire (FOSQ) (Weaver et al 1992) which are designed to assess quality of life as it is affected by sleepiness. All these methods are easy to administer and are not excessively time consuming, however, they are all subject to personal perception. Some people who suffer from OSAHS may not be aware of their own level of sleepiness, perhaps because their perception of what is normal is influenced by their life style, adapted to compensate for the debilitating effects of their sleepiness. Many OSAHS sufferers adapt their social and working lives to avoid situations in which they might struggle to remain awake. Thus when asked if they feel sleepy in meetings or in the cinema for example, they will deny this, not because they are not affected by sleepiness in these situations, but because they avoid these.
Also many clinicians often ask partners of OSAHS patients to indicate how sleepy they perceive their partners to be, and this can different from how the OSAHS patients perceives themselves (Kingshott et al 1995)

Carskadon et al (1986) was amongst the first to try to quantify objectively how 'sleepy' an individual is by developing the Multiple Sleep Latency Test (MSLT). This is a

standardised polysomnographic procedure utilising EEG, EOG and EMG (electrode positions are that described in section 3.1), and is used to assess and diagnose disorders of excessive sleepiness such as OSAHS and narcolepsy. It is administered in five tests across the day in which subjects are asked to actively fall asleep. Sleep onset latency (SOL) is measured as the time from the start of the test until either the first three 30-second epochs of stage one or the first 30-second epoch of any other stage of sleep. The SOL is measured for each of the tests and is then averaged to give an outcome measure of sleepiness. Hence the MSLT measures the drive for sleep or the sleep propensity of an individual.

A modification of the MSLT, the Maintenance of Wakefulness test (MWT) (Poceta et al 1992), also utilising EEG, has been developed to measure ones ability to remain awake in soporific situations. The MWT is also administered in four tests across the day, but patients are instructed to try and remain awake. Again SOL is measured in each test, averaged and used as an outcome measure of objective daytime sleepiness, but with an emphasis on sleep resistance.

For this research the MWT was employed for a variety of reasons. Firstly it is believed that the MSLT and MWT are measuring two separate physiological drives, with the MSLT measuring the tendency for sleep and the MWT the ability to remain awake (Mitler et al 1982, Sangal et al 1992a). As such, the MSLT may be more useful for diagnoses of excessive sleepiness whilst the MWT may be a better tool to measure the ability to remain awake. Therefore MWT may be more valid when occupational or driving safety is a concern. At study inception there were indications that the MWT was able to discriminate sufferers of excessive sleepiness from the normal population (Doghrammi et al 1997) and evidence to support that it is sensitive to treatment interventions (Sangal et 1992b). Because its setting and instruction may be nearer to everyday roles than the MSLT, the MWT may offer better ecological validity.

For this research study the MWT test was conducted in the patient group on their baseline visit. It was administered in four evenly spaced trials at 1000, 1200, 1400 and 1600 hours, to allow for circadian effects on sleepiness. Participants sat comfortably upright on the bed with head and neck supported, they were instructed to try and remain awake and not to use any behavioural methods such as singing, exercising or

reading that may help keep them awake. The tests are terminated if the patient has successfully maintained wakefulness for forty minutes, if three consecutive epochs of stage 1 sleep or one epoch of any other stage of sleep (Poceta et al 1992) is recorded. However we have in-house modification for the termination criteria to allow termination after one epoch of any stage of sleep. This was because sufferers of OSAHS often have respiratory events during episodes of sleep in these tests which may terminate with an EEG arousal making it difficult for patients to maintain stage one for three epochs. However for this thesis, in many cases two consecutive epochs of sleep as defined by Rechtschaffen and Kales (1968) (section 3.2.1) were recorded before the test was terminated to further reduce the chance of the test being stopped in error.
The average SOL (sleep onset latency) from the MWT is used as an objective outcome measure of sleepiness in the patient sample.

3.4.1 Reproducibility of MWT Scoring

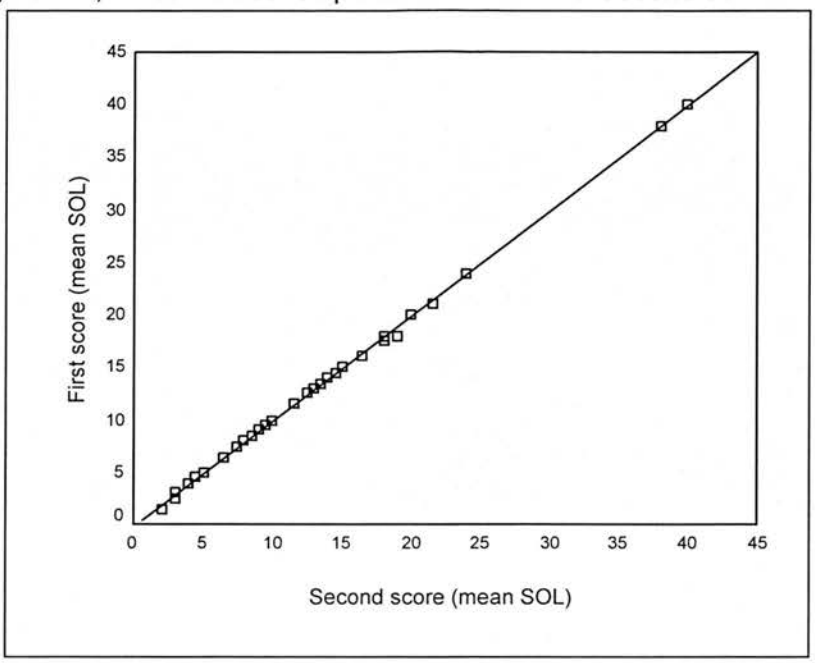
To ensure my scoring of the 45 MWT sets was reliable, 12 sets (48 tests) were chosen at random by our research technician, which I re-scored, blind to patients' identity and previous score, at least one year after the original score.
Reproducibility of the mean (SD) of the SOL for each test time, as well as the overall mean produced strong correlation co-efficients, assessed by Pearson correlation and suggesting high reproducibility. The correlation between these scores is shown in table 3.2.

Table 3.2; Correlation of SOL between the first and second score on MWTs (n=12)

Daytime nap	First score Mean (SD) In minutes	Second score Mean (SD) in minutes	R value*	Difference first score mean - second score mean in minutes
1000MWT	17.8±14.1	17.8±14.1	.98	-0.04
1200MWT	13.3±9.6	13.3±9.7	>.99	-0.08
1400MWT	14.1±13.1	14.2±13.0	>.99	-0.13
1600MWT	21.7±14.4	22.7±14.3	>.99	-0.03
Overall	16.9±12.9	16.8±12.9	.98	-0.07

*All values significant at level $p<0.01$

Figure 3.7; Linear relationship between First and Second scores of MWT



3.5 Recruitment and Procedures for the AusEd Driving Simulator Study

Procedures

Potential patients were identified using the Edinburgh sleep centre patient appointment dairy. Patients booked for a polysomnography investigation night were identified as potential recruits on the basis of their referral letter for assessment of OSAHS. Patients were recruited under the following criteria:

Inclusion criteria: Epworth Sleepiness score (ESS) ≥ eight; an AHI of five or greater; two major symptoms of OSAHS (Whyte et al 1989); aged between 18-70; ability to understand the consent procedure; holds full drivers licence; no serious neurological, cardiovascular or respiratory disease; no other co-existing sleep disorder.

Exclusion criteria: Lives more than 50 miles form sleep centre; driving as their occupation; not been seen by sleep consultant; to receive treatment other than CPAP

treatment; MSLT, MWT, or clinic appointment already booked for day after PSG; CPAP titration night already booked by consultant.

Patients were initially contacted by letter not less than one month prior to their polysomnography (PSG) investigation night and invited to participate. They were also called by telephone to provide further information if requested and confirm their interest in participating in the study.

Patients who agreed to participate in the study attended their PSG investigation and remained in the sleep centre the following day. On the morning after their PSG night, I spoke with the patients and completed the consent procedure. At this point patients completed the ESS on the basis of which they were assigned to a higher (ESS >14) or lower (ESS <14) randomisation schedule. Stratified, within group block randomisation was used to determine both AusEd simulator test time (morning or afternoon) and their treatment group (CPAP or placebo). This served to reduce the effects of circadian rhythms on driving performance, and ensured that neither ESS group were completely randomised to one of the treatments.

On successful completion of baseline testing, patients were given provisional dates to return, initially for their CPAP titration night and subsequently for repeat daytime testing. Patients were informed that continued inclusion in the study was dependent on results of their diagnostic overnight studies, and that they may not progress further within the study.

This was to allow scoring of the PSGs and ensure that if they did not then meet the study criteria (e.g. AHI ≥5) that they could be excluded from the study and returned to the clinical system to be seen at clinic by their consultant. If they were eligible to continue they were then contacted by their consultant to advise them they had been diagnosed with OSAHS. I also contacted them to confirm their study appointment dates.

Letters were sent to the general practitioners of all patients who continued to the treatment limb of the study, detailing their participation in the study and informed the patient would be randomised to either CPAP or a capsule treatment. A sealed envelope was included with this letter containing information on the capsules. With it, a request not to divulge the nature of the capsule treatment and to contact us if the envelope needed to be open.

The sealed enveloped contained the following:

The capsule treatment is a placebo (inactive). Please do not hesitate to contact Professor NJ Douglas or Dr. TW Mackay if you have further queries.

Letters used in the recruiting of the patients are included appendix 1

3.5.1 Second Assessment day

After not less than 28 nights using the CPAP or placebo treatment, patients returned for a half day of testing when they were re-tested on the AusEd-driving simulator and repeated the baseline questionnaires.

The re-test of the AusEd driving simulator commenced no later than 12noon, on the day of testing. No afternoon drives were conducted. Once patients had completed the study, I was un-blinded to the treatment that they received. If the patient had been randomised to CPAP, I re-issued patients with a home CPAP machine, set at the pressure from their overnight CPAP titration. This also allowed me to trouble-shoot with staff help any issues with the mask etc. If patients had been randomised to the placebo capsule, I then re-educated them about the CPAP machine and issued them with a home CPAP machine, again set at the pressure from their CPAP titration night

Table 3.3 shows the demographics of the 45 patients who completed the study.

Table 3.3; Demographics of study population

	Mean and SD	Range
Age (years)	50.9 (8.7)	35-68
TST (mins)	367.7 (63.5)	159-454
AHI (/hr slept)	38.9 (22.0)	8.3-97.1
BMI (kg/m^2)	32.6 (6.2)	23-53.46
Neck (cm)	42.1 (3.5)	31-49.5
MWT SOL (mins)	19.8 (10.4)	3.25-40

3.5.2 CPAP Titration Night

All patients underwent a CPAP titration study regardless of their treatment randomisation. Patients were educated about sleep apnoea/hypopnoea syndrome and CPAP on their baseline visit, fitted with a CPAP mask and offered the opportunity to ask questions. They then had a 30-minute CPAP trial in a darkened room. This not only provided an opportunity to ensure the mask fitted correctly but also provided the opportunity to experience the feeling of the positive pressure before their overnight titration study.

Titrations were conducted using either AutoSet or AutoSet T CPAP machines (ResMed, Australia) under the supervision of experienced specialised sleep nurses. Any problems, for example, mask fitting or leak, inability to get to sleep etc were dealt with as they occurred and remedied. Titration usually commenced between 10.30 and 11.00pm and ended around 6.30-7am the next morning.

3.5.3 CPAP Treatment

Patients randomised to receive CPAP treatment for the month were interviewed by a research technician in the morning. They explained care and usage instructions for the machine and made sure any questions the patients had were answered before sending them home with the AutoSet T unit. Patients were given a number to call if they had any problems during the month. I was blind to the treatment and did not have any contact with them for the month, apart from if their return date had to be changed.

Initially patients were given the AutoSet T machine capable of varying pressure between four and twenty cmH_20. However since these patients were naïve users, some had difficulty in dealing with the ramping pressure from the machine, both in terms of breathing with the higher pressure and the noise from the machine itself. As this problem was listed by patients as one reason why they were limiting home CPAP use in the one month trial, it was decided that a maximal pressure of four cmH_20 above the titrated pressure recommended by their over night titration. This was programmed on the AutoSet T machine. Hence patients received variable pressure across a restricted pressure range.

At the end of the treatment trial, the AutoSet T memory was downloaded and this provided data on night-to-night use, leak and a pressure profile for the period used.

Both the AutoSet and AutoSet T machines calculate the 95th percentile pressure levels required during the titration study and median mask leak values. These values are used to determine if there has been high leak from the mask over the night. If not, the 95th centile pressure value is usually used to determine the fixed pressure for long-term home CPAP treatment.

3.5.4 Placebo Treatment

The current study used a parallel group design to assess effects of CPAP on performance on the AusEd-driving simulator on OSAHS patients before and after treatment. A second arm with oral placebo treatment was incorporated, which allowed quantification and to control for learning and placebo effects with permission from both the local and university ethics committees.

Patients were not randomised to treatment until the morning after their CPAP titration when they were informed that the oral placebo capsule might be useful in the treatment of OSAHS. At the study inception 'Sham' CPAP had not been fully developed and tested and concerns regarding its effect on both sleep disruption and oxygenation existed. Therefore an oral placebo, which has no capacity to harm, was chosen. An oral placebo has been used in a variety of OSAHS studies conducted of physiological changes with treatment (Faccenda et al 2001), neurocognitive changes with treatment (Engleman et al 1994a), and subjective awareness of treatment (Mcardle et al 1999).

As with patients randomised to CPAP, a research technician saw the placebo-assigned patients the morning after their CPAP titration night and issued them with the "capsule treatment". This was given in a sealed white medicine bottle containing 35 white caplets, labelled 'trial medication'. They were instructed to take one capsule with water before going to bed. Patients were also given a number to call if they had any problems during the month. Again I had no contact with patients unless appointment dates had to be changed. It was stressed to patients on each visit that if they were randomised to receive the capsule treatment, they could be placed on CPAP treatment either on completion of, or withdrawal from the study.

3.5.5 Control Subjects

Adverts seeking drivers 30 years and older were placed on notice boards in and around the hospital area. An advert was also placed on the Edinburgh University staff web page and e-mail was sent to all NHS staff in the Edinburgh Royal Infirmary.

An advertisement was placed in the local free paper, as well as in the hospital monthly newsletter. One hundred and forty-four local businesses including food stores, libraries, sports clubs and health centres were contacted by letter, requesting they place a copy of the volunteers wanted poster on their staff and public notice boards.

Copies of the adverts and the letters sent to companies are in appendix 2.

Entry criteria for volunteer subjects were as follows:

Inclusion criteria: ESS <11; holds full drivers licence; no serious neurological, cardiovascular or respiratory disease; aged between 18-70; ability to understand consent procedures;

Exclusion criteria: Symptoms of sleep apnoea, frequent snoring, witnessed breathing pauses, regular napping in day or evening; symptoms of other sleep disorders.

Volunteers were matched with patient's randomised to CPAP, for their age (±5years), sex and time (morning or evening) of their initial AusEd driving test. Volunteers were screened using an in-house questionnaire and telephone interview.

Recruitment and assessments

Patient Study Schedule	Volunteer Study Schedule
Identify possible participants	Advertise for volunteers
Contact possible participants	Send screening questionnaire and
Include in study if initial inclusion Criteria	Information pack
Attend for PSG Night	Telephone interview to confirm
Stay next day for testing (baseline)	Inclusion criteria
Randomised to high or low ESS group	Attend for testing
CPAP titration night	
Randomised to either CPAP or Placebo	
Treatment period (1 month)	
Repeat testing day	

3.6 AusEd Pilot Study

Before patients were recruited for full the randomised control trial of simulated driving performance, a small pilot study was undertaken. Eight members of the Edinburgh sleep centre staff volunteered to 'drive' on the AusEd simulator and to undergo the cognitive tests used for the study. A further two volunteers underwent testing, completing the full day of assessments that patients would undergo at the baseline assessment. Statistical analysis of these limited data was not conducted. The pilot study served to ensure that all methods used for the study were possible in the allocated time and allowed practice of setting up, administering and saving data on all of the procedures of the study. These practise sessions highlighted any problems with the original layout of the study, and were corrected and tested before patients entered the study. Three problems were highlighted by the first eight volunteer subjects. Firstly four volunteers noted that they were unable to feel the accelerator and brake pedals due to the thickness of the soles of their shoes and two volunteers 'drove' in their bare feet, to compensate. Secondly a similar issue was raised that the sole of their shoes could become stuck under the side of the brake pedal whilst their foot was resting on the accelerator and this could inhibit them from moving between the accelerator and

brake pedal quickly (which was part of the task). The third problem concerned the placement of the actual AusEd driving simulator PC. Its initial placement inhibited a clear view of the subjects and the screen of the PC from a video camera overhead. This inhibited the recording of concurrent EEG whilst the patients were driving on the simulator, and would not allow me to see if any problems occurred during the test.

Wearing slippers whilst driving reduced the problems the volunteers experienced with the pedals. The thinner soles of the slippers allowed better feeling and reduced the amount of material around the edge of the feet, which reduced the chance of it becoming stuck in-between the pedals.
The AusEd simulator was also repositioned to allow full view of the patients and the screen of the PC.
These changes were then implemented, and tested by the two volunteers who completed full days of assessment.

Once all ten volunteers had completed the pilot study, recruitment began for the actual AusEd driving simulator study.

3.7 Psychometric measures In the AusEd driving simulator validation study.

All participants in the AusEd driving simulator validation study completed questionnaires concerning sleepiness, quality of life, OSAHS symptoms and driving history, at baseline. Patients completed these again after one month of treatment. Questionnaires included in the validation study were given to the participants in one batch, with verbal instructions on how to complete the questionnaires, and were then left alone to complete them.
The cognitive tests and the SteerClear vigilance task were only administered at baseline in both groups. Figure 3.8 shows the outline of the questionnaires and tasks the two groups completed. Copies of all the questionnaires are in appendix 3.

Figure 3.8; Patient and Control: questionnaires and cognitive tests

PATIENTS

Baseline	Post-treatment
Questionnaires	
SF-36 FOSQ ESS In-house symptom scale In-house driving questionnaire prt1 In-house computer use Karolinska sleepiness scale In-house side effects questionnaire	SF-36 FOSQ ESS In-house symptom scale In-house driving questionnaire prt2 Karolinska sleepiness scale In-house side effects questionnaire In-house treatment & subjective usage questionnaire
Cognitive Tests	
NART RSPM	No cognitive tests were completed
Vigilance /Driving tasks	
MWT SteerClear AusEd	AusEd

CONTROLS

Questionnaires

In-house Sleep/Wake Questionnaire
SF-36
FOSQ
ESS
In-house symptom scale
In-house driving questionnaire prt2
Karolinska sleepiness scale
In-house side effects questionnaire
In-house sleep/wake questionnaire

Cognitive Tests

NART
RSPM

Driving tasks

AusEd

3.7.1 Demographic Measures

Both patients and control subjects had the following data collected.
Height was measured using a standardised height bar; this was recorded as meters and centimetres. Weight was measured using the standard Sleep Centre scales (Seca, Germany), which are calibrated annually, and recorded as kilograms and grams, these were used to calculate BMI (BMI = weight/height$^{2)}$.
Neck circumference was measured at the level of the circo-thyroid membrane, and was recorded in centimetres.
These variables were recorded at each visit.

Education level was recorded at baseline as one of three levels, basic high school education (e.g. O grades), higher education (e.g. A levels or higher grades) or further education (HND or degree). Previous medical history was recorded prior to inclusion in the study, to assess exclusion criteria.

3.7.2 Measures of Daytime Function

Short Form 36 UK Version (SF36 UK)
(Ware 1993, Jenkinson et al 1996)

BACKGROUND: This generic, self-administered, health questionnaire measuring perception of ones own health has 36-items assessing 8 multi domains and a single item on health change in the past year. Responses are either yes/no, true/false or frequency responses. Raw scores from each domain are summed and then transformed, giving each domain a scale of 0 (worst possible health perception) to 100 (best possible health perception). Table 3.4 show the main 8 domains of the questionnaire

Table 3.4; SF-36 Domains – areas of measurement

SF-36 Domain (No. of items)	Low score	High score
Physical Function (10)	Limited a lot in performing physical task e.g. bathing due to health	Able to perform all types of physical tasks without limitation due to health
Social Functioning (2)	Frequent interference of social activities due to physical or emotional health problems	No interference of social activities from physical or emotional problems
Role limitations-physical (4)	Problems with work or daily activities due to physical health	Work and daily activities unhindered by physical health
Role limitations-emotional (3)	Problems with work or daily activities due to emotional problems	Work and daily activities unhindered by emotional problems
Vitality (4)	Feels tired and with no energy all of the time	Feels full of energy all the time
Bodily pain (2)	Activities limited due to bodily pain	No pain or no limitations due to pain
Mental Health (5)	Feels depressed and nervous all the time	Feels calm and happy all the time
General Health perceptions (5)	Believes health is poor and is likely to get worse	Believes Health is excellent

The single item measuring perceived health change in the last year is measured on 5-point scale from 1 (health much better) to 5 (health much worse). The eight scales form two principle components, the physical components summary (PCS) and mental components Summary (MCS). Table 3.5 shows how the summary scores are derived.

Table 3.5; Components comprising the Physical and Mental summary scales

Summary Measures	Derived from scales
Physical component summary	Physical functioning, role physical, bodily pain, general health
Mental component summary	Social functioning, role emotional, vitality, mental health

VALIDATION: This questionnaire was validated and normative data produced by the Oxford Healthy life survey (Jenkinson 1996). This postal survey incorporated the SF-36 with questions on life style and demographics. Completed results were obtained for 9332 respondents from a possible 13,042 randomly unstratified subjects. As normative data was to be calculated, the sample had to be shown to be representative of the population norm. The socio-demographics of the sample were found to represent the

general population when compared to both the 1991 population estimates and social class distribution from the 1981 census.

Using Cronbach's alpha statistics, Jenkinson et al (1996) demonstrated that the internal reliability, which is defined, as the extent to which there is a correlation between each of the variables within a scale, was good for each of the 8 dimensions. There is some disagreement over the acceptable level of alpha for the level of internal consistency, however most well developed scales in practise should gain alpha values of 0.8 or greater (Carmines and Zeller, 1979). The SF-36 scales all produced alpha scales of 0.8 or greater except that of social functioning, which was 0.76, however as there are only two items in this dimension the result is acceptable.
Factor analysis was also conducted for the two summary scales of PCS and MCS. The internal reliability of these two summary scales were broken down to provide estimates for males and females, those reporting long standing illness and those not, all of which gave alpha values of .09 an greater for both the PCS and MCS.

The SF36 has been used to provide health profiles for a large variety of illnesses and is documented in OSAHS studies. Smith and Shneerson (1995) found that the SF-36 was indeed sensitive to OSAHS, with subjects requiring treatment for OSAHS scoring lower on all scales of the SF 36 ($P < 0.05$) than the normative scores for the general population. They reported that after six months of CPAP treatment there was an improvement in all scores. Jenkinson et al (2001) also provided support that the SF-36 was sensitive to change in OSAHS. Comparing CPAP to sham CPAP they reported no significant differences between the groups at baseline, however, at one-month follow up there were significant and substantial improvements on the active CPAP as compared to SHAM. The sub-therapeutic group improved to similar values as the original active group after 5 months of active CPAP, providing evidence for both the sensitivity of the SF-36 and the treatment capacity of CPAP.
The SF-36 has normative data, established internal reliability and previous study results indicate it is sensitive to change in the OSAHS population.
TIME NEEDED FOR COMPLETION: 10 MINUTES

Functional outcomes of sleep questionnaire (FOSQ)
(Weaver et al 1997a)

BACKGROUND: This sleep specific questionnaire assesses the impact of excessive daytime sleepiness (EDS) on multiple daytime activities. This self-administered questionnaire consists of 30 questions measuring five multi-item domains, these five domains being: activity level (9 questions), vigilance (7), intimacy and sexual relationships (4), general productivity (8) and social outcome (2).

Functional status is defined within this questionnaire as

"Everyday behaviours encompassing the areas of physical, mental, and social functioning in daily life" (Weaver et al pg.192).

Thus, each item asks about how sleepiness (instructions distinguish between sleepiness and physical fatigue) affects a variety of daily activities. Respondents choose the answer most appropriate to them at the time from 'no difficulty' to 'extreme difficulty'. For some questions, for example attending a church service or participating in physical exercise there is the option of 'I don't do this activity for other reasons'.

A mean-weighting system for the scoring of the responses is used allowing for analysis only of the activities the respondent participates in. The mean weighted system gives a score out of 4 for each of the domains, and these scores are used to calculate a total score out of 20. However for the current study we omitted from the questionnaire the questions concerning sexual activity and intimacy, to prevent causing offence or diminishing rapport with our patients and volunteer subjects. Hence for analysis in this study the sub-scales are still out of 4 but our total score is 16. A low score indicates that sleepiness is affecting quality of life and functional status.

VALIDATION: This questionnaire has been validated for use with OSAHS patients and control populations (Weaver et al 1997a).

Three groups were used in the validation study for the FOSQ. Group 1 consisted of 133 people seeking medical attention for a sleep disorder and 20 controls of a similar age, groups two (n=23) and three (n=51) comprised of patients from two sleep disorder clinics diagnosed with OSAHS. Factor analysis confirmed the five subscales now routinely used in the FOSQ and internal reliability of these domains were acceptable with Cronbach's alpha co-efficient greater than 0.8 in each domain and an alpha value of 0.95 for the global score. This study was also able to provide evidence to support that the FOSQ is sensitive to the functional outcomes relevant to daily life, by discriminating between patients attending for a sleep problem and controls of a similar age (p=0.0001). A sub-group (n=32) of the patients attending for diagnosis of a sleep disorder were analysed to assess test - retest reliability over a one-week period. This yielded acceptable coefficients ranging from 0.81 to 0.90 for the sub-scales and 0.90 for the global score.

Faccenda et al (2002) used FOSQ as an outcome measure in a randomised placebo controlled trail of CPAP on blood pressure in patients with OSAHS, in which four of the five domains, as well as the global score were significantly improved on CPAP in comparison to oral placebo. General productivity being the only sub-scale not to show a significant difference. Montserrat et al (2001) used the FOSQ as functional outcome measure in CPAP and sham CPAP groups. They found significant improvement for four of the five sub scales and the global score in the active CPAP group compared to their baseline score. Three of the five as well as the global score in the sham improved, again in comparison to their baseline score. Between-group comparison showed significant differences for the domains of vigilance and general productivity only, and not in the global FOSQ score. However the authors themselves suggest this may be a result of the small sample size (n=45).

The FOSQ is a useful tool in OSAHS research as each domain represents a life area which may be adversely affected by sleepiness. The aforementioned studies add support to OSAHS sensitivity to treatment change.
TIME NEEDED FOR COMPLETION: 10 minutes

The Epworth Sleepiness Scale (ESS)

(Johns et al 1991, 1992, 1993, 1994)

BACKGROUND: This is a subjective, self-administered questionnaire. It was developed to measure subjective sleepiness as it occurs in eight every day situations. These situations vary in their soporific nature and respondents rate their chance of falling asleep in these situations on a scale of zero (no chance of falling asleep) to three (high chance of falling asleep). Therefore the maximum score on the test is 24, and the higher the score the sleepier they perceive themselves.

VALIDATION: The ESS is a simple, widely used and, to some extent, a validated scale for measuring perceived sleepiness. As a trait measure of sleepiness the scale aims to quantify sleepiness over a period of time rather that from an instantaneous measure. Ideally the scale would show, all things remaining equal, that scores on the ESS hold over time as well as show that it is sensitive to changes in sleepiness by either treatment intervention or changes within the condition.

Johns et al (1992) were able to provide evidence of reproducibility by re-testing 87 healthy non-sleep disordered medical students at five months apart. Scores from the two administrations did not change significantly and were highly correlated ($r=0.82$). In treatment sensitivity, they found that scores from sufferers of OSAHS reduced to near normal levels (<8) after 3-9 months of CPAP treatment. Factor analysis of the scale found high internal consistency (Cronbach's alpha of 0.88) and showed the ESS had only one factor for both a group of healthy non sleep disorders medical students and a group of patients with various sleep disorders.

The ESS scale has been employed in a variety of studies in which its usefulness as an indicator of sleepiness after treatment (Hardinge 1995, Faccenda 2002) has been established, as well as its use in studies documenting significantly higher scores in OSAHS than scorers and non-sleep disordered breathers (Hayakawa 2002).

TIME NEEDED FOR COMPLETION: 5 minutes

In house symptom scale

BACKGROUND: The Edinburgh Sleep Centre symptom scale consists of 16 symptoms that are classically associated with the sleep apnoea/hypopnoea syndrome, these symptoms being;

- Snoring in sleep;
- Breathing pauses in sleep;
- Choking attacks in sleep;
- Unrefreshed by night time sleep;
- Falling asleep in the daytime;
- Falling asleep in the evening;
- Tiredness;
- Feeling sleepy whilst driving;
- Falling asleep when driving;
- Feeling depressed and 'low';
- Low sex drive;
- Excessive irritability with friends, colleagues or family;
- Concentration problems;
- Forgetfulness;
- Falling asleep at work;
- Poor performance at work.

Respondents indicate how they are affected by these symptoms on a four point scale from 'not present' to 'a constant problem', with the option of 'don't know/NA' for those who have no partner to witness night-time events, or if they are unemployed or retired. Each symptom has a minimum score of one and a maximum of four; these individual scores are added together to give a total score out of 64.
TIME NEEDED FOR COMPLETION: 5-8 minutes.

In house driving questionnaire (Patients baseline) part 1

BACKGROUND: This in-house driving questionnaire investigates driving history for the previous 5 years. It consists of 6 questions and takes around 15 minutes to complete. In it we ask how long the respondent has held a drivers license, how many miles they drive a year, if driving is required by their occupation and how many days a week they drive. It also asks the respondent to indicate how they perceive their ability to drive long distances (>75 miles) as compared to other drivers, on a 5-point scale from 'very poor' to 'very good'. They are also asked how many accidents they have had in the past five years. These are split into:

- Near Miss Accident - Almost had a collision but avoided at last moment
- Minor Accident - Collided with property or person, but no people injured
- Major Accident - Collided with property or person, and people were hurt

They are then requested to indicate how many of these accidents were caused by sleepiness. A second page allows space for a brief description of the accident circumstances.
TIME NEEDED FOR COMPLETION: 10-15 minutes.

In-house driving questionnaire (Patient follow up and Volunteers) part 2

BACKGROUND: This questionnaire repeats the same questions in the same order as in part 1, however, it now asks about driving ability and accidents rates in regards to the last month as well as asking about accident rates in the last five years. This allows comparison of perceived driving ability before and after treatment of our patient groups as well as between our patients and volunteers.
TIME NEEDED FOR COMPLETION: 10-15 minutes.

In-house computer usage questionnaire

BACKGROUND: This is an in-house, self-administered 8-question survey. It is used to assess previous computer experience of our participants. This very basic questionnaire asks about use of computers for work, leisure and games. Answers are in the form of yes/no, frequency response or a choice from an option. Questions include:

- Do you use a computer in your place of work?
- In an average week how many days do you use a computer for work?
- Do you have access to a computer at home?
- In an average week how many days do you use a computer for leisure purposes?
- Do you use your computer to play games?

TIME NEEDED FOR COMPLETION: 6 minutes.

Karolinska sleepiness scale
(Åkersdedt and Gillberg, 1989)

BACKGROUND: This scale is used to assess the level of subjective sleepiness at the time of completion. It is a 9-point, verbally anchored scale, in which respondents indicate how they are feeling. The scale is as follows:
Extremely alert (score 1), Alert (3), Neither alert nor sleepy (5), Sleepy but no difficulty remaining awake (7), Extremely sleepy – fighting sleep (9). The steps in between have a scale value but no verbal label. It is extremely easy to use and takes minutes to complete. This is a useful tool assessing sleepiness ratings at a particular moment rather than general sleepiness level. As a standardised scale it allows comparison between respondents under the same conditions.
VALIDATION: This scale has been shown to be sensitive to increases in sleepiness and shows high correlations with performance tasks (Gillberg et al 1994).
TIME NEEDED FOR COMPLETION: 1 minute

In house side effect questionnaire

BACKGROUND: These questionnaires were designed to assess if patients were affected by side effects from their treatment. For the active treatment group (CPAP), there was a list of 13 common problems associated with using CPAP treatment these being:

Nasal stuffiness/nose bleeds; Dry throat; Wake up with mask off; Red or sore eyes; Difficulty in falling asleep or frequent wakenings; Stomach bloating or 'wind'; Chest Wheeze; Difficulty in exhaling with mask; Sore or rubbing mask; Leaking of air from mask; Unpleasant appearance of CPAP equipment; Excessive noise from CPAP unit (for you or your partner); Inconvenience not worth the benefits.

Each of these side effects were rated on their severity from 5 options these being: Problem not present; Problem present but not affecting CPAP use; Problem present-limiting CPAP use; Problem present stopping use; Problem present even before CPAP use.

Although the 'capsule treatment' was inactive, 'placebo side effects ' are commonly found, and so those randomised to placebo were also given a side effect questionnaire. A balance was sought between listing possible side effects of an active pharmacological treatment and between overloading the questionnaire so 5 possible side effects were listed these being:

- Dry throat
- Difficulty falling asleep or frequent wakenings
- Nausea
- Headaches
- Dizziness

These were graded on severity on the same scale as the CPAP side effects mentioned above, with the word capsule used instead of CPAP. Both questionnaires also gave

the option for the respondent to note any other side effects they felt they had as a result of the treatment and they were asked to rate their severity also.
This questionnaire sought the problems associated with the treatment (which can be used to help assess if the subjective usage report) is accurate and so they can be addressed, which will increase the chance of the patients using the treatment long term.
TIME NEEDED FOR COMPLETION: 10 minutes

In-house treatment satisfaction and subjective usage questionnaire

BACKGROUND: This questionnaire is given to patients after they have completed their one-month of treatment, either using an Auto Set T CPAP machine or taking an oral placebo capsule. The questionnaire asked patients to rate treatment they had been using for the previous month on three 10-point scales. They were asked to indicate how effective their treatment was for improving symptoms (useless and completely ineffective to completely effective), how acceptable they found the treatment (extremely inconvenient and unacceptable to extremely convenient and acceptable) and how satisfied overall they were with the treatment they had been using for the previous month (extremely unsatisfied to extremely satisfied). They were also asked to provide details on how many nights per week they used their treatment, how many hours per night they used it and finally, how long they used their treatment on the night before returning to the sleep centre.

This questionnaire allows comparison of treatment satisfaction between the active and inert treatments and gives a measure of subjective treatment usage.
TIME NEEDED FOR COMPLETION: 5 minutes.

In-house sleep/wake questionnaire

BACKGROUND: The function of this questionnaire in the present study is to screen possible volunteers for inclusion, not for statistical analysis within the study. It was adapted from a clinical questionnaire in use at the Edinburgh Sleep Centre as a method of gaining background information from our patients before attending for their initial consultation. This information included smoking/caffeine and alcohol intake, previous

health issues (including present medications), sleep pattern, nocturnal events, OSAHS symptoms, perception of subjective sleepiness and driving ability, as well as symptoms of other common sleep disorders. The questionnaire was sent to possible volunteers and on its completion and return I reviewed it before calling possible participants to discuss it with them. If an absence of subjective symptoms of sleepiness, sleep apnoea or other sleep disorders was confirmed they were invited to attend the sleep centre for inclusion in the study.
TIME NEEDED FOR COMPLETION: 15-20 minutes.

SteerClear
(Findley et al 1989b)

As discussed in section 2.10.2 this is a thirty-minute PC based vigilance task.
TEST ADMINISTRATION: Subjects sit looking directly at the PC screen. There is presented a birds-eye view of a two-lane road, on which cows randomly appear on either lane. The subjects' aim is to avoid hitting the cows (steers) by pressing the space bar on the PC keyboard placed on the computer table directly in front of them. Subjects are given a one-minute practice test before beginning the thirty-minute test. The test was performed in darkness to enhance any soporific effect.

3.7.3 Cognitive Performance Tests

The National Adult Reading Test (NART)
(Nelson 1982)

This test was designed as a tool for estimating the pre-morbid intelligence of adults who may be suffering from intellectual deterioration.
It is based on the rationale that word reading ability and general intelligence are highly correlated in normal adults and that reading ability is retained even under conditions like dementia. It provides an estimate of intellectual functioning before the onset of illnesses like OSAHS. It consists of 50 words that have generally accepted pronunciation, but that are 'irregular' with respect to the normal rules of grammar. Hence pronunciation using these rules would be incorrect. The correct pronunciation is expected only if the

subject knows and recognises them when written. It was originally designed as a tool for predicting pre–morbid IQ in sufferers of dementia. Research has shown that word reading ability is highly correlated with general intelligence in normal healthy adults and that this ability is both held over time (Nelson et at 1975) and in subjects with dementia (Nelson et al 1978). In recent years the NART has become a widely used tool for to predicting pre-morbid IQ levels of intelligence in neuropsychological research in areas out with dementia sufferers (Bright et al 2002), including OSAHS (Kingshott et al 1999a), diabetes mellitus (Taylor et al 2003) and age related cognitive decline (Starr et al 1997). Recent research has shown that the NART is still a valuable tool for predicting pre-morbid IQ as Crawford et al (2001) were able to correlate current NART performance scores to IQ scores obtained 66 years prior.

The NART is a quick and easy test to administer and is not stressful for the majority of the respondents.

TEST ADMINISTRATION: Participants were given the list of words and are asked to pronounce each of them. They are made clearly aware that there may words with which they are unfamiliar and are asked to give their 'best guess' in these cases. The administrator records the number of words correctly pronounced. This raw score is then translated into predicted IQ scores using published tables (Nelson 1982).
There is no time limit for this test, and it usually takes around five minutes to complete. After robust training in the accepted pronunciations of each of the words it is an easy test to administer and an enjoyable test to complete.

Ravens Standard Progressive Matrices (RSPM), Sets A-E
(Ravens 1998)

The Ravens Standard Progressive matrices are based on observations and theories postulated by Charles Spearman. Spearman proposed a 2-factor theory of intelligence. According to Spearman's theory of general intelligence the performance of any intellectual act requires some combination of a general intelligence factor '**g**', which is available to the same individual to the same degree for all intellectual acts, and of

specific factors or '**s**', which are specific to that act and which vary in strength from one act to another.

The RSPM is a non-verbal assessment of the eductive component of general intelligence '**g**'. Eductive ability refers to the ability to from new concepts, to be able to identify patterns and meaning in confusion, and the ability to identify relationships.
The RSPM test hopes to measure the ability to form perceptual relationships by analogy independently of formal schooling or language. The Ravens Standard Progressive Matrices (RSPM) consists of five sets of

"Diagrammatic puzzles exhibiting serial changes in two dimensions simultaneously" (Ravens 1998, pg. 1)

The term progressive is used because the items are arranged so that the person taking the test is gradually absorbed into the particular frame of thought needed for their solution.
The test has 60 items split into five sets, A-E with each set comprising 12 puzzles. Below each puzzle there are 6 (rising to 8 in set C onwards) possible pieces that can complete the figure, only one piece in each item is correct, the person talking the test must chose the appropriate piece to complete the puzzle. Each of the 5 sets is based upon a different principle 'theme' and items get progressively harder in each set.

As standard, there is no time limit for the test. IQ values are established from the raw scores and converted to a percentile rank by using the appropriate published norms. For this study, completion of the RSPM was limited to 20 minutes to limit both time and patient stress. The 20 minutes method of administering the RSPM has not as yet been validated for use with the published normative data, but has been used elsewhere (Deary et al 2003) in conjunction with other validated IQ tests as a method of estimating general intellectual decrement.

As the RSPM hopes to measure eductive component of general intellectual functioning or '**g**', many studies have used factor analysis to estimate the construct validity of the test as regards its loading on '**g**'. Cross cultural studies conducted on both adults and

children have shown high loading on 'g' ranging from 0.81 in American children to 0.83 on British children and as high loadings in adult samples ranging from 0.86 to 0.94 (Raven et al 1998)

TEST ADMINISTRATION: Subjects were given verbal instructions on the aim of the test. They are then asked if they understand the instructions and are given an opportunity to ask any questions. They are then shown the first item in Set A and asked to choose the appropriate answer to complete the puzzle, if they answer correctly they are then reminded they have 20 minutes to complete the test and asked to continue. If they are unable to give the correct answer the instructions are repeated and they are then asked to choose again, if they give the wrong answer again further training is required before they can progress. All participants in the current study gave the correct answer initially.

3.7.4 General intellectual decrement scores

IQ decrement scores were produced by subtracting the standardised z scores of the raw SPM score from the standardised z scores of the NART raw score. These difference values were named as 'change' scores with a negative value indicating IQ decrement and poorer performance than pre-morbid z-score.

3.8 The AusEd driving simulator

The AusEd driving simulator program was designed in collaboration between Dr. Heather Engleman (Edinburgh Sleep Centre, Scotland), Professor Ron Grunstein (Royal Prince Albert Hospital, Sydney), Dr. David Joffe (Royal Shore Hospital, Sydney) and Mr Ben Constable (University of New South Wales, Sydney). The Program was written using PIRACE © engine technology.

Technical requirements

The minimum specification required to run the AusEd program;

Pentium II processor @350Mhz

Matrox™ G200 or G400 graphics card

64 bit sound card – generic

19 Inch VDU

128Mb RAM

Windows ™ or Windows 2000 operating system

Sound speakers

Internal Zip ™ Drive 250/100

Printer capability

Thrustmaster ™ T2 steering wheel accelerator and brake pedals

As previously noted in section 2.11 the AusEd driving simulator was designed as a potential test for fitness to drive and the research contained in this thesis was a validation study of its usefulness with obstructive sleep apnoea/hypopnoea sufferers. The task was built to provide monotony and visuomotor challenges in turn, in an affordable and portable format, to discriminate driving performance yet be practical and relatively easy to use regardless of previous computing experience.

The following outcome measures from the AusEd simulator are used in chapters 4, 5 and 6*.

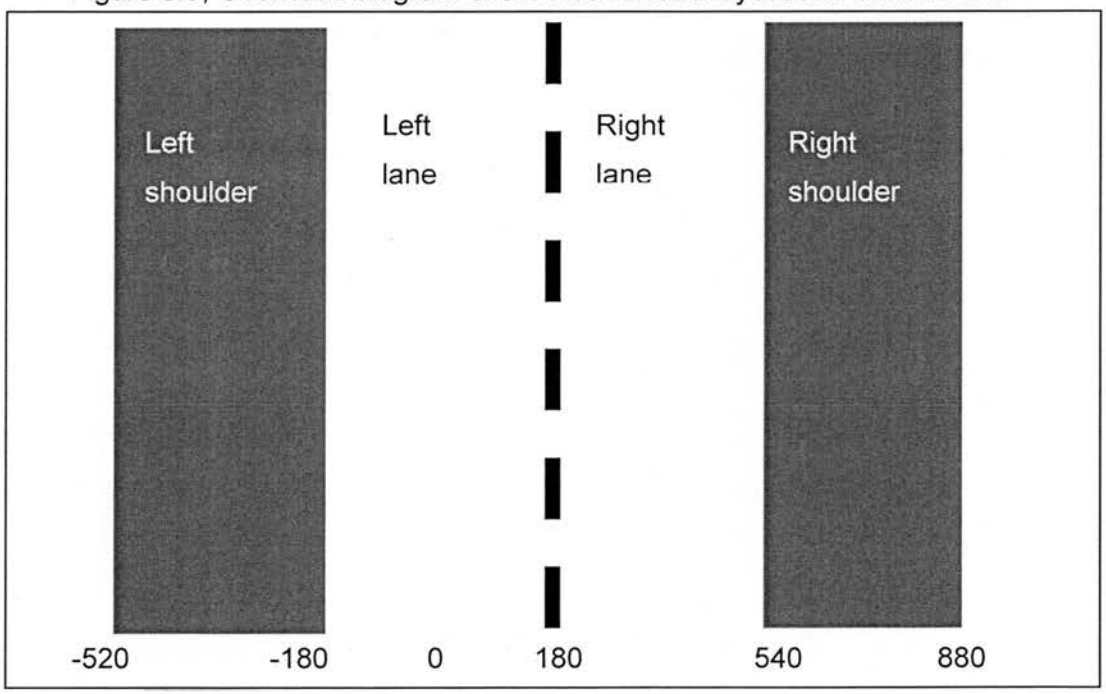
Outcome measures-

- Mean area of deviation from the lane centre (cm)
- Mean area of deviation from required speed (km/h)
- Mean road position
- Mean speed
- Number of driving-off-road events – left and right lanes*
- Number of crashes*
- Brake reaction time

3.8.1 Road layout for the AusEd simulator

The simulator was designed to replicate a lane width of 360cm and a hard shoulder width of 340cm. The analysis program of the simulator provides data based on these real life dimensions. Figure 3.9 demonstrates the layout and size of each lane and hard shoulder. The instructions for 'drivers' is to keep to the centre of the left lane, a mean lateral position of 0cm would indicate that the participant drove along exactly on the centre of the left lane.

Figure 3.9; Overhead diagram of the AusEd road layout and dimensions.



3.8.2 Road Settings for the AusEd Simulator

The AusEd simulator program presents a choice of road characteristics. On entering the set up menu the administrator is prompted by an interactive menu (see figure 3.10) to input both patients details and details on the length of the drive, the number of trucks requested and if left or right hand drive is required.

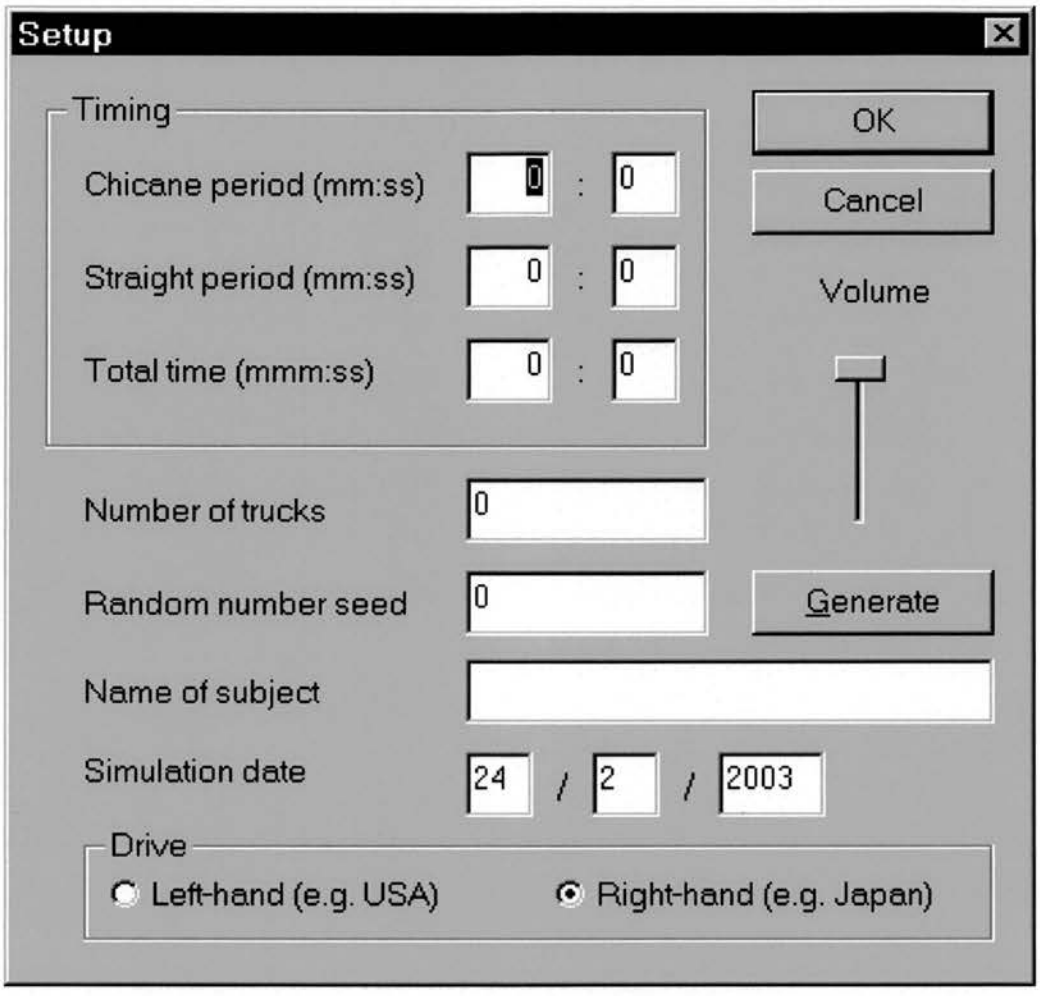


Table 3.6 shows the settings that were used in the current study.

Table.3.6; Variables used in the AusEd set-up menu

AusEd set up variables	Practice run	Test drive
Total time	5 mins	30 mins
Chicane period	1 mins	2 mins
Straight period	2 mins	5 mins
Number of trucks	5	10
Seed number	2611	153

All drives were conducted as a right-hand drives.

The total time refers to the length of the drive, the chicane and straight periods refer to the road layout. Each drive starts with a block of twisting chicane road layout. The lay

out then changes to straight road for the time period requested in the set-up menu. This means that the drive is made up of an alternating road layout of periods chicane road and straight road until the drive is over.
For the ten-minute practice run the road layout consisted of four, one-minute period of chicane road interspersed with three, two-minute periods of straight road. The 30-minute test drive consisted of five, two-minute periods of chicane road interspersed with four, five-minute periods of straight road.

Although the administrator determines the length of the time blocks for the chicane and straight periods, it is the seed number that determines the specific road layout. By pressing the generate button a random seed number would be produced and each drive would be different in terms of the properties of the chicane periods and whether these curvatures of the road were to the left or right. As this is a validation study, seed numbers were kept constant to ensure that each drive was identical in overall road layout.

The AusEd simulator was administered on a PC system via a 19-inch monitor on which a 2-lane road is displayed. White boundary posts divide the edges of both the out side lanes and small grass verges. As the simulator was designed as a night-time drive the areas beyond the grass, the horizon and the sky are all dark. The speedometer is situated on the top left hand side of the screen. Subjects sit with their eye level central to the computer screen and this gives the impression of being "behind the wheel". Although it was designed to be realistic as well as feasible, there is no hood of the car. This ensures that the 'drivers' cannot use the side of the car as indicators of road position.

Patients and controls were given both verbal and written instructions prior to performing the simulator task. After reading these, they were re-iterated to each subject verbally. All subjects were instructed to drive on the left hand side of the road, trying to keep to the centre of the left lane; not to leave the road and to bring the 'car' to a complete halt as soon as they saw a truck appear on the road in front of them. They were also asked to keep their speed between 60-80km as displayed on the speedometer. If they kept

their speed in this area between the 60 and 80 marks the speedometer turned green, if above or below this speed the area appeared red.

AusEd measures three cognitive skills important for driving, tracking ability, visual search and reaction time.

Subjects are given a ten-minute practice drive before commencing on a 30-minute 'real' drive. This practice run was to ensure that subjects understood the instructions and to give them the opportunity to ask questions if required. The results from the practice runs were not used for any statistical analysis.

3.9 Secondary Methods of Analysis

In addition to the main outcomes from the AusEd driving study secondary methods of measurement were employed.

3.9.1 Analysis of on Task EEG

Whilst performing on the AusEd simulator and the 'SteerClear' vigilance task both patients and volunteers had EEG, EOG and EMG recorded. Electrode placement was that described in section 3.2 again utilising a computerised polysomnography system (Series S Compumedics, Australia).

The bedroom in which all daytime recording for this research was performed was equipped with an infra red short circuit camera system, the PC on which both the AusEd and SteerClear programs were installed and were positioned so both the PC and "driver" were visible at all times. This made it possible to acquire concurrent EEG and EOG with AusEd and SteerClear output, as the EEG recording was started when the patients or volunteer commenced their drive.
Each person was given the standardised practice run as appropriate to each test, at this point the EEG and EOG signals were checked to ensure their clarity. If the wires

required maintenance or changing this was done before the 30-minute test commenced.

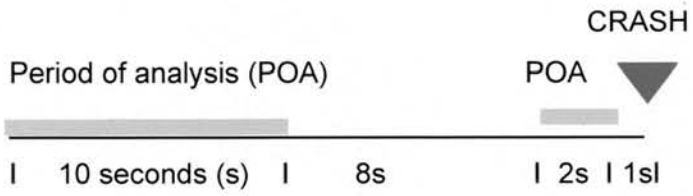
Concurrent EEG recordings from the AusEd driving simulator were produced and were used to analyse parts of the EEG that correspond to the following events;

- Crashes
- Driving-off-road events not leading to crashes

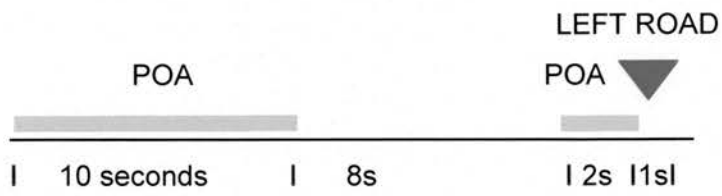
Figure 3.11 shows the types of events that were analysed and the period of analysis (POA) that was conducted.

Figure 3.11; EEG Periods of analysis (POA)

Crashes



Off Road Events Returning to Road



Crashes

Three types of crashes are recorded. These being:

- Off road crashes – the car swerves over the lane boundary and crashes at the screen periphery.
- Stop crashes – the 'car' is brought to complete rest. If the driver does not move off again within 10 seconds it is recorded as a stop crash.
- Truck crashes – the driver fails to reduce their speed and crash into the back of the truck.

For these events the following periods of the EEG were analysed:

- Ten seconds of EEG at 20 seconds before the crash.
- Two-second block of EEG preceding the second of the crash.

Off road events (not leading to a crash)

Off road events are recorded when the driver crosses the lane boundary, either on the left or right lane and travels along the grass strip situated on the outside of both lanes for any length of time before returning back to the lane.

For these events the following periods of the EEG were analysed;

- Ten seconds of EEG at 20 seconds before the of road event.
- Two-second block of EEG preceding the second they cross onto the grass verge.

Differences between 'driving-off-road crashes' and 'driving-off-road events not leading to a crash'

As previously mentioned a driving-off-road crash is recorded only when the car hits the periphery of the screen on either side of the road. However, a driving-off-road event not leading to a crash is different in respect that the car crosses the lane boundary and continues driving for a time before returning to the lane. In a real life situation crossing the lane boundary is a sign that the car is not being kept under control. For both these events the same time periods will be analysed for ten seconds, twenty seconds before leaving the lane and again at two seconds immediately prior to leaving the lane. This is

based on the assumption that slowing of the EEG is likely to happen in the period slightly before the loss of ability to control steering. Therefore the period before the initial event (i.e. the crossing of the lane boundary) is of interest, as any changes in the EEG will have occurred before the actual crash.

Baseline EEG

Further to analysing EEG periods that are associated with events occurring on the simulator, a block of baseline EEG was also analysed for each AusEd record, to allow comparison with EEG associated with an AusEd event. This block of EEG was taken at the start of the second period on the straight road. In all studies this block of EEG was taken from between 601seconds and 620seconds. Ideally all baseline EEG blocks would have started at the same time. However on 11 of the studies artefact on the EEG, most likely caused by movement of the wires, which was not possible to filter out with the band pass filters, prohibited the use in analysis and so the first artefact free block of EEG thereafter was used instead.

For these events the following periods EEG data were analysed:

- Ten-second block of EEG starting between 601 – 620 seconds into test.

It should be noted that all baseline times did not overlap with any events recorded by the simulator.

Overlapping of EEG blocks

On a few occasions' crashes and off road events occurred within seconds of trucks appearing or overlapped with each other. In a real life driving situation, if a person feels sleepy or loses concentration whilst driving they may be more likely to have overlapping off road events and crashes, with several near misses in a short period of time. Due to this it was decided that all events would be analysed regardless of whether they overlapped.

3.9.2 Fast Fourier Transformation

Fast Fourier Transformation (FFT) is a mathematical technique that allows physiological signals to be decomposed into constituent sine and cosine waves and was applied to EEG signals recorded during simulator performance.
The program used for this study was designed in-house (see acknowledgements) and used moving windows of two seconds with a resolution of one second; hence FFT data points were generated for each second.
This FFT analysis program was derived from the program used by Martin et al (1997), which was itself an improvement of an in-house FFT program initially used, by Rees et al (1995) and Drinnen et al (1996).

The FFT analysis program allows the user to define the EEG frequencies used. Three frequency bands were selected for this study,

- Theta (δ) 5-7.9 Hz,
- Alpha (α) 8-11.9 Hz,
- Sigma (θ) 12- 16Hz.

Frequencies of ≤4 Hz and >16Hz were used to limit blink artefact and muscle artefact on the EEG.

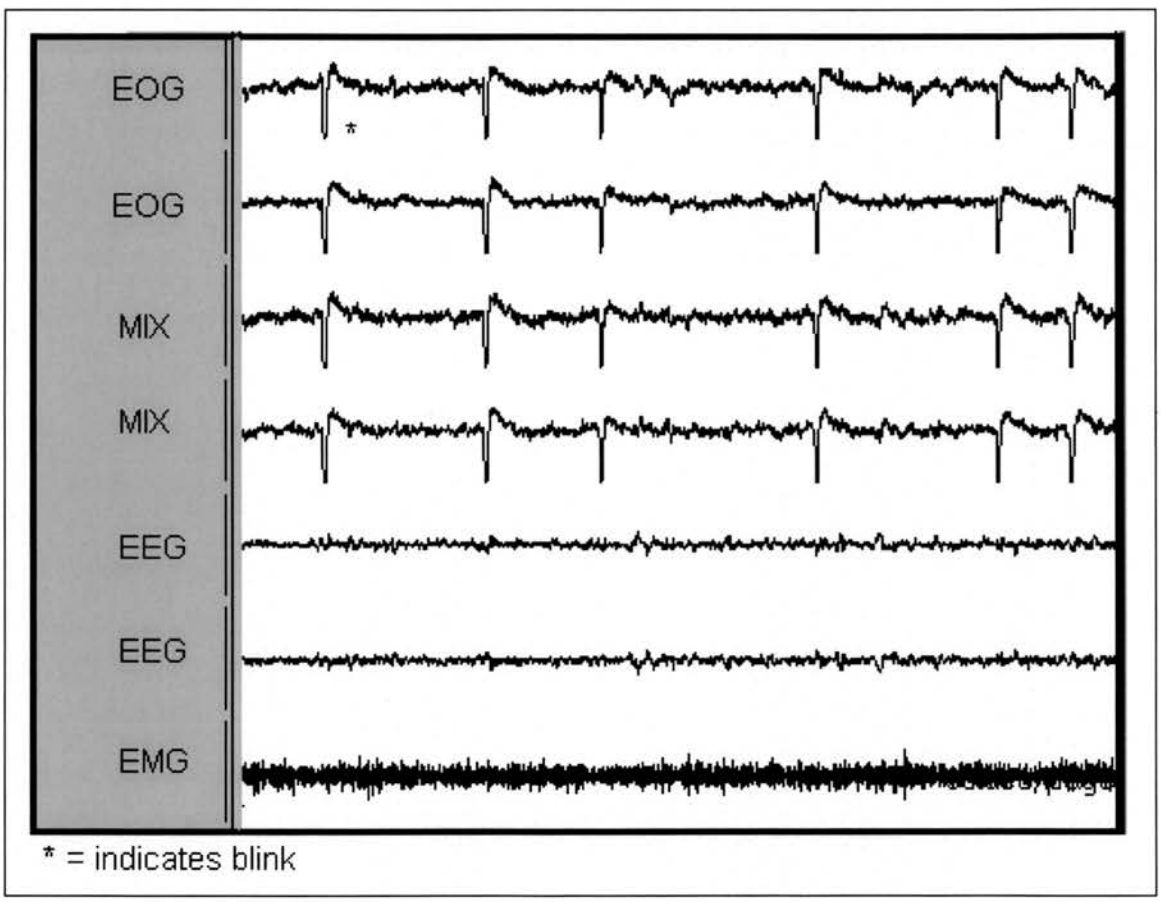
Raw EEG signals were obtained while subjects performed the driving tasks and downloaded from the Compumedics Replay version 5.25, on which they were acquired as European data files (EDF). These raw data files were then processed by FFT analysis program, which produced a power spectral density for each of the specified EEG frequencies in microwatts per hertz (μW/Hz).

These data were then stored as text files and copied to the Microsoft Excel database program. From here, the appropriate EEG periods (discussed in section 3.9.1) were copied to the (Statistical Package for the social sciences) SPSS program and the mean and standard deviation values for the EEG periods were calculated

3.9.2 Blink frequency analysis

Blink rate analysis was also conducted for the 30-minute AusEd and Steer Clear tasks. This was done by scoring the blinks that appeared on the EOG channels recorded whilst subjects were on the driving simulator and SteerClear driving task.

Figure 3.12; EOG artefact associated with blinks.



3.12.3.1 Intra-rater blink rate

To ensure that the scoring of the blinks was consistent I re-scored 20 of the original 105 studies. Five recordings from patient group at baseline on the AusEd drive, five recordings from the patient's group post treatment on the AusEd drive, five recordings from the patient groups on the Steer Clear task and five recordings from controls on the AusEd drive. These were chosen at random by the Research Nursing Sister and I re-scored them blind to their original score. Table 3.7 shows the mean blink rate spilt into the 4 groups and on average.

Table3.7; Correlation co-efficient between first and second score of blinks

Record type	First score mean and SD	Second score mean and SD	R value *	Difference mean first score – mean second score
Patients baseline drive on AusEd	487.2 (249.8)	492.6 (252.4)	>.99	-5.4
Patients post-treatment drive on AusEd	877.0 (245.3)	879.2 (245.1)	>.98	-2.2
SteerClear task	614.0 (428.0)	616.8 (428.1)	>.98	-2.8
Control drive on AusEd	632.0 (729.1)	633.6 (726.7)	>.98	-1.6
All records	652.6 (444.2)	655.6 (443.1)	>.98	-3.0

**All significant at p= 0.01 level*

3.10 Driving Questionnaire Study

The second major study of this thesis was a retrospective questionnaire based survey investigating perceived driving ability, accident rate and sleepiness.

3.10.1 Participants in the Driving questionnaire study

Patients with the obstructive sleep apnoea/hypopnoea syndrome were separated into two groups for comparison. The "on-CPAP" group were patients who had been using

CPAP treatment for the past two years. The "awaiting CPAP" group were patients recently diagnosed but still awaiting CPAP.

The "awaiting CPAP" group functioned as a control group.
Inclusion criteria for both of the patient groups were the same.

Inclusion criteria: Aged18-75, holds full drivers licence, AHI ≥20 (AH/hr in bed, ≥30 if diagnosed on a home based study), ability to complete questionnaire.

The "on-CPAP" group was identified from the sleep centre patient database and the "awaiting CPAP" group were identified through the appointment system for patients awaiting CPAP titration.
Patients who met inclusion criteria were mailed the driving questionnaire and invitation letter, and were requested to return it on completion. A self addressed, stamped envelope was included in each invitation pack.

Control subjects were also recruited for this study. These were matched to the "on-CPAP" group by postal code and were also sent the driving questionnaire and invitation letter. Matching of postal code to cases was done by using the first block of the postcode characters i.e. EH12 or AB3. Matching thus has a greater chance of including people with the same social and educational background as the patient group than by matching people randomly around the country. It also meant that both groups would be likely to use the same road types. For example, matching rural patients to controls in the same rural area. This was hoped to increase the validity of comparing accidents by road type.
Potential controls were identified using the United Kingdom British Telecom telephone directory and as there was no way to screen for inclusion criteria prior to sending out the questionnaire pack, only respondents meeting the following inclusion criteria were included in analysis.
Inclusion criteria: Aged 18-75, holds full drivers licence, ability to understand and complete the questionnaire.

3.11 Self-Ratings in the Driving Survey Study

BACKGROUND: This postal survey was designed to gather information about subjective perceptions of driving ability and accident rates in both patient and control populations. These questionnaires can be seen in appendix 4

As different background information was required for the 4 sub-groups, each group received a slightly different questionnaire. However each questionnaire contained the same questions on driving history in the same order these being:

- How many days a week they drive,
- If they had ever felt sleepy whilst driving,
- If they had ever fallen asleep when driving,
- How they perceived their ability to drive both long and short distances
- Provide information on any accidents they had had
- Type (near miss etc)
- Time of accident
- Road type it occurred on

<u>In-house "On-CPAP" Driving questionnaire</u>

This questionnaire was sent to patients who had been using CPAP treatment for the previous two years. Initial questions concerned their CPAP usage status and driving licence status. They were asked to complete the Epworth Sleepiness Scale both for their current situation and retrospectively for the time before commencing CPAP.

The driving history questions were split into 2 sections. Section 1 regarding the two years prior to starting CPAP and section 2 regarding the last two years whilst using CPAP therapy.

TIME NEEDED FOR COMPLETION: 20 minutes

In-house "Awaiting-CPAP" driving questionnaire

This questionnaire was sent to patients who were waiting to receive CPAP treatment for OSAHS. They were asked to complete the ESS as well as the driving history section which again was in reference to the 'last two years".
TIME NEEDED FOR COMPLETION: 5 minutes

In-house "community sample" driving questionnaire

This questionnaire encapsulated the driving history questions asked to all other groups in reference to the past two years, as well as asking background information. These questions include age, ESS, and enquire about events during sleep e.g. snoring, breathing pauses, excessive movements of limbs, as well as a question regarding whether they have been diagnosed with a sleep disorder or were receiving treatment for one.
TIME NEEDED FOR COMPLETION: 20 minutes.

In-house sleep-wake Questionnaire

This questionnaire noted in section 3.7 was used here as a method of retrieving information on events during sleep from our "awaiting CPAP" patient group. As all recent patients to the Edinburgh sleep centre complete this questionnaire before attending the sleep centre, it was possible to find this information from the notes rather than asking the patient group.

The techniques described in this chapter were used in the studies whose results comprise the following five chapters.

Chapter 4: Treatment effects on the AusEd simulator

4.1 Introduction

The initial clinical study took the form of a parallel group, placebo-controlled, randomised trial of CPAP therapy for OSAHS. The primary outcomes of this study were in performance on the AusEd-driving simulator. Prospectively it was hypothesised that no significant differences would be found between the two patient groups at baseline on the primary outcomes of the AusEd-driving simulator. CPAP treatment was used to investigate the sensitivity of the AusEd-simulator and an inactive capsule was incorporated into the trial design to control for learning and placebo effects. It was hypothesised that significant improvement would occur in patients undergoing active treatment (CPAP) for the OSAHS thus significant differences in the AusEd-simulator outcomes would be found between the two patient groups after the treatment period.

4.2 Recruitment

Consecutive patients suspected of OSAHS and attending the Edinburgh Sleep centre between February 2000 and December 2002 were contacted to participate in the randomised controlled trial (RCT) of fitness to drive on the AusEd-simulator. Patients were approached with a view to recruitment on the following inclusion/exclusion criteria:

Inclusion criteria: Epworth Sleepiness score (ESS) ≥8; an AHI of five or greater; two major symptoms of OSAHS (Whyte et al 1989); aged between 18-70; ability to understand the consent procedure; holds full drivers licence; no serious neurological, cardiovascular or respiratory disease; no other co-existing sleep disorder.

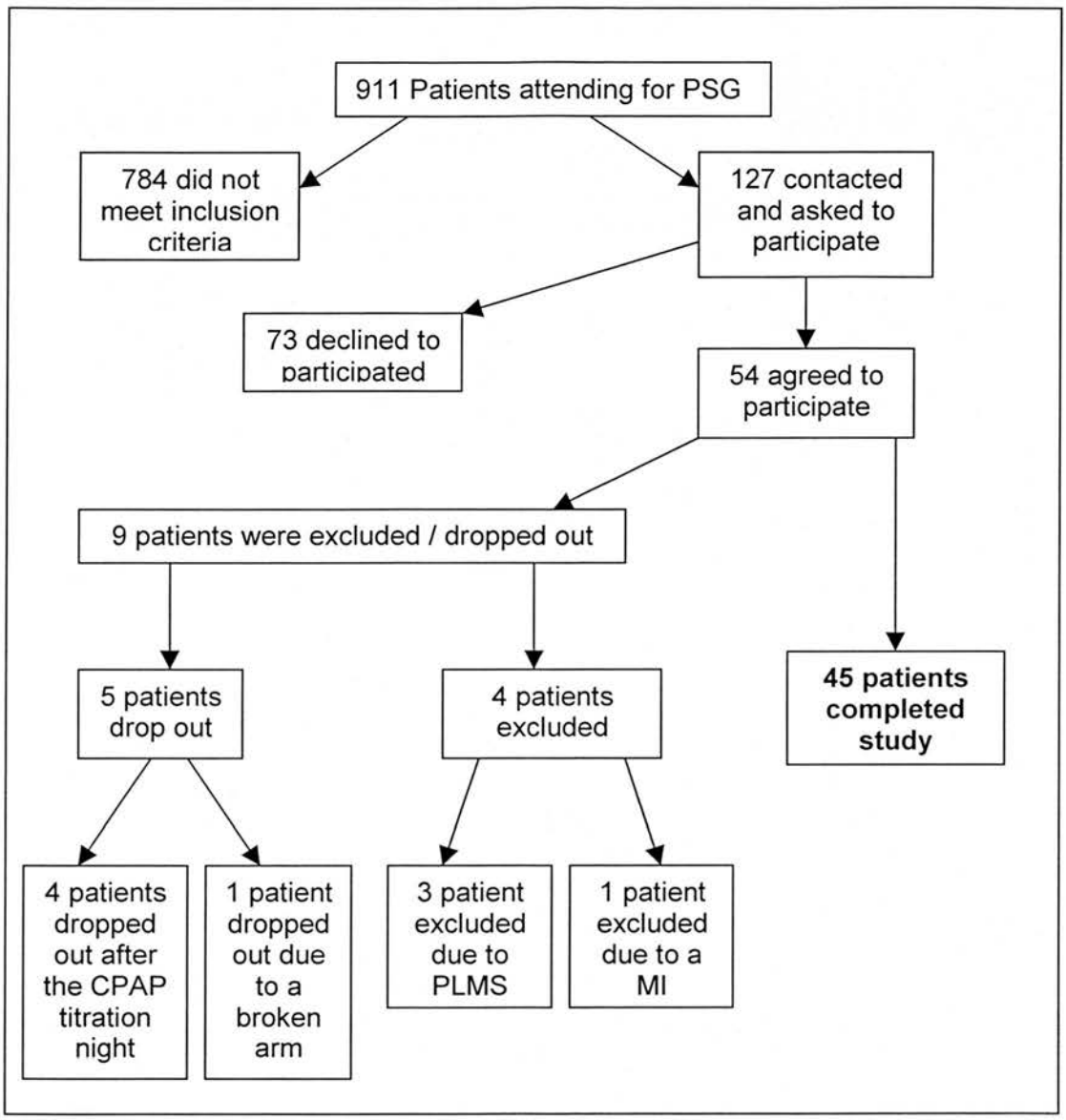
Exclusion criteria: Live > 50 miles from sleep centre; driving as their occupation; not been seen by sleep consultant; to receive treatment other than CPAP treatment; daytime sleepiness testing (MSLT, MWT), or clinic appointment already booked for day after polysomnography (PSG); CPAP titration night already booked by consultant. Previous uvulopalatopharyngoplasty (UPPP) surgery

Overall 911 patients were booked for polysomnography investigations during the study period. Of these 127 were contacted. Table 4.1 illustrates the numbers and reasons the other 784 patients were not contacted. Figure 4.1 demonstrates the progression of possible participants.

Table 4.1; Reasons and number of patients not contacted regarding study.

REASON FOR NOT RECRUITING PATIENTS	Number
New patients still waiting to see their consultant	243
Psychiatric/cardiovascular/respiratory disorder or other illness	99
ESS score <8	57
Did not hold drivers licence	62
CPAP night already booked (for night after PSG)	52
Recruited for other study	47
MSLT/MWT next day	39
Clinic appointment with consultant next day	38
Lived >50 miles from sleep centre	25
Older than 70	24
Having half PSG and half CPAP titration night	24
Driving as occupation	23
Booked for investigation other than OSAHS	17
Receiving or to receive other treatment than CPAP	17
Diagnosed with other sleep disorder	8
English not first language	5
Previously had Uvulopalatopharyngoplasty (UPPP) surgery	4
TOTAL	784.

Diagram 4.1; Patient inclusion/exclusion flow diagram



A comparison of age between patients who agreed to participate in the study and those who declined showed that participants who agreed (n=54) had a mean age of 50.6 SD (9.7) yrs and were significantly older than those who declined (n=73), mean age 45.6 (10.1) yrs, t (123)= -2.92; P<0.05.

However ESS of the participant group (n=54) was not significantly different to that of decliners (mean ESS of 14.2 SD (3.3) vs. 13.2 SD (3.4), t (114)= -1.56; ns), there were

no gender differences between the participant group (n=54, 7 females) and those who declined (n=73, females 13) (x^2=0.549; df=1;p=0.459)

One hundred and twenty seven patients were contacted and asked to participate in the study and 54 patients agreed, giving a response rate of 43%. Of the 54 patients who agreed to participate in the AusEd driving study, only 45 patients completed the study, with nine patients excluded or withdrawing from the study. Four patients declined to continue on treatment after their CPAP titration night, three were excluded as their overnight PSG showed they had periodic limb movements rather than or as well as OSAHS. One patient broke their arm and did not feel up to continuing in the study. Another patient suffered a myocardial infarction shortly after their PSG investigation night and was immediately commenced on CPAP therapy.

4.3 Statistics

The baseline comparisons for ordinal and continuous data for the two groups were conducted using non-parametric Mann-Whitney U tests and dichotomous and categorical level data were analysed with Chi square and Fishers exact non-parametric tests. Correlational associations were assessed using Spearmans correlation coefficients for non-parametric data. Performance changes (time on task) on the AusEd driving simulator were assessed using a one-way ANOVA. The treatment effect analysis was conducted using a repeated measures MANOVA test, with a repeated within subjects factor of time (pre and post-treatment) and a between subjects factor of treatment randomisation was also included. All tests were run on the PC statistical package SPSS (SPSS for windows, Version 12, 2003, SPSS, Chicago, IL, USA).

4.4 Patient Group

A total of 45 patients completed this intention to treat study, 19 (3 women) had a recruitment ESS of 13 or less and 26 (3 women) had a recruitment ESS of 14 or above. With randomisation blocks balanced and stratified for ESS, 21 (11 from the 8-13 ESS

group) were assigned to placebo treatment and 24 (10 from the 14-24 ESS group) were assigned to CPAP treatment.

4.4.1 Baseline daytime schedule

Patients attended the Edinburgh sleep centre the night prior to the testing day and under went full polysomnography. They then stayed the following day for a full day of testing. Throughout the testing day EEG wires were checked before MWT and driving tests. The baseline testing day schedule was as follows:

Randomisation of AusEd simulator/SteerClear order

8.30am Height, weight and neck measurements taken, questionnaires (ESS, FOSQ, SF36, Symptom scale, Driving history, computer usage) to be completed
9.10am NART and Ravens matrices tests
10.00 MWT test 1
10.45 Blood pressure taken
10.55 AusEd / SteerClear driving simulation (randomised order). Completing the Karolinska sleepiness scale before and after the simulation
12.00 MWT test 2
12.40 Lunch
14.00 MWT test 3
14.50 AusEd / SteerClear driving simulation (randomised order) Completing the Karolinska sleepiness scale before and after the simulation
16.00 MWT test 4
16.50 Wires off
17.00 CPAP Education (educational video, mask fitting and CPAP trial)
18.00 Patient leaves
4.4.2 Post-treatment daytime testing

At the end of the treatment period of 4 weeks, patients were scheduled to return to the sleep centre for a half day of testing. To reduce patient time constraints the MWT, cognitive tests and Steer Clear were not performed and all patients underwent the

AusEd simulator task in a morning session, regardless of whether their baseline AusEd drive was morning or afternoon.

The revised schedule for the post-treatment-testing day was as follows;

9.00 Patients arrive at sleep centre
9.30 Patients complete questionnaires (ESS, FOSQ, SF36, symptom scale, driving history questionnaire part2, treatment satisfaction and subjective usage, treatment side effect)
10.00 EEG wires are applied and checked to ensure signal quality
10.40 Blood pressure taken
10.50 AusEd driving simulation
11.40 Wires off

4.5 Baseline descriptive statistics of the patient Group (N = 45)

As a group the patients were on average middle aged, overweight with an AHI (Apnoea + Hypopnoea Index) reflective of moderate OSAHS.

Table 4.2; Patient demographics and baseline characteristics

Variable	Mean and SD	Range
Gender*	39m/6f	-
Age in years	50.9 (8.7)	35 – 68
Weight in kg	97.0 (17.1)	70 – 146
Height in meters	1.7 (0.09)	1.42 – 1.89
BMI (kg/m^2)	32.6 (6.0)	23 – 53.5
Neck size in cm	42.1 (3.45)	31 – 49.5
AHI per hour	38.9 (22.0)	8.3 – 97.1
Arousals per hour	33.2 (18.1)	8.8 – 81.5
Total Sleep Time in mins	367.7 (63.5)	159 – 454
Sleep efficiency %**	78.2 (13.4)	34 – 93
CPAP titration pressure (cmH_2O)	9.3 (2.1)	5 - 13.4
Days on treatment	35.4 (7.7)	28 – 59

** m=male, f=female,** total time asleep divided by total time in bed*

Overall the group demonstrated few crash and driving-off-road events during performance on the AusEd driving simulator. Their mean lateral position was within the

left lane (as instructed) and their mean speed was within the instructed range (60-80km/hour).

Table 4.3; The AusEd simulator outcomes

Variable	Number	
Patients recording one or more crashes/off-road incidents	21	-
	Mean and SD	Range
AusEd truck crash	0.07 (0.33)	0 – 2
AusEd driving-off-road crash	0.42 (0.99)	0 – 5
AusEd driving-off-road incident	0.96(2.9)	0-19
AusEd stop crash	0.47 (1.5)	0 – 9
AusEd mean area of deviation from lane centre (cm)*	94.6 (27.5)	51 – 161
AusEd mean area of deviation from required speed (km/h)**	11.3 (3.8)	6 – 27
Time outside required speed %	27.6 (16.1)	9.5 – 91.8
Mean road position (cm)	84.13 (31)	2 – 158
Mean speed (km/h)	63.8 (5)	44 – 71
Mean reaction time in seconds	2.8 (3.1)	0.86 – 17.86
Median reaction time in seconds	1.9 (1.6)	0.8 – 7.9

** Centimetres, ** kilometres per hour*

Overall the patient characteristics reflected mean ESS and FOSQ scores in the pathologically sleepy range and they reported generally poor health status (SF36).

Table 4.4; OSAHS symptoms, sleepiness and quality of life outcomes

Variable	Mean and SD	Range
Recruitment ESS*	14.1 (2.9)	8 – 21
Symptom score (max 48)	25.2 (7.9)	8 – 44
SF36 health transition**	3.0 (0.7)	1 – 5
SF36 physical functioning**	67.1 (26.6)	0 – 100
SF36 role physical**	46.7 (38.7)	0 – 100
SF36 role emotional**	58.5 (42.1)	0 – 100
SF36 Social functioning**	68.6 (25.8)	12.5 – 100
SF36 bodily pain**	63.4 (27.2)	22 – 100
SF36 mental health**	62.8 (16.9)	29 – 92
SF36 vitality**	36.6 (19.6)	0 – 75
SF36 general health**	51.0 (19.8)	15 – 90
SF36 physical**	38.0 (13.9)	12.8 – 62
SF36 mental**	43.1 (11.1)	21.8 – 65.7
FOSQ productivity***	3.2 (0.6)	1.75 – 4
FOSQ social outcome***	3.3 (0.6)	2 – 4
FOSQ activity level***	2.7 (0.7)	1.22 – 3.89
FOSQ vigilance***	2.8 (0.7)	1.06 – 4
FOSQ total***	11.9 (2.1)	6.97 – 15.89
Ravens score max 60	43.4 (7.5)	22 – 56
NART score max 50¶	32.04 (9.2)	12 – 47
IQ change score	-0.01 (0.15)	-2.34 – 2.13
Karolinska score before AusEd	4.7 (1.5)	1 – 7
Karolinska score after AusEd	5.9 (1.9)	3 – 9
Karolinska score before SteerClear	4.6 (1.5)	2 – 8
Karolinska score after SteerClear	5.8 (1.9)	3 – 9
MWT SOL (mins) #	19.8 (10.4)	3.25 – 40
SteerClear cows hit %	7.69 (6.7)	1 – 39

ESS –Epworth sleepiness score, ** SF36 – Short from 36 * Functional outcomes of sleepiness questionnaire, ¶ National adult reading test, , # Multiple sleep latency sleep onset latency in minutes.*

On average patients reported low numbers of real-world accidents and near-miss accidents in the preceding five-year period. As a group they reported holding a drivers licence for an average 28 years, driving most days and reported a good ability to drive long distances (>75miles).

Table 4.5; Driving questionnaire outcomes

Variable	Number	
Number of patients reporting involvement in an accident last five years	15	-
Number of patients reporting involvement in a near miss last five years	22	-
	Mean and SD	Range
No. of major accidents last 5 years	0.02 (1.5)	0 – 1
No. of minor accident last 5 years	0.4 (0.7)	0 – 2
No. of near miss accident last 5 years	3.4 (8.3)	0 – 50
Years held drivers licence	28.9 (10.3)	6 – 51
Miles driven per year	12,162.2 (8596.1)	200 – 50,000
Days driven per week (scale 1-4)	3.82 (0.6)	1-4
Ability to drive long distances (scale 1-5)	3.6 (1.1)	1-5

4.6 Baseline comparisons of the two patient groups

To determine if any differences were present between the placebo and CPAP group at baseline, comparisons of the two groups on the study outcome measures were undertaken. All baseline comparison tests were analysed with Mann-Whitney U non-parametric tests unless otherwise stated.

The two groups were similar in the demographic, anthropometric and clinical variables and showed no significantly statistical differences in any of these variables at baseline.

Table 4.6; Patient demographics

Variable	CPAP Mean and SD n = 24	Placebo Mean and SD n = 21	p level
Age in years	51.9 (8.3)	49.9 (9.2)	>0.3
Education (scale 1-3)	2.2 (0.9)	1.8 (0.9)	>0.2
*Sex (male or female)	21m/3f**	18m/3f**	>0.9
*Smoke (yes or no)	5y/19n***	4y/17n***	>0.9
Weight in kg	97.9 (18.9)	95.9 (15.2)	>0.9
Height in meters	1.7 (0.1)	1.7 (0.1)	>0.9
BMI (kg/m2)	33.2 (7.2)	31.9 (4.5)	>0.9
Neck size in cm	42.4 (3.7)	41.9 (3.2)	>0.5
AHI per hour	37.3 (23.4)	40.9 (20.7)	>0.4
Arousals per our	31.4 (18.4)	35.2 (17.9)	>0.3
Total Sleep Time in mins¶	367.8 (58.7)	367.7 (70.1)	>0.6
Sleep efficiency %	77.2 (12.4)	79.3 (14.7)	>0.4
CPAP titration pressure (cmH_2O)	9.2 (2.1)	9.4 (2.1)	>0.9
Days on treatment	33.7 (5.1)	37.2 (9.7)	>0.4
MWT SOL	16.9 (8.8)	23.1 (11.4)	>0.1
SteerClear cows hit %	7.9 (7.9)	7.4 (5.0)	>0.8
Systolic blood pressure (mmHg) ₸	135.1 (22.3)	132.8 (18.8)	>0.9
Diastolic blood pressure (mmHg) ₸	86.8 (10.9)	87.8 (10.2)	>0.7

** Fisher's Exact test, ** m=male, f=female, *** y=yes, n=no, ¶ total time asleep divided by total time in bed, # Multiple sleep latency sleep onset latency in minutes, ₸ millimetres of mercury*

There were no significant differences in the two groups on the number of crashes and driving-off-road events recorded on the simulator. Neither were there significantly different frequencies of patients recording crashes or off-road events. Both groups had similar deviations in steering and speed from the required levels, and both groups performed within required mean speed parameters. Although not significantly different the CPAP group on average drove closer to the centre of the left lane than the placebo group, but the mean value for each group was within the boundaries of the left lane.

Table 4.7; The AusEd driving simulator-driving measures at baseline

Variable	CPAP n = 24	Placebo n = 21	p level
	Number and %	Number and %	
Number of participants recording a crash or off-road event*	13 (54)	8 (38)	>0.2
	Mean and SD	Mean and SD	
AusEd stop crash	0.3 (0.7)	0.7 (2.0)	>0.5
AusEd truck crash	0.8 (0.4)	0.1 (0.2)	>0.9
AusEd driving-off-road crash	0.4 (0.7)	0.5 (1.3)	>0.5
AusEd driving-off-road incidents	0.5 (0.8)	0.7 (1.6)	>0.4
AusEd total number of events	1.2 (1.5)	1.9 (3.5)	>0.8
AusEd mean area of deviation from lane Centre (cm)**	93.0 (28.2)	96.5 (27.2)	>0.6
AusEd mean area of deviation from required speed (km/h)***	10.9 (2.8)	11.8 (4.81)	>0.9
Time outside required speed %	26.1 (10.8)	29.3 (20.78)	>0.7
Mean road position (cm)**	78.1 (33.5)	91 (26.9)	>0.2
Mean speed (km/h)***	64.1 (3.5)	63.4 (6.4)	>0.8
Mean reaction time in seconds	2.7 (3.5)	2.8 (2.6)	>0.5
Median reaction time in seconds	1.8 (1.2)	2.1 (1.9)	>0.8
90^{th} centile reaction time in seconds	0.39 (0.78)	0.41 (0.74)	>0.8

** Chi-square, ** Centimetres, *** Kilometres per hour*

There were no differences in the two groups in their level of subjective sleepiness, OSAHS symptoms, general health status and IQ decrement at baseline.

Table 4.8; Baseline OSAHS symptoms, sleepiness and quality of life outcomes

Variable	CPAP Mean and SD n = 24	Placebo Mean and SD n = 21	p level
Recruitment ESS*	14 (2.9)	14.2 (3.1)	>0.8
Symptom score (max 48)	24.7 (6.9)	25.9 (9.1)	>0.6
SF36 health transition**	3.1 (0.7)	2.9 (0.8)	>0.5
SF36 physical functioning**	67.9 (29.6)	66.2 (23.4)	>0.6
SF36 role physical**	51 (42)	41.7 (34.8)	>0.5
SF36 role emotional**	56.9 (43.4)	60.3 (41.7)	>0.9
SF36 Social functioning**	70.3 (27.8)	66.7 (23.8)	>0.5
SF36 bodily pain**	63.5 (29.3)	63.1 (25.2)	>0.9
SF36 mental health**	65 (12.8)	60.2 (20.7)	>0.2
SF36 vitality**	40 (19.9)	32.6 (18.9)	>0.2
SF36 general health**	50.5 (21.9)	51.5 (17.5)	>0.9
SF36 physical**	38.4 (15.2)	37.5 (12.8)	>0.8
SF36 mental**	44 (8.7)	42.1 (13.4)	>0.5
FOSQ productivity***	3.2 (0.6)	3.1 (0.6)	>0.4
FOSQ social outcome***	3.3 (0.6)	3.3 (0.6)	>0.6
FOSQ activity level***	2.8 (0.7)	2.7 (0.6)	>0.3
FOSQ vigilance***	2.8 (0.6)	2.7 (0.8)	>0.9
FOSQ total***	12.1 (2.2)	11.8 (1.9)	>0.5
Ravens score max 60	43.5 (8.0)	43.4 (6.9)	>0.8
NART score max 50¶	33.6 (9.1)	30.3 (9.3)	>0.3
IQ change score	0.15 (0.99)	-0.2 (1.3)	>0.4
Karolinska score before AusEd	4.3 (1.6)	5.1 (1.3)	>0.1
Karolinska score after AusEd	5.8 (2.1)	6.2 (1.8)	>0.6
Karolinska score before SteerClear	4.5 (1.4)	4.7 (1.7)	>0.8
Karolinska score after SteerClear	5.9 (1.9)	5.7 (1.8)	>0.8

ESS –Epworth sleepiness score, SF36 – Short from 36, *** Functional outcomes of sleepiness questionnaire, ¶ National adult reading test*

The CPAP and placebo group reported no statistically significant differences in the number of accidents reported and there were no differences in the frequency of patients reporting accidents and near misses. Further, the number of days driven per week and their ability to drive long distances were not different, however the placebo group showed trends towards higher numbers of near miss accidents and higher mileage than the CPAP group.

Table 4.9; Driving questionnaire outcomes

Variable	CPAP n = 24	Placebo n = 21	P level
	Number and %	Number and %	
No. of patients reporting accidents *	7 (29)	8 (42)	>0.5
No. of patients reporting near-misses*	14 (58)	8 (42)	>0.2
	Mean and SD	Mean and SD	
No. major accidents last 5 years	0 (0)	0.1 (0.2)	>0.3
No. minor accidents last 5 years	0.33 (0.57)	0.5 (0.8)	>0.6
No. near miss accidents last 5 years	2.7 (3.9)	4.1 (11.6)	>0.07
Years held drivers licence	31.3 (8.6)	26.4 (11.7)	>0.1
Miles driven per year	9754.2 (5271.6)	14914.3 (10756.1)	>0.08
Days driven per week (scale 1-4)	3.88 (0.5)	3.76 (0.7)	>0.5
Ability to drive long distances (scale 1-5)	3.5 (1.1)	3.62 (1.2)	>0.7

**Chi-square*

This indicates that the baseline characteristics of the two treatment groups were not significantly different.

4.7 Correlation associations between AusEd outcomes and PSG, sleepiness, quality of life and cognitive variables.

As would be expected with the large number of variables, there were several significant correlations found between some of the AusEd outcome variables and some of the anthropometric, sleepiness, quality of life and cognitive variables, table 4.10 displays the correlation co-efficient data. Indeed 7 of the 84 correlations were significant, only slightly more than the 4 that would have been expected by chance alone at $p<0.05$.

The ESS was positively associated with both time-spent out with the required speed zone (%) and with the mean RT. The physical summary score of the SF36 was negatively correlated with cumulative speed deviation and time-spent out with the required speed zone (%) and positively with mean RT. The FOSQ domain of activity level was negatively correlated with mean RT, as was the FOSQ domain of vigilance that was also negatively associated with time spent out with the required speed (%). The estimate of computer experience was negatively associated with mean RT and the percentage of steers hit during the SteerClear vigilance task was negatively associated

with mean RT. All of these associations were weak in magnitude but all were in the anticipated direction.

Table 4.10; Correlation Results between AusEd variables and PSG, sleepiness and quality of life variables

	Cumulative Steering deviation. Correlation co-efficient (r±) and p level	Cumulative speed deviation. r± and p level	Time spent out with required speed zone (%). r± and p level	Mean lateral road position r± and p level	Mean speed. r± and p level	Mean reaction time (sec). r± and p level
AHI	0.2 NS	0.1 NS	0.03 NS	0.2 NS	0.05 NS	0.1 NS
Arousals	0.06 NS	0.09 NS	-0.004 NS	0.007 NS	-0.07 NS	-0.03 NS
Mean desaturation	0.2 NS	-0.8 NS	-0.1 NS	0.2 NS	0.2 NS	0.004 NS
BMI	0.001 NS	0.1 NS	0.2 NS	0.06 NS	-0.2 NS	0.1 NS
ESS	0.4 NS	0.1 NS	0.3 0.04	0.1 NS	0.01 NS	0.4 0.002
Mean MWT SOL	-0.1 NS	-0.2 NS	-0.2 NS	0.01 NS	0.3 NS	-0.1 NS
MCS (SF36)	0.09 NS	0.7 NS	-0.02 NS	0.1 NS	0.02 NS	-0.2 NS
PCS (SF36)	0.07 NS	-0.3 0.008	-0.3 0.006	0.1 NS	0.3 0.02	-0.2 NS
Activity level (FOSQ)	0.2 NS	-0.03 NS	-0.1 NS	0.2 NS	0.1 NS	-0.3 0.04
Vigilance (FOSQ)	0.1 NS	-0.1 NS	-0.3 0.03	0.1 NS	0.08 NS	-0.2 0.03
FOSQ total	0.2 NS	-0.2 NS	-0.2 NS	0.1 NS	0.1 NS	-0.3 0.04
SteerClear % Steers hit	0.01 NS	0.3 NS	0.39 0.009	-0.03 NS	-0.1 NS	0.2 NS
IQ change scores	-0.14 NS	-0.01 NS	0.03 NS	-0.2 NS	-0.2 NS	-0.4 NS
Computer experience	-0.13 NS	-0.3 NS	-0.2 NS	0.1 NS	-0.3 NS	-0.3 0.038

4.8 Time on task analysis on the AusEd-driving simulator

Because of suggestions that driving performance may be impaired progressively the longer one is driving on a monotonous road, we have examined the relationship between driving time (time on task) and the error measures from the AusEd simulator. As the two patient groups showed no significant differences in the error measurements of the AusEd driving simulator at baseline, time on task effects were analysed for the whole patient group (n=45). This was undertaken by analysing the alternating types of road (straight or chicane) within their own set;

- Blocks of straight road – four blocks of 5 minutes duration's
- Blocks of chicane road – five blocks of 2 minutes duration's

The driving task starts with a two-minute block of a twisting chicane road that in turn becomes a five-minute block of straight road. The road layout alternates between these two road types for the duration of the 30-minute task.

A one-way ANOVA was performed to establish if changes in the mean area of deviation from lane centre, mean area of deviation from the required speed, mean road position and mean speed were different over time. As one might expect the road position and speed to be different between straight and chicane periods of road, time-on-task changes were analysed separately for the two road types.

Straight Road

There were no significant differences over time in the mean area of deviation from the lane centre and the mean road position. Both the mean area of deviation from required speed and mean speed showed significant differences. Table 4.11 shows the means and standard deviations of the four error measures.

Table 4.11; Time on task performance – Straight blocks

	Block 1 Mean (SD)	Block 2 Mean (SD)	Block 3 Mean & (SD)	Block 4 Mean & (SD)	F-value	p Level
Mean area of deviation from lane centre (cm)	86.8 (26.3)	84.3 (27.2)	84.1 (27.6)	84.4 (29.3)	0.485	>0.6
Mean area of deviation from required speed (km/h)	11.1 (4.3)	8.3 (3.5)	8.5 (3.9)	10.5 (4.2)	23.514	0.001
Mean road position (cm)	75.3 (33.1)	73.3 (32.3)	72.3 (32.7)	73.5 (33.1)	2.91	>0.8
Mean speed (km/h)	63.9 (5.4)	67.4 (4.9)	67.7 (5.3)	65.5 (5.6)	18.127	0.001

Cm centimetres, km/h kilometres per hour

Figures 4.1 to 4.4 graph the time changes over the four straight road blocks for the AusEd error measurements. Figures 4.2 and 4.4 would suggest that participants recorded greater variability in speed and a lower mean speed in blocks one and four, than blocks two and three. Although each patient was given a 10-minute practice run before commencing the 30-minute drive, the first block of straight road showed the highest mean area of deviation from the required speed and the lowest average speed that may suggest a learning effect. The fourth block again sees a rise in the variability of speed and a reduction in mean speed. This may represent impairment in performance, however one should note that the mean speed was 65.5 (SD 5.6) and was within the boundaries set by the task.

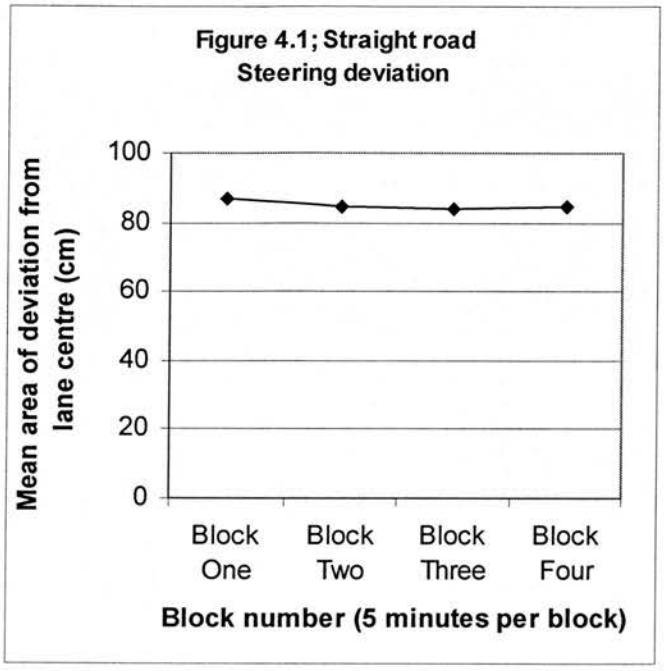


Figure 4.1; Straight road
Steering deviation
Mean area of deviation from lane centre (cm)
100
80
60
40
20
0
Block One
Block Two
Block Three
Block Four
Block number (5 minutes per block)

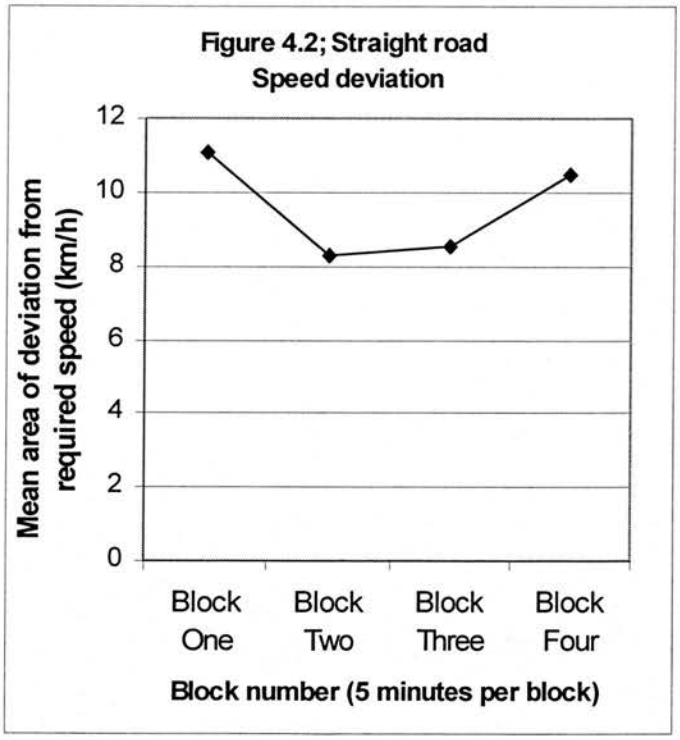


Figure 4.2; Straight road
Speed deviation
Mean area of deviation from required speed (km/h)
12
10
8
6
4
2
0
Block One
Block Two
Block Three
Block Four
Block number (5 minutes per block)

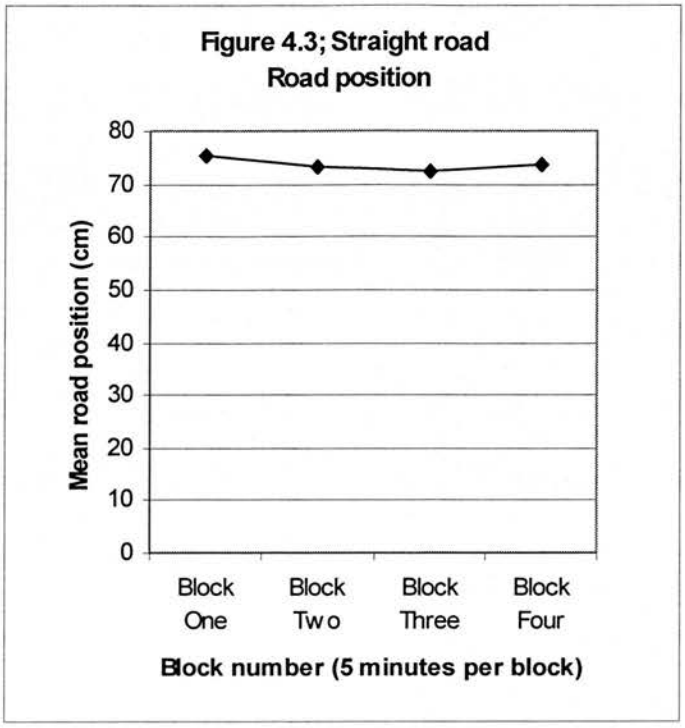


Figure 4.3; Straight road
Road position
Mean road position (cm)
80
70
60
50
40
30
20
10
0
Block One
Block Two
Block Three
Block Four
Block number (5 minutes per block)

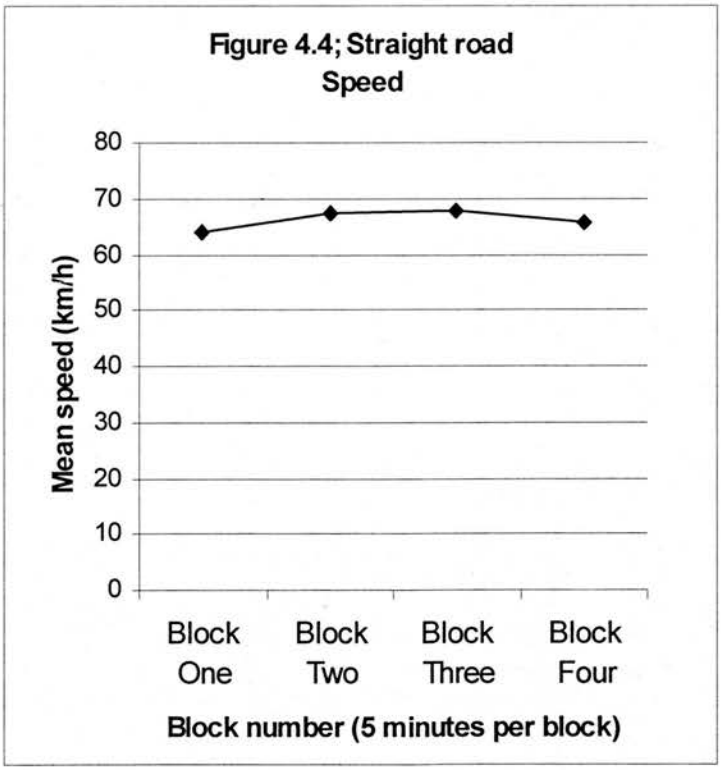


Figure 4.4; Straight road
Speed
Mean speed (km/h)
80
70
60
50
40
30
20
10
0
Block One
Block Two
Block Three
Block Four
Block number (5 minutes per block)

Chicane Road

The chicane road layout yielded significant time-on-task differences in performance on all four of the driving measures, Table 4.12 shows the means and standard deviations of the four performance outcomes. The measures of steering (mean area of deviation from lane centre and road position) showed a similar pattern of trends over the five blocks, with the highest steering deviation and farthest mean road position from lane centre occurring in the first two-minute block. As the mean and standard deviations of the five blocks reduce over time, the significant differences obtained in the ANOVA are in the direction of an improvement in performance. Figure 4.5 to 4.8 graph the changes over time in the chicane road time segments.

The highest mean deviation in speed from the required speed and the lowest mean speed were found in the first chicane block. The mean speed deviation showed a reduction during second and third blocks before a slight increase in the fourth block and levelled off for the fifth and final block. The time-on-task changes in mean speed appeared to resemble an inversion of this pattern.

Table 4.12; Time on task performance - Chicane blocks

	Block 1 Mean (SD)	Block 2 Mean (SD)	Block 3 Mean (SD)	Block 4 Mean (SD)	Block 5 Mean (SD)	F-value	p Level
Mean area of deviation from lane centre (cm)*	139.7 (45.8)	115.6 (45.2)	106.9 (38.9)	109.5 (43.6)	105.5 (35.5)	14.73	0.001
Mean area of deviation from required speed (km/h)**	23.1 (9.6)	13.9 (5.3)	7.4 (4.5)	14.0 (6.9)	14.0 (5.6)	59.07	0.001
Mean road position (cm)*	129.4 (47.1)	103.4 (45.1)	99.9 (41.7)	96.6 (50.9)	91.8 (38.4)	11.75	0.001
Mean speed (km/h)**	50.4 (10.6)	60.7 (6.4)	67.1 (6.1)	60.7 (8.4)	60.4 (7.4)	47.52	0.001

cm - centimetres, km/h - kilometres per hour*

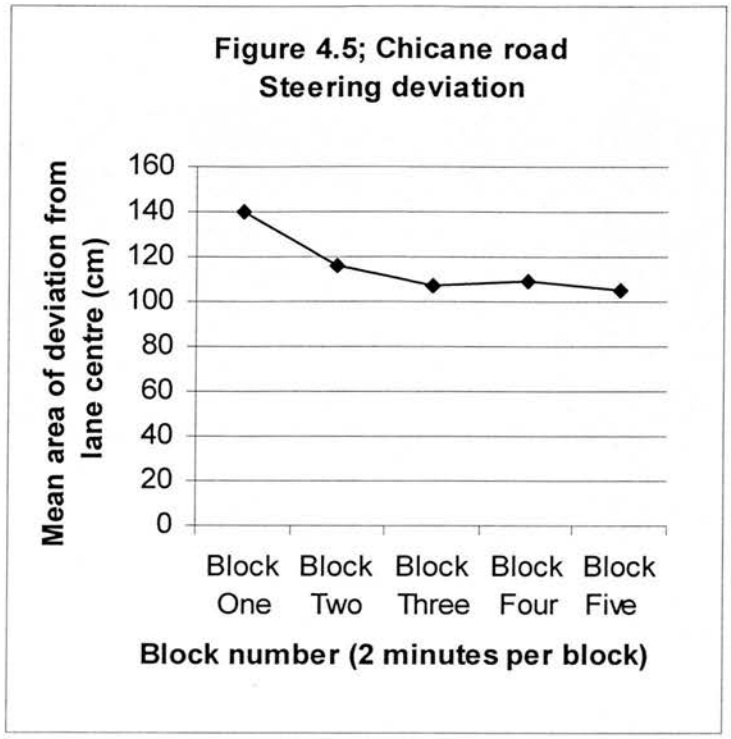


Figure 4.5; Chicane road
Steering deviation
Mean area of deviation from lane centre (cm)
160
140
120
100
80
60
40
20
0
Block One
Block Two
Block Three
Block Four
Block Five
Block number (2 minutes per block)

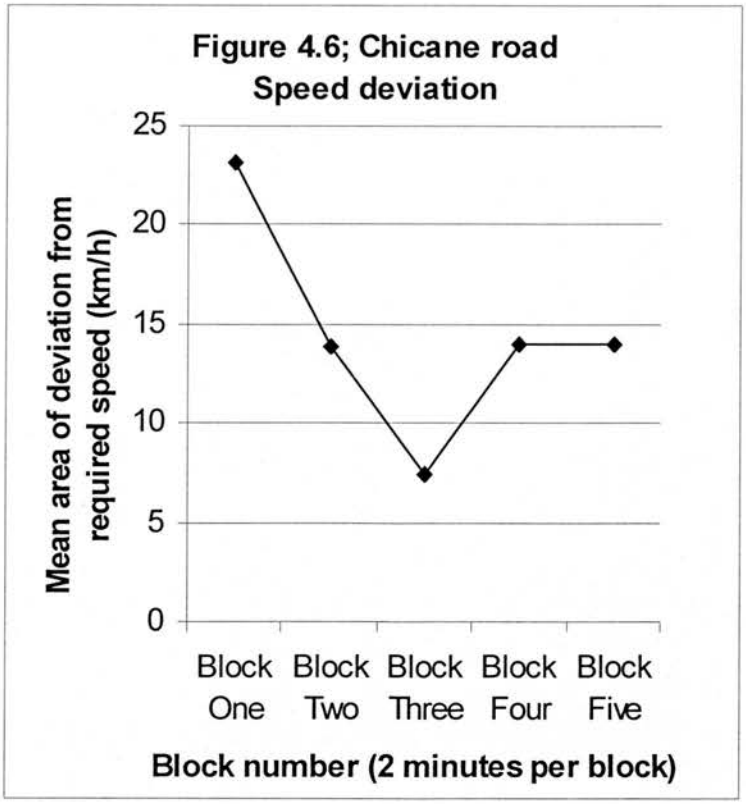


Figure 4.6; Chicane road
Speed deviation
Mean area of deviation from required speed (km/h)
25
20
15
10
5
0
Block One
Block Two
Block Three
Block Four
Block Five
Block number (2 minutes per block)

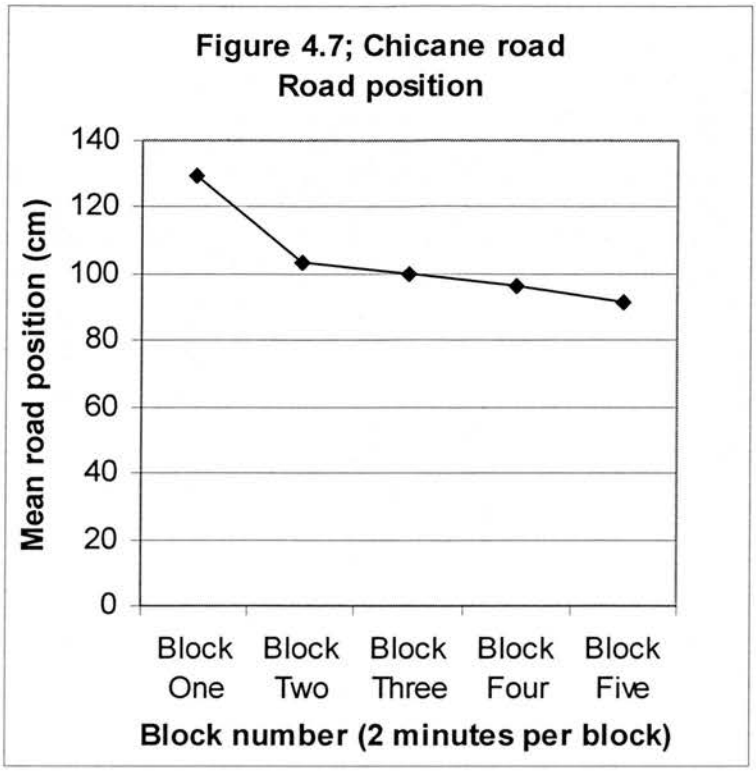


Figure 4.7; Chicane road
Road position
Mean road position (cm)
140
120
100
80
60
40
20
0
Block One
Block Two
Block Three
Block Four
Block Five
Block number (2 minutes per block)

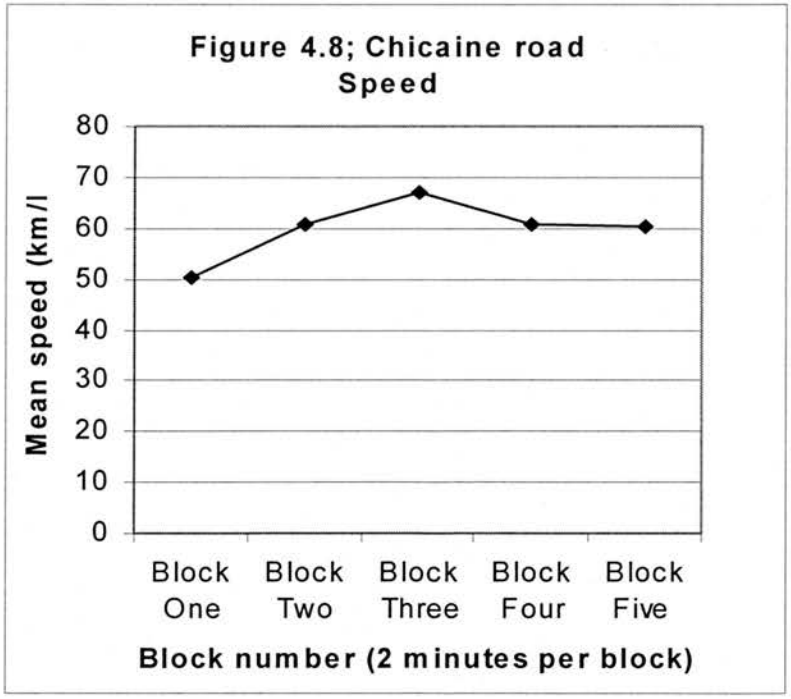


Figure 4.8; Chicaine road
Speed
Mean speed (km/l
80
70
60
50
40
30
20
10
0
Block One
Block Two
Block Three
Block Four
Block Five
Block number (2 minutes per block)

4.9 Results of treatment effects for the two patient groups

To determine if CPAP had a significantly different effect on both the primary (AusEd driving measure outcomes) and secondary outcome measures a repeated measure MANOVA was employed.

Demographic and anthropometric measures

There were no significant differences in BMI, neck size and blood pressure with treatment (table 4.13).

Table 4.13; Anthropometrical data

Variable	Pre Mean and SD		Post Mean and SD		F – value	p level
	CPAP	**Placebo**	**CPAP**	**Placebo**		
BMI (kg/m^2)	33.2 (7.2)	31.9 (4.5)	33.3 (6.6)	33.3 (5.2)	1.88	>0.2
Neck size in cm	42.4 (3.7)	41.9 (3.2)	42.3 (3.7)	42.1 (3.4)	2.99	>0.1
Systolic blood pressure (mmHg) ₸	135.1 (22.3)	132.8 (18.8)	134.8 (22.8)	133.5 (15.4)	0.708	>0.4
Diastolic blood pressure (mmHg) ₸	86.8 (10.9)	87.8 (10.2)	87.1 (10.9)	91.8 (8.9)	0.841	>0.4

₸ millimetres of mercury

Primary Outcomes

No outcome of the AusEd driving simulator program was significantly different after CPAP compared with after placebo. As can be seen in table 4.14, mean scores for the outcomes of area of deviation from lane centre, area of deviation from required speed, and both mean and median reaction time reflected improvement in both the placebo and CPAP treatment groups.

Table 4.14; The AusEd driving simulator outcomes after treatment

Variable	Pre Mean and SD		Post Mean and SD		F – value	p level
	CPAP	**Placebo**	**CPAP**	**Placebo**		
AusEd stop crash	0.3 (0.7)	0.7 (2.0)	0.5 (1.1)	0.3 (0.8)	2.351	>0.1
AusEd truck crash	0.8 (0.4)	0.1 (0.2)	0 (0)	0 (0)	0.128	>0.7
AusEd driving-off-road crash	0.4 (0.7)	0.5 (1.3)	0.8 (2.1)	0.3 (0.6)	1.604	>0.2
AusEd driving-off-road incident	0.5 (0.8)	0.7 (1.6)	1.4 (3.9)	0.5 (1.1)	2.061	>0.1
AusEd total number of events	1.2 (1.5)	1.9 (3.5)	2.7 (6.1)	1.2 (1.5)	2.701	>0.1
AusEd area of deviation from lane centre (cm)	93.0 (28.2)	96.5 (27.2)	87.5 (28.1)	89.6 (27.1)	0.030	>0.8
AusEd area of deviation from required speed (km/h)	10.9 (2.8)	11.8 (4.81)	10.6 (5.0)	10.6 (4.0)	0.907	>0.3
Time outside required speed %	26.1 (10.8)	29.3 (20.6)	25.1 (15.7)	26.1 (16.7)	0.449	>0.5
Mean road position (cm)	78.1 (33.5)	91.0 (26.9)	71.6 (29.3)	81.1 (27.9)	0.257	>0.6
Mean speed (km/h)	64.1 (3.5)	63.4 (6.4)	64.1 (5.5)	65.1 (3.9)	1.387	>0.2
Mean reaction time in seconds	2.7 (3.5)	2.8 (2.6)	2.1 (1.3)	2.6 (2.7)	0.090	>0.7
Median reaction time in seconds	1.8 (1.2)	2.1 (1.9)	1.4 (0.6)	1.7 (1.0)	0.066	>0.7
90^{th} centile reaction time in seconds	0.4 (0.78)	0.4 (0.74)	0.8 (1.9)	0.7 (1.4)	0.467	>0.5

cm –centimetres, km/h kilometres per hour

Table 4.15; Comparison of patients in CPAP and placebo recording accidents on AusEd

	CPAP Number and %	Placebo Number and %	Chi-square. p value
No. of patients recording crash/off-road incident	12 (50)	9 (43)	p>0.4

Secondary outcome measures

CPAP treated patients tended to have better improvement in ESS and had significantly better improvement in OSAHS symptoms. The CPAP treated group also showed significant improvement in the SF36 mental component summary, as well as on the FOSQ domains of productivity, activity level and vigilance and the FOSQ total score. A significant reduction in SF36 bodily pain subscore, linked CPAP with an increase in pain. Placebo treatment was associated with deterioration in health status from the SF36 health transition score.

Table 4.16; OSAHS symptoms, sleepiness and quality of life outcomes

Variable	Pre Mean and SD		Post Mean and SD		F - value	p Level
	CPAP	**Placebo**	**CPAP**	**Placebo**		
ESS*	14 (2.9)	14.2 (3.1)	9.9 (5.2)	12.8 (4.1)	3.55	0.07
Symptom score (max 48)	24.7 (6.9)	25.9 (9.1)	14.2 (11.5)	23.9 (7.8)	9.40	0.04
SF36 health transition†	3.1 (0.7)	2.9 (0.8)	3.1 (0.9)	3.4 (0.7)	6.36	0.02
SF36 physical functioning†	67.9 (29.6)	66.2 (23.4)	66.1 (33.3)	63.6 (23.9)	0.04	>0.1
SF36 role physical†	51 (42)	41.7 (34.8)	57.3 (38.6)	51.2 (39.1)	0.08	>0.8
SF36 role emotional†	56.9 (43.4)	60.3 (41.7)	73.6 (38.0)	53.9 (40.1)	3.88	0.55
SF36 Social functioning†	70.3 (27.8)	66.7 (23.8)	75.9 (23.9)	59.5 (27.9)	2.839	> 0.1
SF36 bodily pain†	63.5 (29.3)	63.1 (25.2)	56.9 (27.7)	70.5 (28.7)	4.110	0.05
SF36 mental health†	65 (12.8)	60.2 (20.7)	70.3 (15.2)	60.6 (19.4)	1.208	>0.3
SF36 vitality†**	40 (19.9)	32.6 (18.9)	50.2 (20.4)	34.8 (21.5)	2.448	>0.1
SF36 general health†	50.5 (21.9)	51.5 (17.5)	49.4 (21.5)	46.3 (20.8)	1.294	>0.2
SF36 physical component summary†	38.4 (15.2)	37.5 (12.8)	36.3 (13.6)	38.1 (13.7)	1.072	>0.3
SF36 mental component summary†	44 (8.7)	42.1 (13.4)	49.5 (9.8)	40.3 (12.1)	5.153	0.03
FOSQ productivity‡	3.2 (0.6)	3.1 (0.6)	3.4 (0.5)	2.9 (0.6)	12.756	0.001
FOSQ social outcome‡	3.3 (0.6)	3.3 (0.6)	3.5 (0.7)	3.0 (0.9)	0.228	>0.6
FOSQ activity level‡	2.8 (0.7)	2.7 (0.6)	3.0 (0.7)	2.5 (0.7)	6.380	0.015
FOSQ vigilance‡	2.8 (0.6)	2.7 (0.8)	3.2 (0.6)	2.6 (0.8)	9.925	0.003
FOSQ total‡	12.1 (2.2)	11.8 (1.9)	13.2 (2.4)	11.1 (2.6)	15.491	0.001
Karolinska score before AusEd	4.3 (1.6)	5.1 (1.3)	3.8 (1.5)	5.2 (4.6)	2.203	>0.1
Karolinska score after AusEd	5.8 (2.1)	6.2 (1.8)	5.3 (1.9)	6.2 (1.9)	0.897	>0.3

** Showed significant time effect at p=0.02, ** Showed significant time effect at p=0.001 †Short form 36, ‡ functional outcome of sleep questionnaire*

Previous research has suggested that pre-treatment patients may under-report MVAs until treatment has been established (Engleman 1997). In the current study, patients were asked at their baseline visit to report the number of accidents they had been involved with in the previous five years, and they were asked this again after their treatment period. Both patient groups reported significantly changed values in minor accidents between baseline and post-treatment. One person from each treatment group reported a minor accident during their treatment period. This may account for the rise in accident reports from the placebo group, but would not account for the reduction reported by the CPAP group. Further, although the two groups at baseline did not report significant differences in the frequency of involvement in accidents and near misses, post-treatment, more CPAP patients reported having near misses in the previous five years.

Table 4.17; Driving questionnaire outcomes

Variable	Pre Mean and SD		Post Mean and SD		F - value	p Level
	CPAP	**Placebo**	**CPAP**	**Placebo**		
Major accident last 5 years	0 (0)	0.1 (0.2)	0 (0)	0.1 (0.2)	3.261	>0.1
Minor accident last 5 years	0.33 (0.6)	0.5 (0.8)	0.2 (0.4)	0.7 (1.0)	4.860	0.03
Near miss accident last 5 years	2.7 (3.9)	4.1 (11.6)	2.5 (3.1)	5.9 (14.9)	1.629	>0.2

Table 4.18; Number of patients reporting accidents and near misses

	CPAP (n=24) Number and %	Placebo (n=21) Number and %	Chi-square p value
Number of patients reporting crashes	5 (21)	9(43)	>0.1
Number of patients reporting near misses	17 (71)	6 (29)	0.05

Perceived benefit of treatment

CPAP treatment was rated as significantly less acceptable than the placebo treatment, but was significantly more effective. Although patients were more satisfied with CPAP, there were also significantly more side effects associated with it. Compliance was higher in the placebo and was trending towards significance.

Table 4.19; Treatment compliance, acceptability, satisfaction and effectiveness

Variable	CPAP Mean and SD n = 24	Placebo Mean and SD n = 21	p level
Compliance %*	76.5 (29.2)	91.9 (13.2)	>0.08
Acceptability of treatment (Scale 1-10)	6.0 (2.5)	7.4 (2.8)	0.05
Satisfaction of treatment (scale 1-10)	6.8 (2.6)	4.0 (2.8)	0.002
Effectiveness of treatment (scale 1-10)	6.0 (2.6)	2.8 (1.7)	0.001
Side effects of treatment %	17.9 (14.0)	10.3 (8.3)	0.036

** Number of night's treatment used divided by number of possible nights usage.*

4.10 Summary of results

As hypothesised there were no differences in baseline demographic, polysomnographic, clinical or symptomatic characteristics and no differences in baseline performance on intellectual tests, driving reports or driving simulation scores between the placebo and CPAP treated patient groups.

Weak, yet significant correlation co-efficients were found between several of the AusEd driving simulator outcomes and subjective sleepiness, sub-domains of the SF36 and FOSQ, vigilance task and subjective rating of computer experience.

The primary outcomes of driving performance as measured by the AusEd simulator on several driving performance measures including steering deviations, lane position, speed and speed variability and a brake reaction time task yielded no significant differences between the two treatment options. Hence, these outcomes do not support the hypothesis that the AusEd simulator would be sensitive to changes in driving performance associated with treatment.

However, the results from the repeated measures MANOVA do indicate a significant improvement in several of the secondary, non-simulator outcome measures with CPAP. The SF36 subscales of health transition and the mental component summary, as well as the scales of productivity, activity level, vigilance and total score from the FOSQ questionnaire, all showed significant improvement with CPAP treatment. Inversely, the SF36 scale of bodily pain was improved in the placebo patient group but declined in the CPAP patient group. Symptoms of OSAHS were also significantly reduced by CPAP treatment, and the ESS scale shows a trend towards a CPAP treatment effect.

For a discussion of these results please see chapter 6.

Chapter 5: Case control comparisons on the AusEd driving study

5.1 Introduction

In addition to the placebo-controlled treatment aspect of the study, healthy community controls were recruited and matched to the CPAP patient group for gender and age, with the aim of identifying differences in performance on the driving simulator between the OSAHS patients and healthy subjects. The primary outcomes of this study were the case-control comparisons of and changes in performance on the AusEd-driving simulator.

Prospectively it was hypothesised that the healthy non-OSAHS control group would show significantly different results on the outcomes of AusEd driving simulator when compared to the pre-treatment CPAP patient group. It was also hypothesised *a priori* that subjective sleepiness, OSAHS symptomology and perceived health status would be poorer in the patient group. It was further hypothesised that these significant differences might no longer be found when comparison was made between the control group and the CPAP treated patient group.

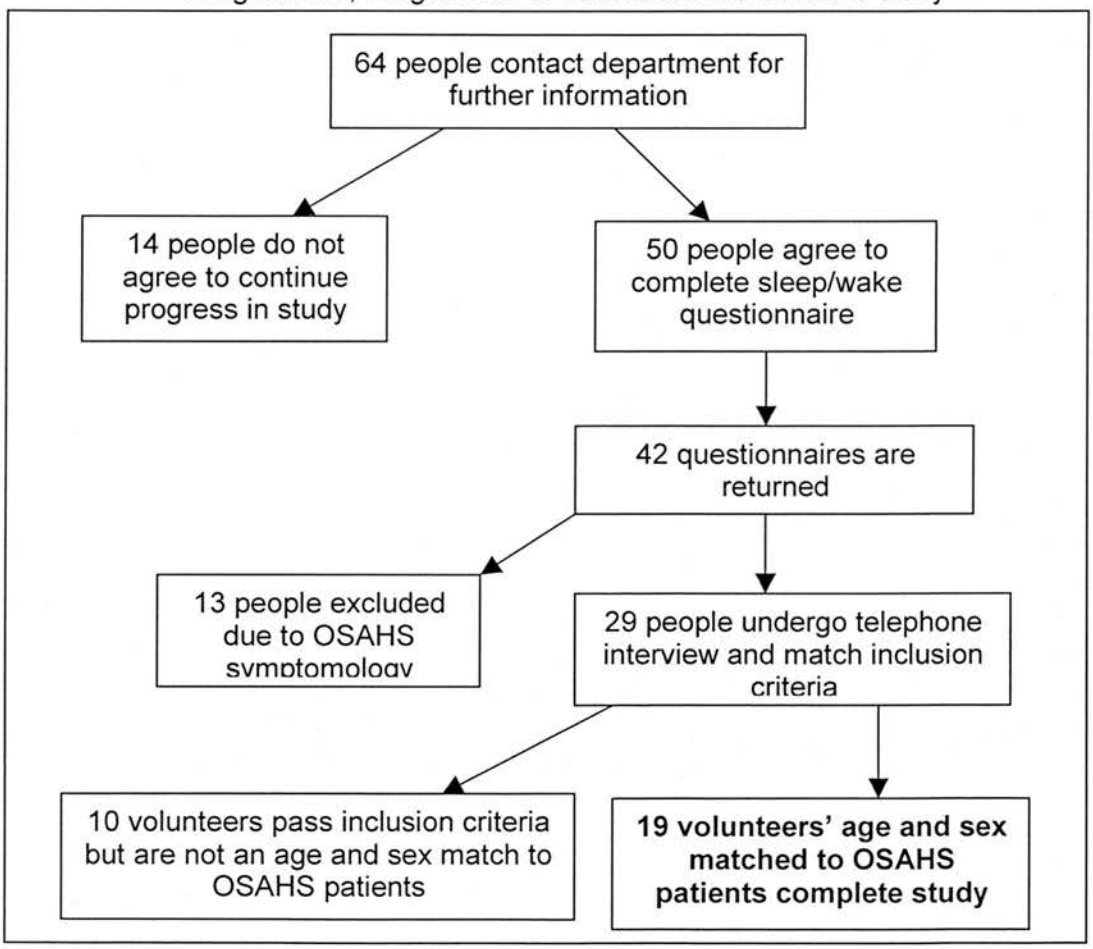
5.2 Control subject recruitment

Volunteers were matched with patients randomised to CPAP, for their age (±5years) and gender, and inclusion/exclusion were as follows;

Inclusion criteria: ESS <11; holds full drivers licence; no serious neurological, cardiovascular or respiratory disease; aged between 18-70; ability to understand consent procedures;
Exclusion criteria: symptoms of sleep apnoea, frequent snoring, witnessed breathing pauses, regular napping in day or evening; symptoms of other sleep disorders.

Over all 64 people responded to the adverts and contacted me for further details. Fifty people then agreed to complete the inclusion questionnaire. At this point, an information sheet, inclusion questionnaire and consent form were sent to the volunteers and a prepaid envelope was included for their return. Of the 50 sent, 42 were returned. Of the 42 questionnaires returned, 13 (2 females) volunteers were excluded due to their ESS (≥11) or symptoms compatible with OSAHS. Twenty-nine volunteers were then contacted and a telephone interview conducted to further ensure all possible volunteers were suitable. All 29 met inclusion criteria however only 19 (2 females) of these volunteers were an age and gender match to CPAP patients, and therefore included. Diagram 5.1 demonstrates the progression of volunteers.

Diagram 5.1; Progression of volunteers in the AusEd study



Mann Whitney U tests were conducted and showed that the 19 controls subjects included in the study (mean age 52.4 SD 10.2) were neither older than the 13 excluded control subjects (mean age 53.7 SD 10.1) $z=-0.386$, $p>0.1$ nor sleepier as measured by the ESS, $z=-1.588$, $p>0.1$ (ESS 4.9 SD 2.1 versus 7.5 SD 4.5 for used and excluded control groups respectively). The Fisher's exact test showed that there were no significant differences in the distribution of gender in the two groups, $p>0.1$.

5.3 Statistics

Between groups comparisons were conducted using the non-parametric Mann-Whitney U test and categorical level data were analysed with Fisher's Exact Test.
All tests were performed on the PC statistical package SPSS (SPSS for windows, Version 12, 2003, SPSS, Chicago, IL, USA).

5.4 Testing schedule

Control subjects matched to CPAP patients for age and sex completed the driving simulator task at the same time (morning or afternoon) as their matched CPAP patient's baseline drive. The control group also had a familiarisation trial of the AusEd driving simulator.

Therefore patients matched to CPAP patients whose baseline AusEd simulator drive was in the morning were asked to attend the sleep centre for 8.45am and their daytime schedule was as follows:

9am Introduction, Height, weight and neck measurements taken
9.15 questionnaires (ESS, FOSQ, SF36, Symptom scale, Driving history, computer usage) to be completed
9.45 NART and Ravens matrices tests
10.10 EEG wires on
10.45 Blood pressure taken
10.55 AusEd driving simulation. Completing the Karolinska sleepiness scale before and after the simulation
11.50 wires off

Patients matched to CPAP patients whose initial drive was in the afternoon were asked to attend the sleep centre for 1pm, as follows:
1pm Introduction, height, weight and neck measurements taken
1.15 questionnaires (ESS, FOSQ, SF36, Symptom scale, Driving history, computer usage) to be completed
1.45 NART and Ravens to be completed
2.10 EEG wires on
2.45 Blood pressure taken
2.55 AusEd driving simulation. Completing the Karolinska sleepiness scale before and after the simulation
3.50 wires off

All control subjects were asked to avoid alcohol and caffeine from 8pm the previous evening. Controls subjects were also questioned regarding when they went to bed, how long they felt they took to fall asleep and when they woke up in the morning.

5.5 Comparison between baseline OSAHS patients randomised to CPAP and Control volunteers

All baseline comparisons were analysed with Mann-Whitney U non-parametric tests unless otherwise stated.

As can be seen from table 5.1 there are several significant differences between the control group and the CPAP patients at baseline.
Anthropometrical data shows the control group were thinner and had a BMI in the normal range, compared to the CPAP patient group. They also had smaller neck sizes and were better educated

Table 5.1; Patient and control demographics results

Variable	CPAP Mean and SD n = 24	Controls Mean and SD n = 19	p level
Age in years	51.9 (8.3)	52.4 (10.2)	>0.1
Education (scale 1-3)	2.2 (0.9)	2.7 (0.5)	0.038
*Sex (male or female)	21m/3f	17m/2f	>0.1
*Smoke (yes or no)	5y/19n	1y/18n	>0.1
Weight in kg	97.9 (18.9)	80.5 (11.9)	0.001
Height in metres	1.7 (0.1)	1.8 (0.1)	>0.06
BMI (kg/m^2)	33.2 (7.2)	25.6 (3.6)	0.001
Neck size in cm	42.4 (3.7)	38.4 (5.4)	0.004
Systolic blood pressure (mmHg)¶	135.1 (22.3)	134.9 (14.8)	>0.1
Diastolic blood pressure (mmHg) ¶	86.8 (10.9)	88.8 (9.9)	>0.1

**Chi-square, ¶ millimetres of mercury*

Primary outcomes

The median reaction time on the AusEd simulator was significantly faster in the control population than the OSAHS population at baseline. However all other driving performance measures were similar between the 2 groups.

Table 5.2; Baseline AusEd simulator outcomes

Variable	CPAP n = 24	Controls n = 19	P level
	Number and %	Number and %	
Number of participants recording a crash or off-road event*	13 (54)	9 (47)	p>0.6
	Mean and SD	Mean and SD	
AusEd stop crash	0.3 (0.7)	0.7 (1.7)	>0.6
AusEd truck crash	0.1 (0.4)	0	>0.3
AusEd driving-off-road crash	0.4 (0.7)	0.2 (0.4)	>0.2
AusEd driving-off-road incidents	0.5 (0.8)	0.3 (0.9)	>0.3
AusEd total number of events	1.2 (1.5)	1.2 (1.9)	>0.6
AusEd mean area of deviation from lane Centre (cm)**	93.0 (28.2)	94.1 (24.2)	>0.1
AusEd mean area of deviation from required speed (km/h)***	10.9 (2.8)	9.9 (2.5)	>0.1
Time outside required speed %	26.1 (10.8)	20.9 (9.7)	>0.1
Mean road position (cm)***	78.1 (33.5)	84.4 (28.1)	>0.1
Mean speed (km/h)**	64.1 (3.5)	65.2 (4.5)	>0.1
Mean reaction time in seconds	2.7 (3.5)	1.7 (1.3)	>0.1
Median reaction time in seconds	1.8 (1.2)	1.1 (0.3)	0.017
90^{th} centile reaction time in seconds	0.39 (0.78)	0.1 (0.1)	>0.1

Chi-square, ** Centimetres, * kilometres per hour*

Secondary Outcomes

As anticipated, because of the selection criteria the control group reported fewer symptoms of OSAHS, were less sleepy in both trait (ESS) and state (Karolinska) measured sleepiness scales and reported better health status both generally (SF 36) and regarding sleepiness (FOSQ). The control group showed higher intellectual function than the patient group, but there were no significant differences in the IQ change scores of the two groups.

Table 5.3; Baseline OSAHS symptoms, sleepiness and quality of life outcomes

Variable	CPAP Mean and SD n = 24	Controls Mean and SD n = 19	Significance level
Recruitment ESS*	14 (2.9)	4.9 (2.1)	0.001
Symptom score (max 48)**	24.7 (6.9)	8.2 (4.1)	0.001
SF36 health transition**	3.1 (0.7)	2.8 (0.6)	>0.1
SF36 physical functioning**	67.9 (29.6)	95.5 (7.6)	0.001
SF36 role physical**	51 (42)	89.5 (28.0)	0.001
SF36 role emotional**	56.9 (43.4)	92.9 (23.7)	0.002
SF36 Social functioning**	70.3 (27.8)	86.8 (19.3)	0.045
SF36 bodily pain**	63.5 (29.3)	85.1 (21.5)	0.02
SF36 mental health**	65 (12.8)	76.8 (14.9)	0.016
SF36 vitality**	40 (19.9)	73.9 (13.8)	0.001
SF36 general health**	50.5 (21.9)	78.8 (15.2)	0.001
SF36 physical**	38.4 (15.2)	52.2 (7.4)	0.004
SF36 mental**	44 (8.7)	52.7 (7.6)	0.002
FOSQ productivity***	3.2 (0.6)	3.9 (0.1)	0.001
FOSQ social outcome***	3.3 (0.6)	4.0 (0)	0.001
FOSQ activity level***	2.8 (0.7)	3.9 (0.1)	0.001
FOSQ vigilance***	2.8 (0.6)	3.7 (0.3)	0.001
FOSQ total***	12.1 (2.2)	15.6 (0.4)	0.001
Ravens score max 60	43.5 (8.0)	49 (7.9)	0.021
NART score max 50¶	33.6 (9.1)	41.2 (5.8)	0.006
IQ change score	0.15 (0.99)	0.0 (1.1)	>0.1
Karolinska score before AusEd	4.3 (1.6)	2.7 (1.0)	0.001
Karolinska score after AusEd	5.8 (2.1)	3.2 (1.6)	0.001

ESS –Epworth sleepiness score, SF36 – Short from 36, *** Functional outcomes of sleepiness questionnaire, ¶ National adult reading test*

Both groups reported holding their driving licenses for similar periods of time and reported similar distances driven annually. However the CPAP group drove more frequently per week (scale 1-4), but reported a reduced level of ability to drive long distances (scale 1-5) compared to the control group. Accident frequency was not significantly different in the two groups for the preceding five years, although more patients reported significantly more near miss incidents than controls.

Table 5.4; Baseline driving questionnaire outcomes

Variable	CPAP n = 24	Controls n = 19	p level
	Number and %	Number and %	
Frequency of participants reporting accident last 5 years*	7 (29)	6 (32)	>0.9
Frequency of participants reporting near accidents last 5 years*	14 (58)	6 (32)	0.03
	Mean and SD	Mean and SD	
Major accident last 5 years	0 (0)	0.1 (0.2)	>0.1
Minor accident last 5 years	0.33 (0.57)	0.4 (0.8)	>0.1
Near miss accident last 5 years	2.7 (3.9)	0.9 (1.6)	>0.06
Years held drivers licence	31.3 (8.6)	30.8 (13.1)	>0.1
Miles driven per year	9754.2 (5271.6)	8789.5 (4366.3)	>0.1
Days driven per week (scale 1-4)	3.88 (0.5)	3.47 (0.8)	0.05
Ability to drive long distances (scale 1-5)	3.5 (1.1)	4.5 (0.7)	0.001

** Chi-square*

5.6 Comparison between post-treatment OSAHS patients randomised to CPAP and Control volunteers

All comparison were analysed with Mann-Whitney U non-parametric tests unless other wise stated.

The outcomes from the control group were also analysed in comparison to the CPAP group after the treatment period.

Demographic and anthropometric data

There were no improvements changes in the patient's weight, BMI or neck size during the treatment period and as such, these outcomes remained significantly different from the control group.

Table 5.5; Post-treatment Patient and control demographics

Variable	CPAP Mean and SD n = 24	Controls Mean and SD n = 19	p level
Weight in kg	99.1 (19.5)	80.5 (11.9)	0.001
Height in meters	1.7 (0.1)	1.8 (0.1)	>0.06
BMI (kg/m^2)	33.3 (6.6)	25.6 (3.6)	0.001
Neck size in cm	42.3 (3.7)	38.4 (5.4)	0.05
Systolic blood pressure (mmHg)*	134.8 (22.8)	134.9 (14.8)	>0.1
Diastolic blood pressure (mmHg)*	87.1 (10.9)	88.8 (9.9)	>0.1

** millimetres of mercury*

Primary outcomes

As with the baseline results, there were no significant differences in the two groups in the crash/off-road events, steering and speed outcomes. However the significant difference between the groups at baseline regarding the median brake reaction time was not present in the post-treatment/control analysis, signifying an improvement in the CPAP group.

Table 5.6; Post-treatment AusEd driving simulator outcomes

Variable	CPAP n = 24	Controls n = 19	P level
	Number and %	Number and %	
Number of participants recording crashes*	12 (50)	9 (47)	>0.9
	Mean and SD	Mean and SD	
AusEd stop crash	0.5 (1.1)	0.7 (1.7)	>0.9
AusEd truck crash	0	0	>0.9
AusEd driving-off-road crash	0.8 (2.1)	0.2 (0.4)	>0.3
AusEd driving-off-road incidents	1.4 (3.9)	0.3 (0.9)	>0.1
AusEd total number of events	2.7 (6.1)	1.2 (1.9)	>0.6
AusEd mean area of deviation from lane Centre (cm)*	87.5 (28.1)	94.1 (24.2)	>0.1
AusEd mean area of deviation from required speed (km/h)**	10.6 (5.0)	9.9 (2.5)	>0.8
Time outside required speed %	25.1 (15.7)	20.9 (9.7)	>0.4
Mean road position (cm)*	71.6 (29.3)	84.4 (28.1)	>0.4
Mean speed (km/h)**	64.1 (5.5)	65.2 (4.5)	>0.7
Mean reaction time in seconds	2.1 (1.3)	1.7 (1.3)	>0.1
Median reaction time in seconds	1.4 (0.6)	1.1 (0.3)	>0.1
90^{th} centile reaction time in seconds	0.8 (1.9)	0.1 (0.1)	>0.2

** Chi square, ** Centimetres, *** kilometres per hour*

Secondary Outcomes

As would be expected after treatment the CPAP patients reported fewer OSAHS associated symptoms and this abolished the significant difference from the controls found at baseline. However this result was not mirrored by the ESS outcome, which remained significantly higher than the control group, however there was a reduction in the mean ESS score of the patients from baseline to post-treatment. The Karolinska sleepiness scale score also remained significantly different between the two groups both before and after the simulated drive.

As with baseline the two groups remained significantly different in all domains of the FOSQ. However, the SF36 domains of health transition the SF36 health transition remained non-significantly different as at baseline, mental health and the mental health summary score were not significantly different post-treatment, showing an improvement in this area associated with depression and tension.

Table 5.7; Post-treatment OSAHS symptoms, Sleepiness and quality of life outcomes

Variable	CPAP Mean and SD n = 24	Controls Mean and SD n = 19	p level
ESS*	9.9 (5.2)	4.9 (2.1)	0.001
Symptom score (max 48)	14.2 (11.5)	8.2 (4.1)	>0.1
SF36 health transition**	3.1 (0.9)	2.8 (0.6)	>0.1
SF36 physical functioning **	66.1 (33.3)	95.5 (7.6)	0.001
SF36 role physical**	57.3 (38.6)	89.5 (28.0)	0.002
SF36 role emotional**	73.6 (38.0)	92.9 (23.7)	0.029
SF36 Social functioning**	75.9 (23.9)	86.8 (19.3)	0.074
SF36 bodily pain**	56.9 (27.7)	85.1 (21.5)	0.001
SF36 mental health**	70.3 (15.2)	76.8 (14.9)	>0.1
SF36 vitality**	50.2 (20.4)	73.9 (13.8)	0.001
SF36 general health**	49.4 (21.5)	78.8 (15.2)	0.001
SF36 physical summary score**	36.3 (13.6)	52.2 (7.4)	0.001
SF36 mental summary score**	49.5 (9.8)	52.7 (7.6)	>0.1
FOSQ productivity***	3.4 (0.5)	3.9 (0.1)	0.001
FOSQ social outcome***	3.5 (0.7)	4.0 (0)	0.001
FOSQ activity level***	3.0 (0.7)	3.9 (0.1)	0.001
FOSQ vigilance***	3.2 (0.6)	3.7 (0.3)	0.002
FOSQ total***	13.2 (2.4)	15.6 (0.4)	0.001
Karolinska score before AusEd	3.8 (1.5)	2.7 (1.0)	0.04
Karolinska score after AusEd	5.3 (1.9)	3.2 (1.6)	0.001

ESS –Epworth sleepiness score, SF36 – Short from 36, *** Functional outcomes of sleepiness questionnaire,*

After treatment the CPAP patient group were also asked to re-estimate the number of major, minor and near miss accidents they had had in the preceding five years. As baseline, the two groups reported no significant differences in the major and minor accidents, the CPAP patient group reported significantly more near miss incidents.

Table 5.8; Post-treatment Driving questionnaire outcomes

Variable	CPAP n = 24	Controls n = 19	p level
	Number and %	Number and %	
Frequency of participants reporting accident last 5 years*	5 (21)	6 (32)	>0.4
Frequency of participants reporting near miss accidents last 5 years*	17 (71)	6 (32)	0.01
	Mean and SD	Mean and SD	
No. of Major accidents last 5 years	0 (0)	0.1 (0.2)	>0.1
No. of Minor accident last 5 years	0.2 (0.4)	0.4 (0.8)	>0.1
No. of Near miss accident last 5 years	2.5 (3.1)	0.9 (1.6)	0.008

** Chi-square*

5.7 Summary of results

Contrary to the hypothesis the baseline comparisons of the two groups on the AusEd driving measures showed no significant differences in the number of crashes/off-road events, steering and speed outcome measures, however the control group did show higher median brake reaction time than the CPAP group. The lack of differences in the crash/off-road events, steering and speed measures was replicated when post-treatment CPAP and controls were compared. However, there was no longer a difference between the two groups in the median brake reaction time, signifying an improvement in the CPAP group with treatment.

As hypothesised there were differences at baseline in the anthropometric, symptomatic, sleepiness and quality of life outcomes between the CPAP group and the matched controls. Significant differences were also found in the scores of intellectual tests although no differences were found in the IQ change scores, and the CPAP group reported higher number of near miss accidents. Although CPAP treatment did not significantly reduce subjective sleepiness by ESS or FOSQ outcome, there were no longer differences in the two groups in relation to OSAHS symptomology, and the mental health and mental component summary scores of the SF36 also showed no significant differences.

The improvement in the median reaction time seen in the CPAP group post-treatment has real life implications, as a slow or reduced reaction time could be fatal especially when travelling at high speeds. However as the simulator did not detect differences in any of the other driving measures between the two groups, either before or after CPAP treatment the outcomes do not support the hypothesis that the AusEd simulator would be sensitive to differences in performance between OSAHS patients and healthy volunteers.

For a discussion of these results please see chapter six.

Chapter 6: Discussion of results for the treatment effects and case-control outcomes of the AusEd driving simulator.

This chapter will address the results and outcomes of the main AusEd driving simulator study.

6.1 Summary of the treatment effect of the AusEd driving simulator study

Forty-five OSAHS patients with mean AHI 38.9 completed the laboratory-based AusEd driving simulator study. Patients were randomised to a low (8-13) or high (14+) ESS group and within block stratification was used to assign them to receive placebo (n=19) or CPAP treatment (n=24). In addition to nocturnal polysomnography and the AusEd simulator driving measures, patients were tested on objective and subjective daytime sleepiness, intelligence tests, quality of life measures, OSAHS symptomology, a vigilance task and perceived driving ability.

Baseline comparisons of the anthropometric and demographic data between placebo- and CPAP-treated patients showed the groups were similar in age, weight, BMI, and educational status. The two groups were not statistically different in any of the nocturnal variables of AHI, arousals, sleep efficiency or total sleep time. Further, the two groups showed no statistical differences in their level of objective daytime sleepiness, although the placebo group had higher mean sleep onset latency. This coupled with the fact that no differences were found between the two groups in subjective reports of sleepiness, general health, driving ability, OSAHS related symptoms, and their level of objectively measured vigilance (SteerClear), suggests that the randomisation process produced two similar groups.

<u>AusEd driving measure outcomes</u>

The two patient groups recorded no significant differences in any of the baseline driving measurements of steering deviation, road position, speed deviation and mean speed.

Neither were they different in the number of crashes and driving-off-road events recorded by the simulator, further there were no differences in any of the reaction time variables.

However, both groups recorded a mean lane position which was congruent with them driving within the left lane boundary, and both groups also had a mean speed which was within the task instructions to maintain speed in the range 60-80 km/h.

Post Treatment outcomes

Treatment effects on the AusEd driving simulator were analysed using a repeated measures MANOVA. The post treatment drives on the simulator yielded no significant differences between the two groups in any of the driving measured outcomes, returning the null hypothesis.

Some treatment effects were found. The CPAP group reported fewer OSAHS symptoms compared to the placebo group. ESS was not significantly improved in the CPAP group over placebo, but there was a time effect in this variable, with both groups improving from the baseline value. QOL of life measures were significantly improved in the CPAP group, this is especially evident in the FOSQ questionnaire in which all but one of the domains showed a significant improvement over the placebo group.

6.2 Summary of the case control aspect of the AusEd driving simulator study.

Nineteen OSAHS symptom free control subjects, matched to the CPAP treated group for age (±5 years) and gender, and the 24 CPAP treated OSAHS patients completed this aspect of the AusEd driving simulator trial.

The control group was significantly thinner, and had higher intellectual functioning, although the IQ change scores of the two groups were not significantly different. Both groups reported similar driving habits, and reported similar number of accidents for the

preceding five-year period. However, the CPAP group did report a significantly reduced ability to drive long distances compared to control subjects.

Baseline AusEd driving outcome measures

In contradiction to the hypothesis, the two groups showed no significant differences in the steering, speed and off-road/crash driving measures. However the control group recorded a significantly faster median reaction time than the patient group.

CPAP post treatment comparisons

Post-treatment CPAP patients' scores from the AusEd driving simulator and their secondary outcome measures were also compared to the outcome measures of the control group.

AusEd driving simulator outcome measures.

There were no significant differences in the two groups on any of the steering, speed and crash/off-road events. The significant difference in the median reaction time seen at baseline was not found in the post treatment drive.

Secondary outcomes

CPAP treatment reduced OSAHS related symptoms and these were not significantly different from the control group post treatment. ESS remained significantly higher than the control group but was lower than pre-treatment. Two domains of the SF36 were no longer significantly different from the control group, although the significant differences found in the FOSQ scores remained evident post-treatment.

6.3 Discussion of the AusEd driving simulator and secondary outcome measures

AusEd outcomes

The AusEd driving simulator was designed as a portable laboratory based tool to assess fitness to drive in OSAHS patients. The results of the parallel-limb placebo controlled and case-controlled trials could not support the validation of this simulator as an effective tool for distinguishing OSAHS patients with poor driving performance either from other patients or healthy controls. No significant differences were found between the CPAP and placebo treated patients groups on the driving outcome measures of the simulator, either before or after the treatment period. The only driving outcome measure to discriminate between untreated and control subjects was median reaction time during braking to the stimulus of a vehicle ahead. However, the lack of differences may not be due to the insensitivity of simulator.

The driving simulator aimed to assess tracking, visual search and speed control, three aspects of real life driving. For these three areas participants were instructed to drive along the centre of the left lane, bring the car to an immediate stop when a truck appeared on the horizon (to assess reaction time) and to keep their speed between 60-80km/h. Outcome measures for the tracking task were; the mean deviation from lane centre (to assess steering deviation) and mean road position (to assess where participants positioned themselves laterally on the road). The visual search component was measured by brake reaction time recorded when drivers reacted to a truck appearing on the horizon. Speed control was measured by the mean deviation from the required speed and the percentage of time out-with the required speed (to assess if participants were driving above or below the speed guidelines), and mean speed was also recorded.

As this was a validation study no normative values for each of these outcomes exist. Therefore it is not possible to determine if the outcome measures of mean deviation from both the lane centre and required speed were within an acceptable margin. However, it is possible to determine whether the groups had a mean lateral position

within the left lane and a mean speed between 60-80kph. In fact all three groups (on all drives) recorded a mean speed over the 30-minute drive that was within the 60-80kph limits. Further, both patient groups (pre and post treatment) and the control group recorded a mean road position between -180 and 180cm. This is the centimetre range of the left lane of the AusEd simulated road. As these measures (on average) were within the task parameters on the patients' baseline drives, one might speculate that the lack of significant differences were not as a result of the insensitivity of the simulator, but because the groups as a whole, were not impaired in these task areas. There is further support for the sensitivity of the simulator as the median reaction time was significantly slower in the pre treated CPAP group compared to the controls and this difference was abolished with CPAP treatment.

Only one other study comparing OSAHS patients and control subjects utilised a brake reaction time (BRT) task. Control subjects in the Haraldsson study (1991) recorded a mean BRT of 1.3 seconds, which is similar to the BRT of 1.7 seconds in the current study, suggesting the RT task might be potentially accurate and useful.

In the present study the baseline vigilance task SteerClear was run at a different speed from the Findley studies (1995) due to improvements in computer processor speeds. Hence, although it is possible to report that the performances on the vigilance task of the two patient groups at baseline were not significantly different, it is not possible to report if their scores would be classed within the normal range (Findley et al 1995). This inhibits one from providing objective evidence that the pre-treatment patient groups showed no vigilance decrements at baseline. Therefore, it is not possible to speculate if the patient group were likely to have a reduced RT. The baseline sleep onset latencies on the MWT of the two groups were 20 minutes. This may be considered pathological, indicating the groups were sleepy. As sleepiness is linked with a reduction in vigilance this may support the increased RT of the patient group compared to control subjects. However as discussed in section 2.7 the inability to remain awake for 40 minutes does not automatically mean one cannot safely control a vehicle.

The patient population in the current study would be classed as having moderate OSAHS. Some evidence exists that it may be patients with severe OSAHS who are at

increased risk. Aldrich (1989) reported those patients with an AHI greater than 60 were twice as likely to have an MVA than those with an AHI <60. While Findley reported that only the severe patients reported higher MVAs than all licence holders on a state registration, they do not report the AHI of this OSAHS group. However George et al (1999) reported that significantly more MVAs were reported in an OSAHS group AHI>40 as compared to a control population. This level of disease severity is similar to the current patient population.

Perhaps the moderate degree of OSAHS in this patient population may not produce severe driving impairment on a driving simulator and as such only BRT and not tracking and visual search were affected. However, the driving history elicited from the groups would also suggest that the patient groups and controls were similar in MVA involvement for the previous five years. Although there is a discrepancy in the number of minor accidents in the patient group between baseline and post treatment, overall the two groups reported similar numbers of actual accidents and the frequency of participants reporting accidents was similar. The control group and CPAP treated group also did not differ in actual crash rate and frequency of participants reporting accidents. Evidence that actual MVA rate in OSAHS patients is linked to poor simulated driving performance has been reported (Findley 2000, Turkington 2001). If simulated driving were an accurate reflection of real life driving one would expect this association. However as the frequency of participants reporting actual MVAs and the number of MVAs reported is not significantly different in the patient and control group in the current study, one would not necessarily expect to find a difference in performance on the simulator.

OSAHS and other driving simulators

The studies cited in section 2.10.2 are not congruent with the current study in that both the DADT (George et al 1997, 1996a) and Swedish Road and Traffic Research Institute's driving simulator (Haraldsson et al 1990) recorded significantly poorer tracking and visual search outcomes in pre-treated OSAHS patients, compared to controls. However the studies cited in section 2.10.2 did not utilise a parallel OSAHS

patient group free from active treatment, and therefore it is not possible to directly compare the treatment-effects trial of the current study with these.

However driving simulator studies published since the inception of the AusEd validation study are also not congruent with the results from this study. The PC based Divided Attention Steering Simulator (DASS, Stowood scientific instruments 1999) assesses tracking and visual search. This task utilises the steering wheel configuration of the DADT and does not employ a speed task. The tracking task is based on a screen view of a single track winding road with a car bonnet in the foreground, during which one must steer the 'car' down the road maintaining one's position in the lane. The visual search task is similar to the DADT simulator. Digits are displayed in the four corners of the monitor and subjects must press buttons mounted on the steering wheel, corresponding to each corner, when the target number is displayed. The drive lasts 30 minutes and the program allows the administrator to select a road view from three options. The standard view shows the car bonnet and the full road layout to the horizon. The other views show only the car bonnet and near road (as in fog) or the car bonnet and far road (the aspect just in front of the horizon). The outcome measures included deviation from the lane, reaction time and the number of off-road-events. Off-road-events were categorised as crashes if they remained out with the lane for 15 seconds. Several studies (Juniper et al 2000, Hack et al 2000, 2001, Turkington et al 2001, 2003) have used the DASS and found that untreated OSAHS patients perform poorer on all aspects of the steering simulator than treated OSAHS and controls subjects.

Juniper et al (2000) compared the performance of 12 OSA patients diagnosed with oximetry and 12 healthy matched controls on all three road-types in a randomised order. Overall, the OSA patients had slower reaction times, greater steering deviations and higher numbers of off-road events. Although the OSA group showed performance decrements on all drives compared to the controls, the near drive (fog like conditions) had the greatest magnitude of difference in the three driving outcomes. This suggests that not only could OSA patients have poorer driving performance than controls, but also this decrement in driving performance could be worsened by poor driving conditions. The authors, however, did not gather information on the MVA rate of the

participants, so it is not possible to elicit a judgement as to whether the OSA group were at increased involvement in MVAs in real driving.

A similar protocol was used by Hack et al (2001) to establish if the simulator could detect differences in driving performance in several conditions. Driving performance was compared in 26 OSA patients before and after four weeks of CPAP treatment. Further driving performance was compared in 12 controls that drove in a pseudo randomised condition of alcohol consumption or a non-alcohol consumption drive. A second control group (n=12) was also employed and their driver performance was compared after a night of normal sleep or after 24 hours of sleep deprivation. All the groups completed the three road-view conditions in a randomised order and the total drive time was 90 minutes in each driving session. The untreated OSA group showed significantly poorer steering control, longer RT and more drive-off the road events compared to after CPAP treatment. This pattern was mirrored by both the alcohol and sleep deprivation groups, with their driving performances' being significantly poorer when compared to their 'normal' drives.

Hack et al also compared steering error at the start of each drive within each condition and its progress over the 90-minute driving sessions. The alcohol group started poorly and remained poor over the course of the drive, compared to their normal (alcohol free) drive. The pattern was different in the sleep deprived and untreated OSA group. Compared to their own 'normal' drives these two groups showed little steering error initially when they were new to the task, but performance degraded with time-on-task. This indicates that not only can PC based simulators detect differences in performance, but that they can detect differences in the pattern of performance also.

Hack et al (2000) also compared driving performance in 59 male OSA patients, with ≥10 4% dips in arterial oxygen saturation per hour. Patients were randomised to receive either active CPAP (n=33) or sham CPAP (n=26). Baseline drives on the DASS (road conditions and RT task as described above) were compared to post treatment drives after one month of treatment. In the baseline drive, the two groups did not differ in any of the driving measure outcomes of the steering simulator and were not significantly different in age, weight or BMI.

Post treatment drives showed a significant improvement in the therapeutic CPAP group in all driving measure outcomes including RT, steering deviation and the number of off-road events. They also reported significantly improved objective and subjective sleepiness. However the sham CPAP group also recorded significant improvements in subjective sleepiness (the ESS) and in the number of off-road events. To compare between the groups, the authors compared the change scores in the driving outcome measures by subtracting pre-treatment scores from post-treatment scores. All driving measures showed a greater magnitude of change in the therapeutic CPAP group. This was the first placebo-controlled parallel limb study to compare driving performance on OSA patients. It further supports the hypothesis that driving simulators can indeed separate driving performance between treated and untreated OSA patients, but highlights the important issue of placebo effects. The decrease in the number of off-road events as well as the subjective improvement in sleepiness shown in the sham CPAP treated patients in this study may limit the conclusions that can be drawn from the previous studies that have not included a control population.

Despite lacking a placebo controlled patient group, Risser et al (2000) used the Systems Technology, Inc. Driving simulator (STISIM) to assess differences in performance between 15 OSAHS patients (mean AHI 47/hour) and matched control subjects. This is a PC based, fully interactive driving simulator. Like the AusEd simulator it assesses steering deviation, speed control and the number of of-road crashes but contains no measure of reaction time. Unlike the AusEd set-up, subjects sit in a fully adjustable mini-van seat, and engine and tyre noises reflect the speed of the vehicle. The road layout was of a two-lane road with both bends and straight periods, with on-coming vehicles. Subjects were required to drive at 55mph for 60 minutes. OSAHS patients performed significantly more poorly than the controls in the aspects of steering variability, speed variability, number of crashes and lane position variability. Both groups showed a time-on-task decrement in lane position, but the slope of this was higher in the untreated patients. Further the OSAHS groups also showed a time-on-task performance decrement in the number of crash events, with the peak number of crashes occurring in the last ten minutes of the drive. Unlike the AusEd simulator, the simulator studied here demonstrates that a measure of speed can show significant differences in OSAHS and controls, however this study did not measure RT,

which is an important resource required while driving. The severity of patients in this study was similar to the current study, indicating that driving performance decrements do occur in groups with a moderate disease severity. The simulator was slightly more sophisticated than AusEd and also one should note that the driving task was longer in the STISIM study (60 minutes vs. 30 minutes) and the peak difference in crash events occurred in the last block of driving, a full 20 minutes after the AusEd drive at its assessed duration would have finished.

These studies illustrate the possibility of separating driving performance between treated and untreated OSAHS patients and community controls, at least in some aspects of driving. However, these studies generally did not enquire about real life driving accidents and near miss incidents. This is crucial in deciding if the simulator performance is indeed a reflection of real life driving. Although the AusEd driving simulator only discriminated untreated OSAHS patients and controls by RT, the lack of differences in real life driving (as measured by self-reported accident levels) were also not different between the two groups. However, as only RT (from visual search) showed decrements in performance, one cannot accurately determine whether the lack of differences in the other driving outcome measures were due to the fact that the OSAHS patients did not have global driving performance problems (i.e. all three areas driving of tracking, visual search and speed control).

To try and detect a relationship between simulated driving performance and real life MVAs, Turkington et al (2001) used a logistical regression technique on data obtained from a twenty-minute version of the DASS with subjective reports of driving ability and accident frequency from 150 OSAHS patients. The mean RDI of the group was 26.1, but 20% of the group had a RDI less than 15/hour. 25% reported having an accident in the past 3 years, 35% reported a near miss and 15% admitted falling asleep at the wheel. Using results from previous simulator studies Turkington et al defined poor performance as a tracking error >0.2, RT >2 seconds and 10 or more off-road events an hour. The median tracking error, RT and the number of off-road events in the sample were all higher than the defined impairment cut-offs the authors defined as a poor performance. Results indicated that factors not directly associated with both driving and OSAHS (age, gender, and alcohol intake) were better indicators of performance on

the driving simulator than driving-related variables. However, the number of near misses in the previous 3 years was associated with both poor tracking error and the number of off-road events. Further the number of off-road events predicted the reported number of accidents in the previous year, but the statistical method employed only correctly classified 10% of the population who had experienced an accident in the previous year. Both falling asleep at the wheel and the number of near-miss accidents were associated with the ESS. There were no other factors associated with poor driving performance. Although this study identified near miss accidents as predictor of tracking error, the results from this study highlight the issues with driving simulators as a method for screening OSAHS patients for driving ability, especially with a view to suspending patients' driving licences. Although the patients who performed well on the simulator were unlikely to have had an accident in the previous year, no relationship was found between those who performed poorly and previous accident rate. Further, no patients recording less than 10 off road events per hour reported an accident in the preceding year, while only 10% of those who had 10 or more drive off-road events reported any accidents in the previous year.

These results may have been partially due to the self-report methods for establishing previous accident rate and, as reported in section 2.10.2, PC based driving simulators which do not asses all three areas of driving (tracking, visual search and speed control) lack both face validity and an adequate measure of all areas of actual driving performance. Therefore the lack of associations between actual driving ability and simulated performance may also stem from the fact that not all facets of driving ability were measured in this simulator.

Other simulator tasks have shown differences in performance in only 20-30 minute trials. One may speculate that although AusEd was designed to be monotonous and was run in darkness to make it soporific. As it incorporates tracking, visual search and speed control tasks the simulator may be more stimulating, initially than the others, and as such a longer period of time may have been required to show a time-on-task decrement in driving performance. However, it must be noted that in the current study, time-on-task results for the patient group baseline drives (section 4.10) may suggest a learning effect. Although each group were given a 10 minute practice run before

commencing the 30 minute drive, steering and speed outcomes showed a change over the 30minute drive, with the first block of 7.5 minutes showing the highest level of deviation from test requirements. If a learning effect was present during the initial part of the main drive this may have inhibited a true effect of deterioration in driving performance from presenting during the 30-minute task. Therefore studies utilising simulators must ensure that practise periods are both long enough and cover all aspects of the driving task to ensure that learning effects are adequately controlled for, prior to the main drive.

Hack et al (2001) reported the steering deviation at the start of the drives were similar in both treated and untreated OSA patients, but worsened with time on the task in the untreated group, over three 30 minutes drives. The Swedish transport simulator is state of the art and is fully interactive, and Haraldsson reported that although patients were instructed to drive for 90 minutes several stopped driving after one hour due to sleepiness. Risser (2000) et al reported a time-on-task effect in their driving study with the greatest number of crashes occurring in the last 10-minute block. These results may indicate that if sleepiness is a causal factor in driving impairments one must provide a long enough period for it to manifest itself and as a consequence impair driving.

Despite the minor limitations of these studies, they consistently show differences in driving performances in untreated OSAHS patients from treated patients and controls, an association that the AusEd driving simulator was unable to replicate. The lack of differences in both tracking (which has been shown to be consistently poorer in untreated patients in the studies cited previously) and speed may be partly due to methodological issues with the study design. These include study power, patient selection, CPAP use, driving simulator malfunction and software faults.

Methodological issues with the AusEd driving study

Firstly the sample size of the study population was lower than we had sought. At study inception a sample of 60 patients (30 to each treatment) and 30 control subjects was anticipated to give a power of 0.8 at the 5% level. In fact we recruited only 45 patients

and 19 controls. Nevertheless studies on other simulators (Haraldsson 1990, George 1996a + 1997, Juniper 2000, Hack 2001, Turkington 2003,) have shown differences in OSAHS and control subjects' performance with numbers of participants similar to the current study, suggesting that the simulator may not have been as discriminating as other devices.

The low acceptance rate in the treatment effects trial may have been a product of the recruitment method. OSAHS patients were contacted and asked to participate in the study prior to their polysomnography investigation. Hence, they were being asked to participate before they were diagnosed with the condition. On telephoning patients to establish if they would be willing to participate, many communicated their hesitation in committing to taking two days of off work. This recruitment method was chosen to ensure that all daytime testing of patients was completed on the day after their polysomnography night. Despite heavily advertising for control subjects there was a low level of recruitment, and this may have been due to the time required to complete the study.

Other factors which may have contributed to the lack of major differences in our study, include the poor correlations between nighttime variables and daytime testing (Kingshott 1999b). Due to financial constraints and waiting time for polysomnographic investigations, it was not practical to ask patients already diagnosed to undergo a further PSG night. Hence, to limit the time participants would require to take of work, the follow-up investigation day was limited to one morning. This in itself may have limited the conclusions one can draw from the current study. Restriction to a morning's testing required dropping of the MWT and SteerClear. Both these instruments have shown improvement with CPAP (Findley et al 1989b, 1991 + 1999, Sangal 1992a, Engleman et al 1994a, Jenkinson et al 1999 + 2001, Kingshott et al 2000). Their use in this study would have helped to clarify by objective methods if the CPAP group had improved on both sleepiness and vigilance over the treatment month.

The treatment issued for this treatment effects study was either auto-titration CPAP or an oral placebo. The use of auto-titration CPAP has been show to be at least as effective as fixed-pressure CPAP (section 1.9.3.2), and previous studies have

employed an oral placebo for comparison with a mechanical treatment (Barnes 2002, Faccenda 2002, Engleman 1999).

Issues in the use of placebos in medical research have been raised (Karlawish and Pack 2001). It has been argued that placebo-controlled trials result in patients being denied active treatment. However, in the current study patients were started on the treatment limb between one and two months after their polysomnography study. At the start of the study the local waiting time for a CPAP titration appointment and CPAP unit issue after diagnosis was made was around 6-8 months. As patients would not be denied active treatment for prolonged periods of time, I felt justified in using a placebo. At study inception, concerns of safety and acceptability existed concerning sham CPAP (Kreiger et al 1983, Loredo et al 1999) and this coupled with the fact that the early use of CPAP predicts long term CPAP use (Mcardle 1999, Weaver 1997b) provided grounds for caution in using sham CPAP. Although it is essential to ensure treatment effects are the result of active treatment, the issues concerning sham and the long-term benefits patients can receive from CPAP an oral placebo was selected. As such, the oral placebo was actively sold to patients, with the approval of the local ethics committee, as a potential treatment for OSAHS. I believe this is the reason that subjective ESS was significantly improved in the placebo group, although it was not within the normal range (usually <10). Compliance in the oral placebo group was based on the number of capsules returned at the end of the treatment limb. Compliance expressed as the number of nights used divided by the total number of nights on the treatment limb was similar in both groups. A statistical trend towards higher nights of use of placebo was observed. The mean CPAP use was 76% of the nights issued, with an average usage of 4.2hours/night. Five people used CPAP for less than 50% of the days on treatment and 12 people used it for less than an average 4 hours per night. As the number of participants in the CPAP group was small, the small numbers of patients not using CPAP regularly or for at least four hours per night may have been a major reason that more of the subjective secondary outcomes were not significantly different between the CPAP treated patients and those on the placebo.

A longer period of treatment may have given patients more time to adjust to wearing CPAP and settle into a routine. Given the issues with delaying treatments for those

patients on placebo and the fact that other studies have shown significant improvements in both subjective and objective outcomes after a similar period of time (Engleman 1999, Jenkinson 1999, Stradling 2000, Montserrat 2001), one month of treatment seemed justifiable. Turkington et al (2004) reported significant improvements in performance (including steering error, reaction time and the number of off-road events) on a 20-minute DASS trial in 18 OSAHS patients after only 7 days of treatment compared to 18 OSAHS patients who were not treated. The CPAP treated patients then stopped using CPAP for one week. The significant differences in driving performance were still evident in these areas between the two groups at 7 days, although the magnitude of the differences were lower than had been found while using CPAP. Although the control group were not given a placebo treatment it does suggest that driving performance can improve quickly with CPAP. Subjective improvements in the Stanford Sleepiness Scale (SSS) also showed significant improvement in the CPAP treated group compared to the controls, and this unlike DASS performance deteriorated quickly with the removal of CPAP. Although, this serves to suggest the insensitivity of the AusEd simulator, one should note that the DASS-tested patients were all clinically severe (>50 apnoeas/hypopnoeas per hour) and used CPAP on average for 4.9hrs/night.

Most patients in the current study could be considered to have moderate OSAHS, but 15% of the patient group had an AHI less than 15. Although previous studies have indicated that mild OSAHS patients experience subjective improvements with CPAP (Engleman 1999) others have reported that increased MVA rate in untreated OSAHS patients may be highest in severe cases (Findely 1989a, Adrich 1989, Cassel 1990). Therefore the moderate disease severity may have reduced the possibility of the patient sample having driving impairment. Conversely, although the control subjects were vigorously screened (both by questionnaire and a telephone interview) for lack of snoring and sleepiness before participating in the case control study, no objective monitoring, to detect OSAHS and no objective measure of sleepiness were undertaken. Although unlikely, it is not possible to exclude entirely the possibility that some of the control group may have had OSAHS. Further the baseline characteristics of the control group (lower mean BMI, mean higher IQ, mean lower weight, higher education level) would have served to discriminate the controls from the patients. It should also be

noted that the level of subjective sleepiness inclusion criteria was different between the patient and control groups. An ESS of 8 or greater was used as inclusion criteria for the patient groups however controls were accepted with an ESS of up to 11. This overlap of ESS between the 2 groups served to increase the possible numbers of participants. As no objective measures were used to assess the presence of OSAHS in the control group ESS was used in this group as a possible indication of OSAHS symptomology. Within the Department an ESS of 11 or over is classed as pathological sleepiness and therefore this was the level was used as the cut-off for subjective sleepiness. However an ESS of 8 was used with the patient group to inhibit the exclusion of patients who may not have recognised their level of sleepiness. Further although sleepiness most likely plays a large part in MVAs in the OSAHS population, one did not wish to exclude patients solely on ESS, as a lack of subjective sleepiness does not necessarily exclude these patients from the risk of MVAs.

However if these discrepancies had effects on the simulator performance, one might presume this would, overall, increase the performance differences between the two groups with the control group performing better. It is unfortunate that the control group were not tested on the SteerClear task, this could have provided further indication if the patients and control group were similar in their performances. This may have helped clarify if the AusEd simulator was not sensitive enough to discriminate differences in performance. Further, although the performance of the placebo treated patients did not change significantly over the one-month period suggesting that the AusEd does have a level of test-retest reliability, the reproducibility was not tested in the control group who would have been free from possible placebo/nocebo effects. Therefore it is not possible to conclude that the lack of performance differences between the three groups was due to real measures of actual performance as opposed to poor reproducibility of the simulated tasks.

Several factors built into the AusEd driving simulator may have reduced the sensitivity of the program. A problem concerning the recording of RT was noted on several drives. On each drive 10 trucks were requested to appear, but on occasions the simulator did not record one or more of the actual reaction times. This may have been due to a software 'bug' in the original base programming, but due to copyright restrictions, our in-

house programmer was unable to have access to this part of the program to investigate or repair this. We have speculated this could have been a consequence of the program only recording a RT when the brake was depressed by 90%, when it was therefore possible to reduce speed without recording a reaction, and as such several people 'tailgated' the truck (despite strict and clear instructions to stop immediately when a truck appeared). As this was both a validation study and an intention to treat study no data were filtered or removed. A second 'bug', also on occasion, caused 'time-outs' in which the computer would close down the driving simulator program. This occurred several time during the practise runs but only once during the 30-minute drive. To limit this problem, the PC the AusEd program was run on was used only for the AusEd and SteerClear programs, and was only switched on immediately prior to the running of the tasks, which appeared to help. Further, the AusEd output program only measured driving-off road events when the periphery of the outside lanes was crossed, and therefore any drifting across to the on-coming lane was not recorded. These incidents could prove fatal in real life, and information on these events, if they occurred, may have shown differences between the patients and control groups. It was extremely unsatisfactory that we were unable to access and improve the software for the device which we had jointly designed. This had a major deleterious effect on this study.

The outcome measures of the simulator were recorded as means and no standard deviations were recorded for steering and speed performances, as has been incorporated in some other simulators. As the outcome data for the steering and speed deviations for each individual drive were reported as a mean value, it did not make sense to report the group outcomes as a median value.

Although the data were non-parametrically distributed, a repeated measure MANOVA was used to assess treatment effects between the patients groups. If non-parametric statistics had been used, due the number of comparisons being made, a correction for multiple comparisons would have been required. Hence the loss of power in the parametric test would be similar to that of the multiple comparisons with correction and I felt justified in using the parametric tests. I do not believe the choice of statistical tests used produced a type two statistical error. MANOVA analysis has been commonly used

in psychological performance research, so this was not a methodology avoided by others.

OSAHS and professional drivers

OSAHS patients who were professional drivers were excluded from this study, due to the nature of the placebo and the ethics of withholding treatment. However, one should not forget this population. Previous reports on this population have shown high prevalence of snoring and SDB in bus drivers (Hui 2002) and in a self report survey Engleman (2005) reported weak correlations between ESS and work related accidents in Scottish bus drivers. Truck drivers with SDB were twice as likely to be involved in an MVA than those without OSAHS (Stoohs 1994). This population may be at increased risk to OSAHS due to the sedentary lifestyle associated with professional driving, as BMI and obesity are risk factors in OSAHS.

6.4 Conclusion

In summary, the AusEd driving simulator did not produce outcome measures congruent with other driving simulators assessing performance in an OSAHS patient population. Reasons that the simulator may have failed to find a difference between treated and untreated patients and also controls have been discussed above. The AusEd driving simulator was designed as need for a clinical tool to assess driving was required and previous simulators did not appear to measure all areas of driving (section 2.10.2). As such, further research is much needed to find a tool that can assist in discriminating OSAHS patients who may be at increased risk of MVAs.

Several issues regarding driving simulators as a method to assess driving performance exist. Despite most published simulator studies showing that driving performance is poorer in untreated compared to treated OSAHS patients and controls, there is still the issue of poor correlations between simulator outcomes and real world driving. Before any type of simulator can be used as a discriminative and valid guide to suspend driving in sub-populations, a clear and justifiable correlation between real world driving and

simulated driving must be shown. Although limited evidence exists that simulated performance predicts past actual MVA rate (Turkington et al 2004, Findley et al 2000), further research is essential before driving simulators can be used in day-to-day clinical settings. Further, although simulator studies have shown an improvement in driving performance after CPAP, the outcome measures for treated OSAHS on the majority of simulators do not return to the same levels as controls, which raises the issue as to what level of impairment is actually clinically relevant. Some authors have suggested cut-off levels of impairments (Turkington et al 2001) on steering deviations, RT and number of drive off- the road events, based on results from control populations and treated CPAP patients. For example a steering deviation of 2cm or over and more than 10 off-roads an hour has been suggested as equating to poor performance. However one might argue that any off-road events are 'pathological' as this should not occur with any real regularity in real life driving.

A second issue would concern which areas of driving would require to be 'pathological' before driving is suspended. In any given individual, if steering deviation was regarded to be higher than normal but all other outcomes were not, would one be considered dangerous to drive? Further, if a patient was considered to be impaired in their driving abilities but had never previously been involved in an MVA, would one be justified in suspending their licence? Although, the fact that an event has not happened previously does not inhibit one from happening in the future, any method of limiting person actions should be based on strong evidence to support this. At this time strong evidence does exist that as a population OSAHS patients are at a higher risk of being involved in an MVA. However, most driving simulator studies as well as studies investigating numbers of actual MVAs in OSAHS samples report large degrees of variability within this population. Further, as poor correlations exist between the indicators of disease severity, simulated driving performance and accidents rates, one cannot report that it is only severe OSAHS patients who are at increased risk. At this time our level of understanding as to why sub-populations of OSAHS have higher number of MVAs is poor, but this is coupled with limited evidence to support the fact that simulated driving performance is an actual reflection of real life driving. As such driving simulator research in the OSAHS population has not developed to a point where these instruments would be reliable tools to assess fitness to drive.

OSAHS patients appear to be at an increased risk of MVAs. Hence further extensive research should be under taken to assess if a PC based simulator such as the AusEd can discriminate driving performance using the tracking, visual search and speed outcome measures. This safe, economic and portable, potential method for screening drivers and in turn reducing the number of potential accidents and fatalities as a consequence of OSAHS, would be desirable

However, on the basis of the data presented in this thesis, the AusEd simulator as available to us is not the ideal device to use in further studies, unfortunately.

Chapter 7: Secondary Methods of Analysis from the AusEd Driving Study

7.1 Introduction

Motor vehicle accidents (MVAs) associated with sleepiness or falling asleep at the wheel may be implicated in up to 16-23% of accidents involving the general driving population. As previously reviewed, research concerning MVA rates in OSAHS patients has also indicated that this population may be at increased risk, with estimates ranging from 2-7 times that of healthy matched controls (George et al 1987, Young 1995, Findley et al 1988).

Brown (1994) defined fatigue (which is often used interchangeably with sleepiness) as a subjective experience of diminished inclination to continue performing the current task. During driving this may manifest itself as an increasing need for sleep that is often described as a feeling of sleepiness. Sleepiness may reduce mental alertness which in turn increases the likelihood of an MVA by reducing one's attention available to the driving task, by slowing responses to external stimuli (i.e. other road traffic) or as a result of falling asleep at the wheel.

However, investigating the cause of accidents after the fact may be unreliable, especially in sleep-related accidents. Bonnet and Moore (1982) concluded that healthy adults who fell asleep unexpectedly tend to deny having fallen asleep if the sleep period is less than two minutes. This may be coupled with the evidence that although drivers (free from sleep disorders) are aware of their level of sleepiness during driving, they may underestimate their likelihood of actually falling asleep. When subsequently asked about levels of sleepiness, they have a poor recollection of it (Reyner and Horne 1998a, Horne and Reyner 2004). Hence, drivers may not attribute any accidents to feeling sleepy or actual sleep periods.

Therefore research investigations into sleepiness and sleep periods, as precursors to accidents may be best suited to prospective studies. One method of measuring driving performance is to monitor vehicular events such as crashes, near misses, and lane

drifting and speed deviations. The frequency of these events may establish that sleep deprived or OSAHS individual may have greater numbers of these events, but will not necessarily establish their cause. Therefore, such a metric may be complimented by investigating a further aspect of performance, for example physiological measures, i.e., analysis of EEG, heart rate variability and eye activity measures, or behavioural measures i.e., verbal reports of subjective sleepiness. In addition it is not clear whether the increased rates of accidents in sleepy drivers relates to falling asleep or to delayed responses when awake. Recording of EEG during driving simulation may help clarify this.

Electroencephalograms record the electrical activity of the brain and although any one frequency of activity may be dominant (i.e. theta whilst in stage two of sleep) other frequencies are also present albeit at very small thresholds. Recordings of electroencephalograms (EEG) during driving can be used to assess whether periods of sleep (for example, 15 seconds or more of any sleep stage in a 30 second epoch as defined by R&K (1968)) or micro-sleeps (defined as an intrusion of alpha or theta for greater than 3 seconds) are occurring. Fast Fourier transformation (FFT) can also be applied to the EEG trace. This is a method for dividing biological signals into its constituent parts. FFT analysis gives one the absolute power or spectral density power of each frequency band. Time changes in these bands can be used to speculate on changes in cortical arousal, for example increases in delta and theta spectral density power could indicate increased levels of sleepiness and in turn a reduction in vigilance.

Mitler et al (1997) conducted physiological sleepiness monitoring, including EEG recordings during real world driving on a group of 80 male long-haul truck drivers, who were monitored as they performed evening/night shifts for work. Two of these drivers were polysomnographically diagnosed with OSAHS. In addition, the authors found that as a group these drivers were sleep deprived, and that their actual hours of sleep were lower than their subjective reports of ideal hours of sleep. On analysis of concurrent EEG monitoring obtained during driving, two drivers (not those diagnosed with OSAHS) exhibited seven episodes of stage 1 sleep during evening and early morning driving, with one episode of stage 1 sleep lasting for 80 seconds. Further behavioural signals obtained from video recordings of the drivers faces, were sampled every 30

minutes (in six minute blocks) and of 29,310 video segments. 7% of these showed the driver to be drowsy, determined by drooping eyelids and a bobbing head.

During this study none of the drivers were involved in any accidents, suggesting that sleepiness and sleep periods do not always result in MVAs. However the end result of sleepiness is often sleep and it is not ethical to sleep deprive or withhold treatment of OSAHS to determine if drivers will eventually show EEG changes prior to driving incidents. Therefore, several studies have been conducted more safely on driving simulators and vigilance tasks to assess changes in EEG and performance.

Kingshott and Douglas (1999a) recorded concurrent EEG whilst participants underwent the sustained vigilance task SteerClear. They reported that only 3 of a possible 71 OSAHS patients and none of the 9 normal controls had microsleeps (theta for >3 seconds). This is congruent with results of Mitler, however, SteerClear does not realistically assess driving performance and due to the nature of the SteerClear task it would not necessarily be possible to relate these microsleeps to actual events. Risser et al (2000) recorded driving performance (lane drifting, speed variability, steering rate and crash frequency) on a driving simulator in a 60-minute drive with concurrent EEG recordings in 15 OSAHS and 15 control patients. Overall lane position showed more variability in the OSAHS patients than controls and the OSAHS patients experienced more crashes. Both these measures of driving-based performance showed deterioration over time in the patient group. Steering rate and speed variability were also significantly different between the two groups although these did not worsen with time. Overall the OSAHS group had greater number and longer durations of EEG defined microsleeps (alpha or theta >3seconds) and both of these EEG measures showed a time-on-task effect for the patient group. Strong correlations were found between EEG measures and lane position and crash rate, further supporting the hypothesis that as sleepiness increases measures of driving performance deteriorate.

Kinnari et al (2000) conducted a simple visual reaction time task in 21 male patients with moderate OSAHS, who underwent concurrent EEG recordings during the task. The 90-minute EEG recordings were divided into segments of 0.5-2seconds using an automated computer program and these segments were classified (initially by a

validated computer program and then checked manually) as one of seven stages, including; alert eyes open; alert with alpha; sleep stage one and sleep stage two. The authors report that duration of the reaction time was linearly correlated with the vigilance state and that RT increased as alertness deteriorated. However they also reported that the presence of slow eye movements was more consistently related to changes in performance than changes of the EEG.

Therefore, if driving performance can also be affected by sleepiness as opposed to actual sleeping at the wheel, overt changes in EEG i.e. microsleeps may not always be seen. Researchers from the Sleep Research Centre in Loughbourgh University (UK), have undertaken a variety of studies investigating driving performance in healthy young drivers in sleep deprived states to investigate drivers' awareness of sleepiness (Horne and Baulk 2004), and a range of possible sleepiness reducing (Horne et al 1996, Reyner and Horne 1998b, Reyner and Horne 2002) and enhancing measures (Reyner and Horne 2000, Baulk et al 2001, Horne et al 2003). Within these experimental protocols utilising a real-world driving simulator, subjects undergo a thirty-minute practise run before commencing a two-hour drive. During these studies concurrent EEG recordings were produced. Instead of manually scoring these EEG traces for the intrusion of alpha or theta frequencies, these EEG recordings are subject to Fast Fourier transformation (FFT), a process that can transform a single biological signal into its component parts, and give the absolute power/spectral density power for a frequency range. The Loughbourgh University team used the standardised values from the frequency band of 4-11 Hz (theta + alpha) and averaged this band over every one-minute period during the total two-hour drive. To standardise these frequencies, they used the difference of each minute epoch from the average power from the thirty-minute baseline value and then divided by the standard deviation of the baseline power. Using concurrent video footage of driver and road, sleep related driving incidents and incidents caused by other factors, are distinguished using signals of sleepiness (eye rolling, staring or eyes closed).

This research team have shown that in sleep deprived young adults, time-on-task increases in sleepiness occur, both through verbalisation of sleepiness (using the Karolinska sleepiness scale) (Reyner and Horne 1998b, Horne et al 2003) and with

increases in the standardised FFT alpha/theta power (Reyner and Horne 1998b, Horne et al 2003). These are often associated with a time-on-task decrement in sleep-related incidents as recorded by the driving simulator (Reyner and Horne 1998b, Horne et al 2003). These findings are consistent with those of Kecklund and Åkerstedt (1993) who found positive correlations between subjective reports of sleepiness (reported hourly) and EEG alpha plus theta power increases in nighttime long distance truck drivers.

However Horne and Baulk (2004) have also reported that after a normal night of sleep there is still a time-on-task decrement in sleep-related driving incidents, but is not accompanied by the same time-on-task decrement in the standardised FFT alpha/theta power.

Lal and Craig (2002) recorded EEG from 19 bipolar channels on 35 healthy but sleep deprived participants during a simulated driving task. Participants had a 10-15 minute baseline drive and then a further drive lasting for up to two hours. The EEG was first classified as one of four stages depending on the presence or absence of alpha, and theta. The authors described the cycle through these phases as a cycle of micro-sleep to arousal. The first full cycle of each of these phases and the baseline EEG of the 19 channels was subject to FFT. The EEG was defined into four frequencies; delta (2-4hz), theta (4-8Hz), alpha (8-13Hz) and beta (13-20Hz). The power for each frequency was an average of each band over the 19 channels and was averaged over 30s. Each frequency band (delta, theta, alpha and beta) showed increases in mean power from the baseline EEG during the transition to fatigue. Delta and theta showed greater changes in magnitude (22 and 26% respectively) than the alpha and beta bands (9% and 5%). This study demonstrates that changes in the EEG can be seen during driving and that these changes are accompanied with individual increases in each of the component frequencies of the EEG, with delta and theta showing the largest increases. However although the authors comment that increased levels of fatigue were accompanied by increasing numbers of participants having "driving related errors and accidents," they do not report if these changes in driving performance were significantly different from that of baseline or throughout the drive.

These previous studies suggest that definite time-on-task increases in EEG power (especially alpha and theta) occur in relation to sleep debt in non-sleep disordered participants. However conventional sleep scoring is done in 20-30 second epochs, with intrusions of alpha and theta usually requiring 3 or more seconds to be scored as micro-sleeps. Further, there is a low level of correlation found between micro-sleep intrusion and performance vigilance tests (Kingshott 1998a). It is still not clear if driving accidents are a direct consequence of changes in the EEG (i.e. increases in power of EEG bands) immediately before an incident, or as a result of the increasing demand of sleepiness seen over time. For these reasons the concurrent EEG recorded during the AusEd driving task was subject to Fast Fourier transformation (FFT) to allow smaller blocks of time to be analysed and investigated to see if changes in EEG spectra occur with driving incidents.

Therefore the hypothesis that changes in the EEG power would occur immediately prior to driving incidents was evaluated using small time blocks of EEG recorded prior to all driving incidents on the AusEd driving simulator and compared to a ten second period of EEG not associated with driving incidents. Crashes and driving off the road incidents are seen as exemplars of complete loss of control during the driving task (whether recorded by controls or patients either before or after treatment), and as such all the EEG prior to all driving events were to be analysed to investigate changes.

A second physiological measure, that of eye movements, has also been linked to increasing sleepiness. In a review of blink rate as a measure of fatigue, Stern (1994) reports that blink rate among other measures, (including blink duration and blink amplitude) appears to increase with time-on-task over several conditions. These include reading, vigilance tasks and performing on driving simulators. However reports of blink rates vary, Horne and Reyner (1996) found no differences in the blink rate from the first to second hour of their driving task, despite increases in both subjective and objective sleepiness. However, Hakkenan et al (1999) investigated blink duration as an indicator of sleepiness in 20 bus drivers, ten with mild to moderate OSAHS and ten non sleep-disordered, matched controls. Eye blinks were recorded using in-car cameras, and scored frame by frame with a resolution of 400ms. They compared the sleep latency on the MWT; blink duration, maintenance of speed and lane drifting in the two

groups. After the OSAHS group underwent an average nine weeks of CPAP treatment, all underwent the same driving task again. At baseline the OSAHS group had higher mean blink duration and a shorter sleep latency score than the matched controls, but they noted no differences between the two groups on blink frequency. Both blink duration and MWT sleep onset latency were not significantly different to matched controls after an average nine weeks of treatment, suggesting that some measures of eye movement may be sensitive to sleepiness. However, there were no differences between the two groups at either time period for speed maintenance or lane drifting (as determined by an in-car automatic inspector).

Increases in blink rate may be affected by factors other than the levels of sleepiness. Stern and Skelly (1984) highlight the issue that blink rate may be affected by task difficulty. In their study Stern and Skelly (1984) compared blink rates of pilots and co-pilots in a flight simulator. They reported that pilots show an increase in blink rate compared to the co-pilot and this difference in rate is held when the co-pilot takes flight control. However, a study by Richter et al (1998) suggests the opposite. In their study analysing psychophysiological variables during rural driving, they report blink rate significantly reduces in proportion to the change in curvature of the road. In other words that as task difficulty increases (controlling speed and lane position through a chicane), blink rate reduces.

However, few studies have investigated blink rate as a function of time-on-task in a standardised driving procedure in a sleep disordered population. Hakkenan et al (1999) used real world driving, and so were unable to control for traffic exposure and weather conditions etc. To investigate whether it is possible to detect a relationship between sleepiness and blink rate in OSAHS patients compared to controls during a driving task, EOG recording was to be analysed and compared for time-on-task effects between patients and controls.

This chapter will investigate changes in EEG and blink rate in OSAHS patients and matched controls undergoing a 30-minute simulated driving task.

7.2 Study Population

Of the forty-five OSAHS patients and 19 control subjects who participated in the AusEd driving simulator study, 61(19 controls) participants underwent concurrent electroencephalographic (EEG) and electro-oculographic (EOG) recordings whilst "driving" and these EEG and EOG data were analysed for this component of the thesis. Of these 53 were male and 8 were female, demographic and anthropometric data is reported in section 4.5 and 5.5.

7.3 Acquisition of the Electroencephalograph (EEG) Recordings

Each of the OSAHS patients underwent two simulated drives one before treatment of OSAHS and again after one month on treatment, while the control subjects completed one simulated drive. Each simulated drive lasted 30 minutes and EEG recordings were produced for the same length of time.

Electrode placement was as previously described in section 3.1. A total of 102 EEG tracings lasting 30 minutes were obtained. Due to problems with the sleep recording equipment, one patient had no concurrent EEG for both his pre- and post-treatment drives and a second patient did not have EEG recordings on his post treatment drive. During four simulated driving performances the EEG signal was lost. This occurred in one patient both in his pre and post treatment drive and twice in two other patients' post treatment drive. To determine the cause of the signal degeneration I would have had to enter the room and this disruption may have acted as a stimulus to the drivers, thereby distorting the driving simulator results. Thus the EEG electrodes were not replaced and EEG signals are unavailable for analysis. On inspection after the simulated drive two of these signal losses were due to the EEG wires having been dislodged from the recording device, one was an error in the recording device and the last was due to the patient scratching at the EEG electrode and damaging the wire.

7.3.1 EEG – Periods of Analysis

Periods of Analysis

To investigate if EEG frequency distribution changes occur prior to driving events, i.e. crashes; periods of EEG preceding the following events were recorded;
Stop Crash
Off road crash
Truck Crash
Driving-off-road – crossing lane boundary to roadside verge

Changes in EEG occurring prior to the three types of crash events (n=95) were analysed in one batch and changes in the driving-off-road events (n=74) were analysed separately.

For each of the crash and driving-off-road events recorded, a ten-second-time block of EEG starting 20 seconds before the event and a two-second-time block of EEG immediately before the event were batched.
Each of these EEG blocks corresponding to events were compared to a ten-second time block of EEG, designated a baseline EEG period (see section 3.9.1). This was taken from the period 601 to 620 seconds of the driving simulation and corresponds to the first twenty seconds of the second block of straight road surface. This period was used to allow within-subject comparison of a block of EEG free from overlap from driving events and RT activities.

Using two separate periods of EEG preceding off roads and crashes allowed comparison to each other and the random time to try to determine if any EEG slowing is evident up to twenty seconds before an event.

Fast Fourier Transformation (FFT) of the EEG

Each 30-minute EEG trace was recorded on the Compumedics system version 5.2; saved in European data format files (EDF files). These raw files were then analysed

using an FFT program (see section 3.9.2 for details). To limit the effect of blinks and muscle artefact on the EEG, frequencies of lower than 4.9Hz and greater than 16Hz were excluded by band pass filters. The FFT program provided power spectral density values in microwatts/Hz (μW/Hz) for the three spectral bands on a second by second basis. The three frequency bands used were;

High theta 5-7.9Hz (light sleep)
Alpha 8-11.9Hz (feeling drowsy with eyes closed)
Sigma 12-16Hz (awake)

These data were stored as excel files and the appropriate blocks of EEG, i.e. ten second or two second blocks were transferred to the SPSS package and mean values were obtained giving the mean absolute value per EEG frequency band.

No between-subjects analysis was performed. The three time points (baseline EEG, ten-second time block of EEG before an event and two-second time block of EEG before an event) were analysed on a within-subjects basis. This meant the EEG data was 'self-calibrating' and required no standardisation of the EEG data.
On occasion EEG signals were temporarily lost due to excessive movement of the wires (participants moving or scratching at wires) or muscle activity. Although the EEG signals were subject to band pass filtering, each EEG block (either two or ten seconds) to be used for analysis was checked by eye to ensure signal clarity.
Overall there were 169 driving events, of which 74 were classed as driving-off-road events and 95 were classed as crashes. Of these only one, ten-second time block of EEG before a driving-off-road event was unable to be analysed due to movement artefact. Three of the remaining 168 ten second blocks corresponding to a driving event consisted of only 8 seconds of mean standardised data, and again this was due to brief loss of signal.

Table7.1; Progression chart for EEG periods of analysis

	Task performed
Step 1	AusEd driving simulator outputs – obtain driving events
Step 2	Note time (in seconds) for each event to be analysed
Step 3	Manually check EEG traces to detect loss of signal
Step 4	Note any time periods unable to analyse
Step 5	Transfer EEG traces to EDF format
Step 6	Perform FFT analysis on the raw data –provides absolute power for frequency bands
Step 7	Transfer appropriate period to SPSS and compute the mean and SD for each time period.

7.4 Acquisition of Blink data

In addition to the EEG recordings, electro-oculograms (EOG) were also recorded for each patient and control subject for each of their 30-minute 'drives'. Electrode placement was as previously described in section 3.1.

A total of 105 EOG recordings were obtained. EOG recordings were not possible for one patient in both his pre and post-treatment drive due to problems with the neurophysiological recording equipment, and a further two post-treatment drives were unavailable due to loss of signal. The simulated drive was not interrupted to investigate the cause of the loss of signal.
Further EOG recordings were obtained for 34 of the 45 patients on the vigilance task SteerClear, performed by all patients pre-treatment. Due to technical problems, concurrent EOG was unable to be recorded in 11 patients. Control subjects did not undergo the SteerClear vigilance task.

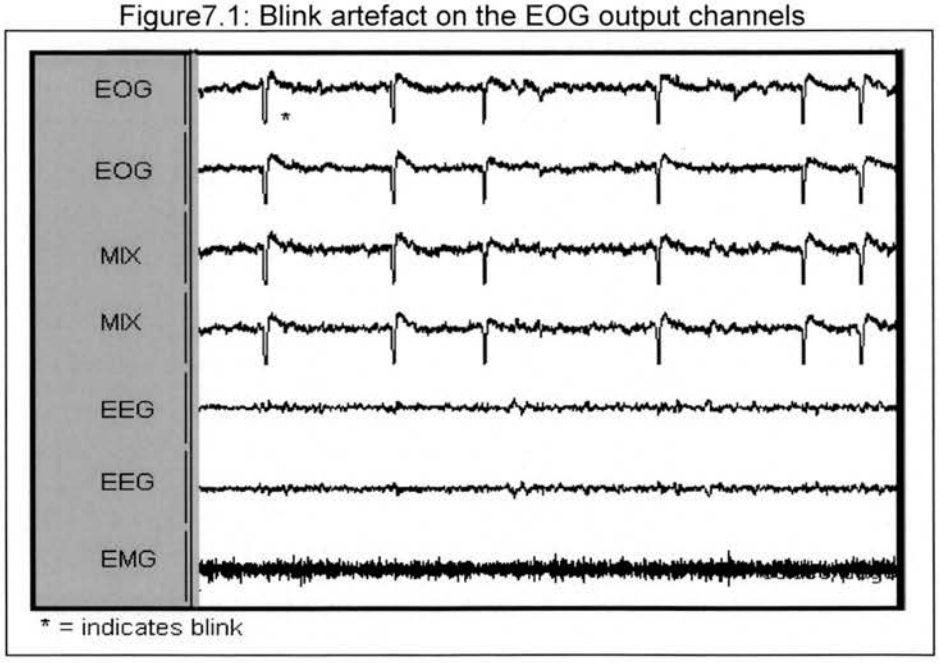
7.4.1 Scoring blinks

The computerised polysomnography system provides real time outputs for both EEG and EOG recordings. Blinks were manually scored from the EOG channel output.
Figure 7.1 shows a typical EOG trace with blink artefact. An in-house scoring criterion was established with blinks only being scored if they appeared on both EOG channels. Figure 7.1 demonstrates the blink artefact on the mix channels (corresponding to Cz/Pf1 and Cz/Pf2), however these channels were not used for the scoring of blinks.

Each 30-minute drive was scored for the presence of blinks using a 30-second epoch window. The system allows for creation of scoring user defined events and this was used with blinks being manually highlighted on the polysomnographic recording system. An automated analysis program from the Series S Compumedics system was modified to analyse the total number of blinks scored. Outputs reported the total of blinks per study as well as the number of blinks per minute and per 30 second (1 epoch). This data was available only on hard copy printed directly from the analysis program and was manually inputted to the SPSS database. To ensure accuracy the data was inputted twice one day apart and compared, any record showing differences were deleted and the procedure was started over.

The SPSS system was used to compute the number of blinks in each quarter (7.5 minutes) of the simulated drive or vigilance task.

Figure7.1: Blink artefact on the EOG output channels



7.5 Statistics

7.5 1 EEG Data

Continuous data were analysed using two-tailed non-parametric Wilcoxin signed-rank test.

7.5.2 Blink Data

Within-subject comparisons for continuous data for time-on-task analysis were analysed using the non-parametric Friedman test and between-subjects comparisons were conducted with Mann-Whitney U non-parametric tests.

All tests were run on the PC statistical package SPSS (SPSS for windows, Version 12, 2003, SPSS, Chicago, IL, USA).

7.6 Results

7.6.1 EEG results

Crash events

Within subjects comparisons of the EEG frequency bands corresponding to crash and driving-off-road events showed significant statistical differences between the baseline EEG and the ten-second time block of EEG and two-second time block of EEG before the event. Tables 7.2 and 7.3 show the mean and standard deviation of the spectral density power in microwatts/hertz (μW/Hz) and significance levels for the three EEG spectral bands.

Table 7.2 Changes in spectral density power of the EEG bands in crash events (n= 95)

EEG band	Event A Ten-sec time block of baseline time Mean + SD	Event B Ten-sec time block of EEG before crash Mean + SD	Event C Two-sec time block of EEG before crash Mean + SD	A vs B p level ¶	A vs C p level ¶	B vs C p level ¶
Sigma μW/Hz	0.255 0.161	0.292 0.210	0.394 0.654	0.1	0.04	0.2
Alpha μW/Hz	0.565 0.508	0.690 0.653	0.950 0.217	0.5	0.006	0.2
Theta μW/Hz	0.570 0.457	0.812 0.851	1.829 0.863	0.006	0.003	0.02

¶ *correction applied*

Baseline EEG and the ten-second time block of EEG before an event

There was no significant change in the mean spectral density power of the sigma and alpha bands, however there was a significant increase in the mean spectral density power of the theta frequency band between these two time periods.

Baseline EEG and the two-second time block of EEG before an event

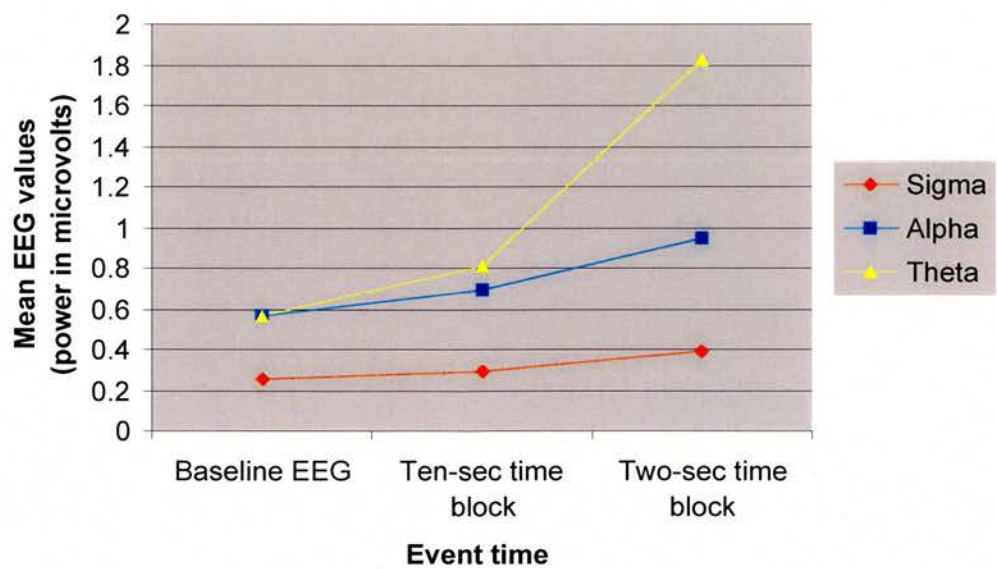
There were significant changes in all three of the EEG bands between these two time periods, with all three bands showing increased mean spectral density power from baseline.

Ten-second and two-second blocks of EEG before an event

There was no further significant increase in the sigma and alpha bands between the ten-second and two-second time blocks of EEG before an event. However the theta band showed further significant increases in the mean spectral density power.

Figure 7.2 shows the changes in the three spectral bands across time.

Figure 7.2; Changes in mean spectral density power of power of sigma, theta and alpha for crash events



Driving-off-road events

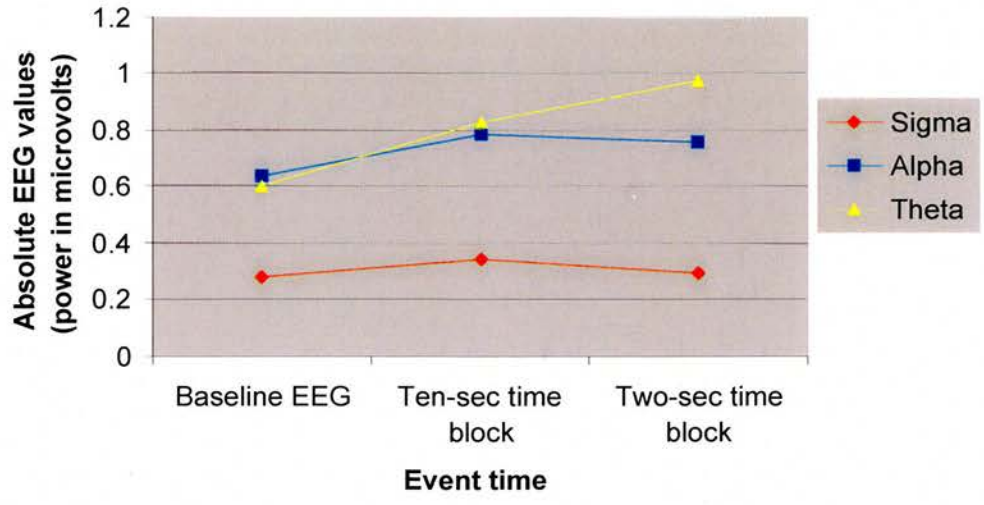
Seventy-four events were classed as driving-off-the road not leading to a crash. In these events the subject continued to drive on the roadside before returning to the road. Table 7.3 shows the means and significance levels of baseline and at 10 and two seconds before driving off road. Figure 7.3 shows the changes in the mean absolute power of the three bands.

Table 7.3: Changes in spectral density power of the EEG bands in driving-off-road events not leading to a crash (n=74)

EEG band	Event A Ten-sec time block of baseline time Mean + SD	Event B Ten-sec time block of EEG before off-road event Mean + SD	Event C Two-sec time block of EEG before off-road event Mean + SD	A vs B p level ¶	A vs C p level ¶	B vs C p level ¶
Sigma _W/Hz	0.281 0.154	0.347 0.198	0.293 0.210	0.006	0.7	0.001
Alpha _W/Hz	0.636 0.836	0.787 0.709	0.760 0.725	0.04	0.1	0.3
Theta _W/Hz	0.602 0.435	0.826 0.641	0.973 0.162	0.003	0.05	0.5

¶ *Bonferroni correction applied*

Figure 7.3; Changes in mean spectral density power of the sigma, alpha and theta bands for driving-off-road events



Baseline EEG and the ten-second time block of EEG before an event

There were significant increases in the mean spectral density power value of all three EEG spectral bands between the baseline and the ten-second time block before going off-road.

Baseline EEG and the two-second time block of EEG before an event

Unlike the crash events the only significant increase in mean spectral density power in the two-second block before the event was found in the theta EEG band, with no significant changes being noted in the mean spectral density power of the sigma and alpha EEG bands.

Ten-second and two-second time blocks of EEG before an event

Again these events showed a different pattern of change than the crash events. The only band to show a significant change in mean spectral density power was the sigma EEG band and this showed a reduction in the mean power from the ten-second time block to the two-second time block.

7.6.2 Eye-blink analysis results

Eye-blink rate comparisons have been made between the three groups using four 7.5 minute time periods. Splitting the 30-minute drive into these four quarters was performed due to the set-up of the AusEd driving simulator, wherein road type alters from two minutes of chicane road to five minutes of straight road. As there has been previous evidence to suggest blink rate differs on straight and chicane roads, the 30-minute drive was split into four quarters each of 7.5 minutes. Each 7.5-minute quarter contains five minutes of straight road and 2.5 minutes of chicane road.

To investigate possible sleepiness related effects on eye-blink rate, comparisons of eye-blink rate were made between the OSAHS patients before commencing treatment (n=44) with both the CPAP treated OSAHS patients (n=24) after one month of treatment and the control group (n=19).

As can be seen from table 7.4 there were no significant differences between the three groups after comparing the mean number of eye-blinks in each time quarter. However as the standard deviations suggest, there were very large differences in individual eye blink rate seen across participants.

Table 7.4; Mean eye blinks per quarter between patients and controls.

	Group A Patients (pre treatment) n= 44 Mean (SD)	Group B CPAP patients post treatment n=24 Mean (SD)	Group C Controls n=19 Mean (SD)	A v B p level	A v C p level	B v C p level
1st Quarter	88.6 (64.9)	114.8 (77.8)	110.8 (101.7)	>0.1	>0.3	>0.6
2nd Quarter	101.9 (68.5)	121.6 (66.5)	125.1 (110.5)	>0.2	>0.3	>0.6
3rd Quarter	109.8 (64.6)	128.6 (67.4)	134.8 (122.6)	>0.2	>0.4	>0.5
4th Quarter	127.6 (73.2)	144.3 (72.4)	143.1 (126.9)	>0.3	>0.6	>0.7
Total	427.9 (263.5)	509.3 (267.6)	513.7 (454.9)	>0.1	>0.5	>0.6

To investigate if blink rate changes across time, eye-blink rate across the four quarters were also analysed by a Friedman test. There were significant changes in blink rate found in all three groups by time-on-task (see table 7.5). These changes are highlighted in graph 7.4.

Table 7.5; Within-subjects comparison of blinks per quarter for patients and controls

	1st Quarter Mean and SD	2nd Quarter Mean and SD	3rd Quarter Mean and SD	4th Quarter Mean and SD	p-value
Patients pre-treatment (n=44)	88.6 (64.9)	101.9 (68.5)	109.8 (64.6)	127.6 (73.2)	0.001
CPAP patients post treatment (n=24)	114.8 (77.8)	121.6 (66.5)	128.6 (67.4)	144.3 (72.4)	0.001
Controls (n=19)	110.8 (101.7)	125.1 (110.5)	134.8 (122.6)	143.1 (126.9)	0.01

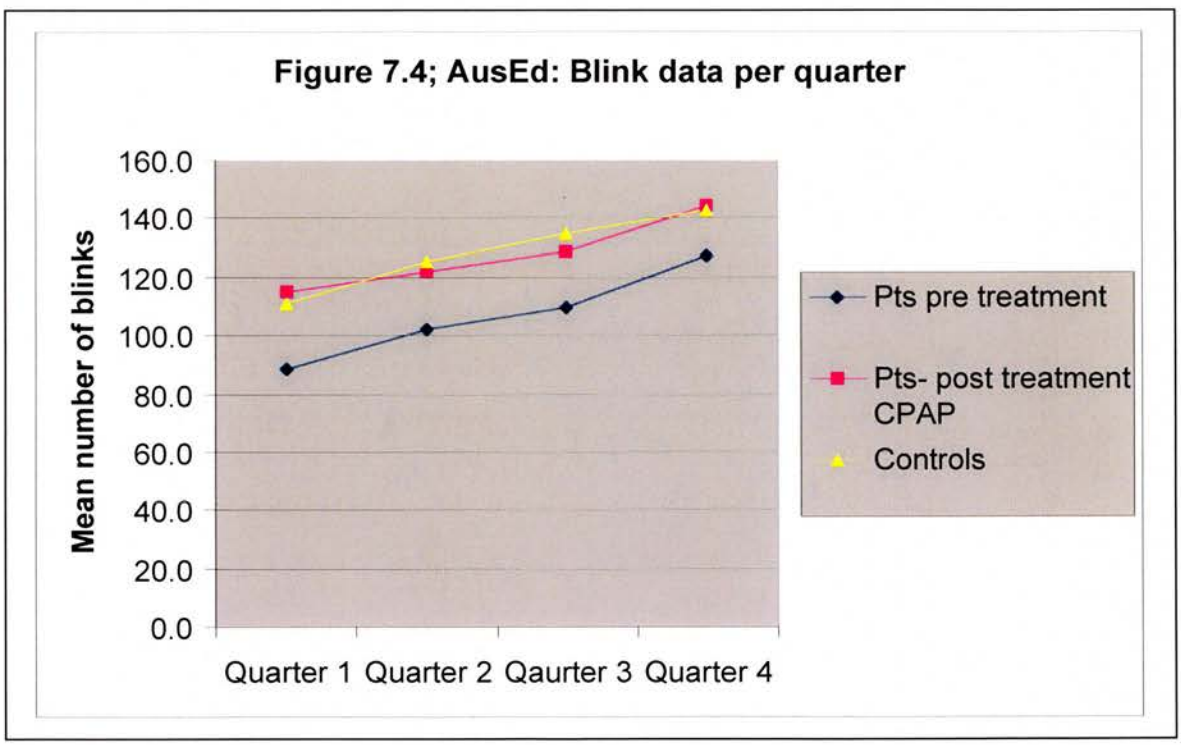


Table 7.6 shows the quarters that differ significantly, due to the number of comparisons Bonferroni corrections were applied.

Table7.6; differences in mean blink rate per quarters

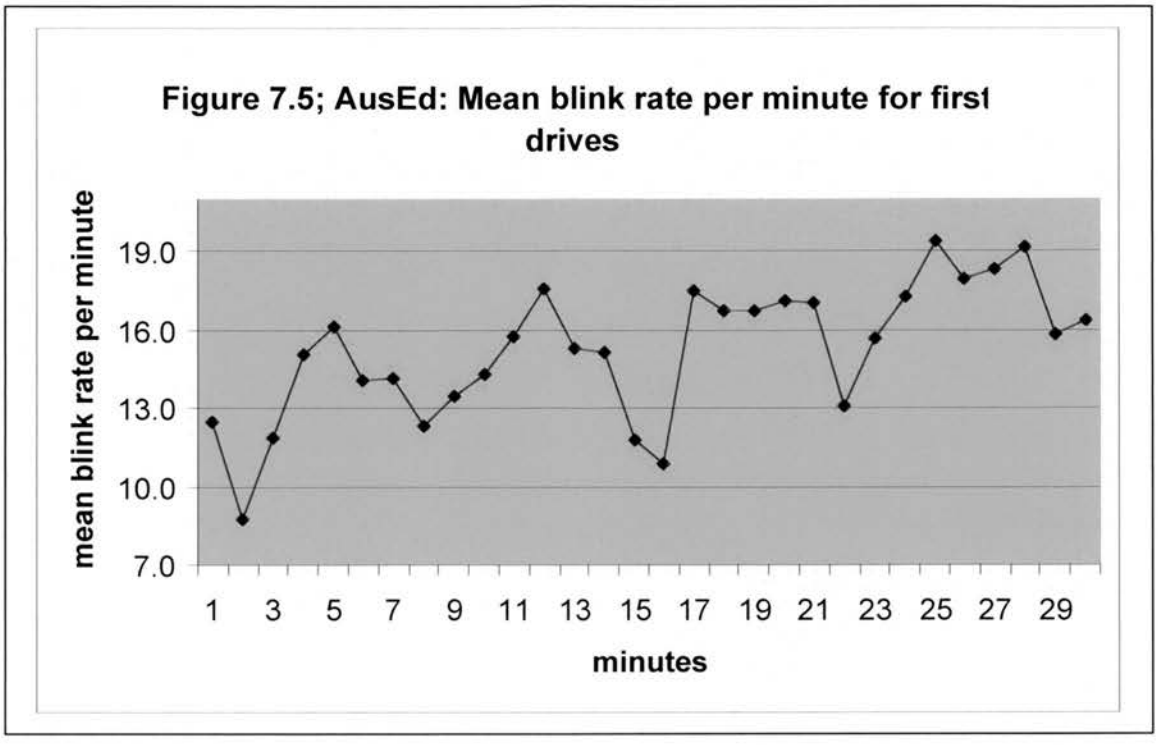
	Q1-Q2 p level¶	Q1-Q3 p level¶	Q1-Q4 p level¶	Q2-Q3 p level¶	Q2-Q4 p level¶	Q3-Q4 p level¶
Pre treatment patients	0.003	0.003	0.003	0.02	0.003	0.003
CPAP treated patients	0.03	0.05	0.003	0.17	0.003	0.03
Controls	0.02	0.021	0.03	0.39	0.083	0.22

¶ *Bonferroni correction applied*

Figure 7.5 displays the mean blink rate per minute for the three group's first drive on the AusEd simulator. As can be seen from figure 7.5 five dips in blink rate are noted around minutes 2, 8, 15, 22 and 29. Table 7.7 shows corresponding minutes and road types and these times correspond to periods of chicane road surface.

Table 7.7; Minutes and corresponding road type

Minutes	Corresponding road type
1 + 2	Chicane
3, 4, 5, 6, 7	Straight
8 + 9	Chicane
10, 11, 12, 13, 14,	Straight
15 +16	Chicane
17, 18, 19, 20, 21	Straight
22 +23	Chicane
24, 25, 26, 27, 28	Straight
29 +30	Chicane



The three groups differed in their level of sleepiness. The pre-treatment patient group had higher ESS and scored higher on the Karolinska sleepiness scale before starting the simulator than both other groups. They also scored higher scores on the post drive Karolinska sleepiness scale as compared to the controls but not the CPAP group. The CPAP group and controls also differed with the control group scoring lower ESS and a higher post-drive Karolinska sleepiness scale score.

Table7.8; Sleepiness outcomes for the three groups

	Group A Pre treatment patients n=44	Group B CPAP Treated Patients n=24	Group C Controls n=19	A v B p value ¶	A v C p value ¶	B v C p value ¶
ESS	14.1 (2.9)	9.9 (5.2)	4.9 (2.1)	0.002	0.002	0.002
Karolinska pre drive	4.7 (1.5)	3.8 (1.5)	2.7 (1.0)	0.03	0.002	>0.08
Karolinska post drive	5.9 (1.9)	5.3 (1.9)	3.2 (1.6)	>0.15	0.002	0.002

¶ *Bonferroni correction applied*

7.6.2.1 Events per time

To assess if this increase in blink rate was a physiological signal of fatigue, event rates (crash or drive-off-road) were compared between the three groups and again over the four quarters. Table 7.9 shows the means and standard deviations of events per quarter. As with the eye-blink rate there were no statistically significant differences in the three groups per quarter. However unlike the blink rate there was no time-on-task effect (see table 7.10), and no significant differences were found within any of the three groups over time.

Table 7.9; Comparison of Events by time (quarter) in patients and controls

	Group A Patients (pre treatment) n= 44 Mean (SD)	Group B CPAP patients post treatment n=24 Mean (SD)	Group C Controls n=19 Mean (SD)	A v B p level	A v C p level	B v C p level
1st Quarter	0.42 (0.87)	0.71 (1.3)	0.26 (0.56)	>0.5	>0.7	>0.4
2nd Quarter	0.38 (0.72)	0.46 (1.2)	0.42 (061)	>0.5	>0.5	>0.2
3rd Quarter	0.22 (0.70)	0.83 (2.2)	0.26 (0.56)	>0.1	>0.5	>0.5
4th Quarter	0.33 (0.74)	0.63 (1.7)	0.21 (0.63)	>0.7	>0.3	>0.5

Table 7.10; Distribution of crash and off road events by time (7.5min per quarter) within-subject comparison

	1st Quarter Mean and SD	2nd Quarter Mean and SD	3rd Quarter Mean and SD	4th Quarter Mean and SD	p level
Pts pre	0.42 (0.87)	0.38 (0.72)	0.22 (0.70)	0.33 (0.74)	p>0.7
CPAP	0.71 (1.3)	0.46 (1.2)	0.83 (2.2)	0.63(1.8)	p>0.2
Controls	0.26 (0.56)	0.42 (0.61)	0.26 (0.55)	0.21 (0.63)	p>0.4
Overall	0.40 (0.89)	0.35 (0.79)	0.36 (1.2)	0.38 (1.0)	p>0.8

As can be seen from figure 7.6 each of the three groups have relatively small numbers of events over the four time periods. This is a product of the small number of events being recorded in total. Table 7.11 shows events by subject category and the number of participants in each group reporting events. Only 12 patients recording a driving event in the pre-treatment drive also recorded an event post treatment.

Overall the rate of events per drive is 1.5, and therefore the chances of finding a time-on-task effect were low.

Figure 7.6; Driving events distribution over quarters

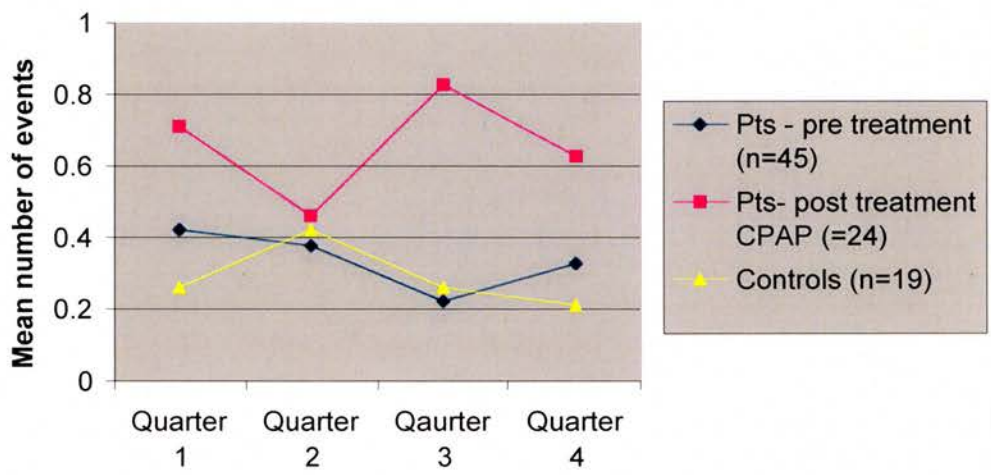


Table 7.11; Number of event and participants recording events

	Total Number of events recorded (Crashes or drive-off-road)	Number of patients recording events
Pre treatment patients	65	21
CPAP treated patients	63	12
Placebo treated patients	19	9
Controls	22	9
Total	169	51

7.6.2.2 SteerClear

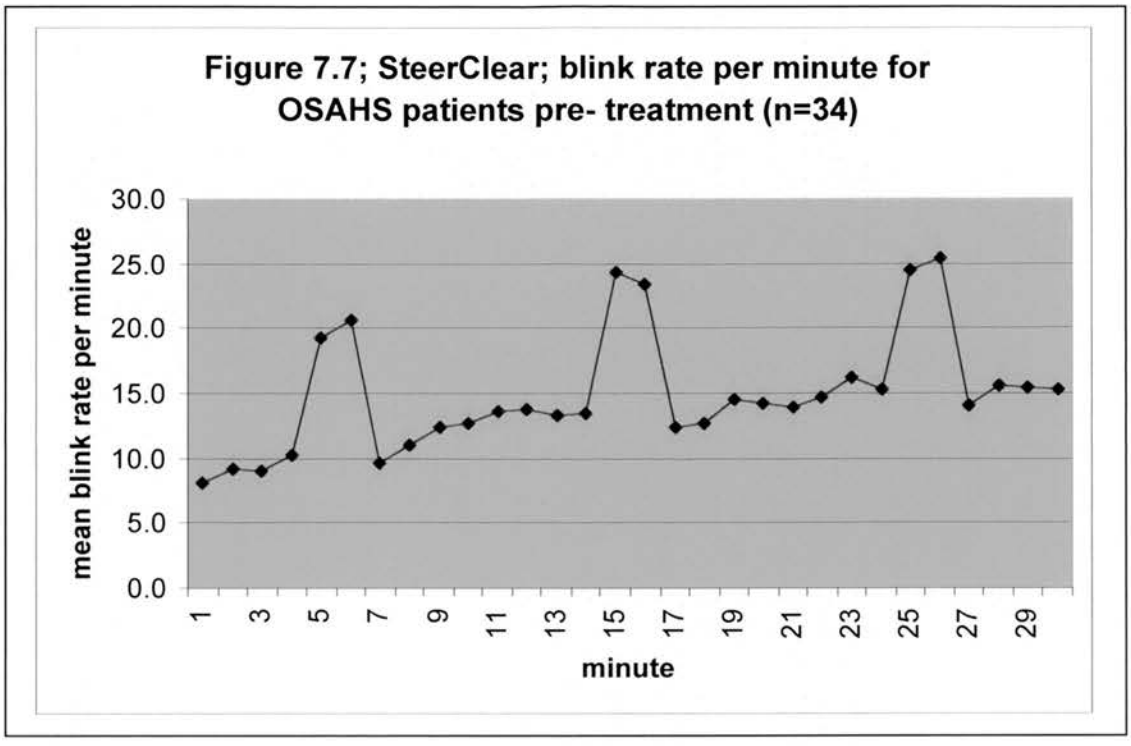
A time-on-task analysis was conducted to investigate eye-blink rate across time in the sub sample of pre-treatment OSAHS patients who underwent EOG recording whilst performing the SteerClear test. As with the AusEd data the 30-minute test was split into 4 quarters table 7.12 shows the mean eye-blink rate per quarter. Graph 7.5 illustrates the three two-minute blocks with increased eye-blink rate; these three blocks correspond to time periods when no steers were produced during the task. To investigate if these blocks were influencing the time-on-task analysis they were not included on a secondary analysis (four quarters of six minutes) table 7.12 shows the mean and significance level for these comparisons. As with the AusEd simulator eye-blink rate showed an increase over the four quarters, this held when the three time blocks without steers were analysed. Again as with the eye-blink rate in the AusEd simulated drive there were large individual differences between patients and this is apparent when looking at the magnitude of the standard deviations.

Table 7.12: Eye-blink rate on the SteerClear test over four quarters and differences between quarters

	Including Steer-free 2 minute blocks	Excluding Steer-free 2 minute blocks
Quarter 1 Mean and SD	91.4 (64.3)	57.2 (45.5)
Quarter 2 Mean and SD	109.2 (78.7)	79.2 (64.6)
Quarter 3 Mean and SD	114.6 (84.5)	82.6 (67.5)
Quarter 4 Mean and SD	133.3 (96.1)	91.9 (77.2)
Significance level	P=0.001	P=0.001

	Q1-Q2¶	Q1-Q3¶	Q1-Q4¶	Q2-Q3¶	Q2-Q4¶	Q3-Q4¶
SteerClear (including steer free minutes)	0.01	0.001	0.001	>0.2	0.002	0.004

¶ *Bonferroni correction applied*



7.7 Discussion.

As hypothesised there were changes in the mean spectral power density of FFT EEG bands immediately prior to a crash incident compared to a period of EEG that was free from incidents or the appearance of trucks on the simulator. These changes in comparison to the baseline EEG time were seen up to ten seconds, 20 seconds before the incident as an increase in the mean power of the theta EEG band. In the two-second EEG time block immediately prior to the crash incidents all three EEG bands showed significant increases in mean spectral power density from the baseline levels. The theta band also continued to increase in power between the ten-second and two-second time blocks prior to the crash incidents.

The pattern of EEG change was somewhat different in the 74 driving-off-road incidents that did not result in a crash. All three bands showed increases in mean power between the baseline and 10-second time block. A significant increase in the mean theta power was noted between the baseline and two-second time block before an event, but no

significant differences were found between alpha and sigma EEG bands. A significant reduction was also noted in the mean spectral power density of the sigma EEG band between the ten-second and two-second time blocks before going off road.

Due to the very different methodologies used between the current study and those reported in section 7.1 it is not possible to compare these results directly to others' outcomes. However, the results reported from this study, would seem to corroborate previous research that has shown that an increase in objective sleepiness (increasing power of alpha and/or theta) is linked with driving incidents. These data would suggest that at around ten seconds, 20 seconds before a serious driving event (crashing as opposed to crossing the lane boundary) increases in the mean theta and mean alpha power density are evident, and this increase in theta continues to grow between the ten-second and two-second time block. However this is also accompanied by an increase in power of wakeful (sigma) EEG frequencies. One might speculate that this is an attempt to counteract the increase of theta and alpha. The presence of sleepiness and falling asleep behind the wheel if very different to that of sleepiness and falling asleep in bed. Whilst driving, if one feels sleepy and does not pull over, one is continuing to try and perform the task at hand and would try to resist sleep, unlike in bed when one would willingly let oneself sleep.

The picture seems to be somewhat different in events that do not lead to crashes. For these an increase in mean power density of all three EEG bands is seen at ten seconds, 20 seconds prior to crossing off-road (compared to the baseline values). However the only significant difference between the baseline EEG and the two-second time block immediately prior to going off-road is seen as an increase in the theta band. One might speculate that the increased power seen in the sigma and alpha bands at ten seconds, 20 seconds before going off road (which is not seen in those events which end in a crash) might somewhat counteract the increases in theta and these increased levels of power in the wakeful band plus the stimulus of crossing the boundary are enough to alert the driver and allow them to retake control of the vehicle. However this would not necessarily explain the reduction in power of the sigma band seen in the two-seconds immediately prior to crossing the road.

Attempts to explain the differences in patterns of EEG changes found between the two types of driving event would be speculative only. However, as one event leads to the driver losing complete control of the vehicle (crash) and the other leads to momentary lose of control that is re-gained, one might speculate that differences in EEG might occur. Nevertheless even momentary loss of control at high speeds can be fatal.

Overall these results would seem to support the hypothesis that driving incidents are linked to physiological EEG changes and may not be solely driver inattention.

With regards to a relationship between blink rate and sleepiness the results are less clear. As has been reported by Horne and Reyner (1996) there were very large individual differences in blink rate, as demonstrated by the standard deviations. Nevertheless, there were no statistically significant differences between the three groups (patients pre treatment, CPAP treated patients and the control group) in the mean number of total blinks recorded for 30 minutes, or between the mean number of blinks in the four 7.5 minute quarters in the AusEd simulated drive. There was however a time-on-task effect shown in this study within each of the three groups. When Mann-Whitney U tests were computed these showed that pre treatment and CPAP treated patients each showed the same time-on-task decrements with each quarter, more mean blinks excepting quarters two and three. However within the control group the first quarter was different only from blocks 2 and 4.
The significant difference between blocks 1 and 3 did not hold with the Bonferroni correction, with evidence for a ceiling effect in blocks 2, 3 and 4, which did not differ significantly.

This pattern makes it difficult to comment on a possible relationship with sleepiness, as the CPAP treatment group reflected the same pattern of change as the untreated patient group. However, Richter et al (1998) proposed that blink rate was reduced with task difficulty (blink rate reduced with the change in curvature of the road). Speculatively, this may explain the reduced number of blinks seen during the first quarter in the control group. It may be that there is still a learning effect in the first quarter despite all subjects having had a 10 minute practise run, and the overall evening out of blink rate over the rest of the task may be due to increased familiarity

with the task. This theory would also explain the qualitative dips in blink rate shown on graph 7.4 at minutes 2, 8, 15, 22 and 28, which correspond to periods of chicane road layout on the driving simulation. It is unlikely that the differences in blink rate between the patient and control groups for time-on-task are related to a driving performance measure as there were no differences between the three groups on the mean number of driving incidents per quarter and no time-on-task effects for driving incidents were seen in any of the groups.

Blink rate in the SteerClear task also shows a time-on-task effect and this mirrors the patients' blink rate pattern in the AusEd simulator tasks with all quarters except 2 and 3 showing significant differences from each other. Graph 7.4 shows increased blink rates in the three two minute blocks where no steers were present, further supporting the notion that blink rate is reduced with task difficulty.

As there was a difference in the patient groups versus the control group in both ESS score and the post drive Karolinska sleepiness scale, the differences seen in time-on-task between the patients and control groups may be a function of sleepiness, with the increased blink rate in the patients owing to increased difficulty in maintaining task due to sleepiness.

However this remains somewhat speculative, as all groups show a time-on-task effect and without an ongoing episodic or continuous measure of sleepiness during the driving task (i.e. subjective ratings, changes in EEG either by power or intrusions of alpha or theta) it is not possible to rule out other possible factors.

The control group were screened prior to participation in this study for symptoms of sleep disorders and required as an entry criterion to have an average of six hours sleep per night. This in addition to the fact that they had a mean ESS which was in the normal range and showed only slightly increased score on the Karolinska sleepiness scale (which was lower than both patients groups for their pre drive score) may argue that driving incidents that they experienced on the simulator were unlikely to be sleep-related. However, if the driving incidents in this group were caused by other factors this would have served to reduce the chances of finding changes in the EEG power bands. Therefore any future studies employing similar methods of investigating sleepiness and driving incidents may provide clearer answers by excluding this group. However, as the

general driving population have been shown to have accidents related to sleepiness, perhaps a more prudent measure would be to assess these incidents on the basis of behavioural sleepiness as conducted by the Loughborough research team.

Further the AusEd driving simulator was not programmed to detect crossings of the central white line. Therefore if any such incidents happened during driving on the AusEd simulator they would have been missed. Overall only 169 driving incidents were recorded from 54.5 hours of subjects' driving. This might be an accurate reflection of real world driving, but due to possible missing data from crossing of the central line it is not possible to conclude that all possible sleep-related driving incidents were accounted for.

It is also not possible to determine whether the changes in theta power were due to the increasing blink rate (or possibly visa versa). Although bandpass filters excluded frequencies under 5Hz, it is not possible to rule out the possibility of blink contamination on the EEG. Also as EEG was measured using only two channels of frontal EEG and as frequencies under 5Hz and over 16Hz were excluded, it is possible that the full scope of changes occurring during sleepiness were not fully investigated using these adopted methods. Nevertheless changes in EEG were noted prior to driving incidents. Further the baseline period used as a comparator for changes in EEG prior to incidents was taken at ten minutes from the start of the driving simulation. It is therefore possible that slowing of the EEG towards sleep had already commenced by the baseline time, and again this would limit the level of change detected, as such in future studies it may be advisable to use a baseline block of EEG prior to commencing the drive. One could also argue that the comparisons should be made both with baseline and with a random sample during the drive so that differences between alert and normal driving and between normal driving and pre-incident could be identified. It could also be argued that the small time bands used to assess changes in the EEG would have little real world validity. However in the real world, two to ten seconds of sleepiness or sleep behind the wheel could have fatal consequences especially at high speeds. Nevertheless, the validity and reproducibility of EEG changes over such small time bands are required.

The FFT EEG bands were not subject to any form of standardisation although others have used FFT without standardising the outputs (Lal and Craig 2002). This inhibited the comparison of between EEG spectral band comparison, as well as between subject or between driving event type. These methodological issues with the EEG component of this chapter, including sample size might limit the ability of the study to detect changes in EEG prior to driving incidents. Nevertheless significant changes were found prior to both crashes and off-road events.

Methodological issues could also affect the results of the blink rate analysis. Although blinks were scored using strict criteria it is possible that blinks were missed due to other eye movements, especially those corresponding to the participants checking the speedometer. Stern (1994) noted the possibility of blinks and saccadic eye movements occurring together and postulated that this may occur to reduce the length of time that ones attention is not on task.

Thus it is possible that if blinks occurring during or at the end of these saccadic events appear different to the blinks in graph 7.1, or are not visible on the EOG they may have not been scored. Using concurrent video images as well as scoring from EOG channels could have been a more reliable tool for blink rate analysis. Due to the limitations of the study previously mentioned it is not possible to determine if increased blink rate is a consequence of sleepiness. However, as previous research has suggested that blink duration and slow eye movements show correlations with sleepiness in OSAHS patients (Hakkenan 1999, Kinnairi 2000) and others have hypothesised that blink amplitude and as well as these factors have accounted for larger proportions of variance in flight simulator studies (Stern 1994), these maybe the best eye movement measures to investigate in future studies to determine if eye movements are an indicator of sleepiness, and therefore a potential method for warning against declining performance.

The valid use of blink rate as a measure of sleepiness cannot be confirmed from the outcomes of this study.

The results contained in this chapter suggest that driving incidents may be linked to neurophysiological changes indicating sleepiness, and that these may be apparent from 20 seconds before the incident. This may indicate that driving incidents are not solely due to inattention caused by sleepiness, but may in part be due to changes in the density of the constituent EEG frequencies.

Chapter 8: Driving history questionnaire study

8.1 Introduction

Surveys of motor vehicle accidents (MVAs) have been the commonest means through which MVAs have been associated with sleepiness both in the general driving population and in OSAHS patient series. Sleepiness, or the inclination to sleep most likely affects driving performance due to a progressive reduction in attention on both the road and surrounding traffic, slowed reaction times and aversive actions, and eventually by a reduction in responsiveness with sleep onset (Brown 1994, Dinges 1992).

Recapping findings from some population-based surveys in the general public, as reported in section 2.3, shows sleepiness to be a significant factor in a substantial proportion of MVAs.

McCartt (1996) reported that 55% of 1000 people polled had felt sleepy whilst driving in the previous year, 3% claimed that over their driving lifetime they had fallen asleep while driving which led to a crash and an additional 2% reported having an MVA due to sleepiness. Maycock (1997) reported that 29% of 4621 participants in their Transport Research Laboratory questionnaire study reported having felt close to falling asleep whilst driving in the previous year. Sagberg et al (1999) found that of 9200 respondents questioned regarding the last accident they had reported to the insurance company, 3.9% of all accidents were related to sleep or feeling drowsy.

Accidents caused by sleepiness in the general population are most likely due to sleep deprivation, and young males (25 years and younger) are over represented in sleep related crashes (Pack 1995). These accidents also seem to mirror the circadian cycle of sleepiness, with two peak times for sleep related accidents in the early hours of the morning and mid-afternoon (Pack 1995, Garbarino et al 2001).

As OSAHS patients often report significant levels of daytime sleepiness, research has been undertaken to assess the role of sleepiness and falling asleep behind the wheel in

their MVAs. Such studies, as noted in section 2.5, find frequent self-reports of sleepiness and sleep episodes behind the wheel in OSAHS patients. In OSAHS, the clinical picture is complicated by the coexistence of sleepiness and nocturnal hypoxia. Driving impairment in patients may thus occur as a consequence of sleepiness impairing performance or through hypoxia-related cognitive deficiencies.

To recap, patients with OSAHS are between two (George et al 1987, Aldrich 1989, Barbe 1998, George and Smiley 1999) and 7 (Findlay 1988) times more likely to have an MVA than the normal population. The level of severity of OSAHS is, in some studies, associated with MVA rate (Aldrich 1989, Young 1997, Teran-Santos et al 1999), suggesting that there is a dose-response relationship between AHI severity and MVA rates (Shiomi 2002 and Findley et al 1989a).

Small retrospective based studies report that many OSAHS patients report feeling sleepy whilst driving (Guilleminault 1978). They also suggest that OSAHS patients with an AI greater than 5 report significantly more sleepy spells whilst driving as compared to people with an AI less than 5 and that these episodes contribute to the development of MVAs (Cassell, 1990). In small studies the number of OSAHS patients reporting MVAs ranges from 9% (Shiomi 2002), 12% (Hortsmann 2000) through 33% (Barbe 1998, Yamamoto 2000) to 44% (Cassell 1996), and 43% in a heterogeneous sample of symptomatic snorers (Haraldsson 1995b).
Sleepiness related accidents have been reported by 9% of 60 patients (Lloberes 2003), 19% of 44 patients (Noda 1998) and 31% of 253 patients (Wu 1995) respectively.

The studies cited in section 2.6 suggest that OSAHS patients report that CPAP treatment improves EDS, vigilance, ability to drive long distances, and reduces the number of near miss and actual MVAs (Minemura 1993, George 1995, Engleman 1996, Krieger 1997). Follow-up of 59 OSAHS patients by Cassell (1996) found a five-fold improvement in self reported accident rates after one year's CPAP treatment. In Yamamoto's (2000) prospective study of CPAP-treated patients the prevalence of those reporting MVAs fell from 33% to none of 39 patients for a period of two years. In a prospective study, 56 pathological snorers treated with UPPP, reported accident prevalence fell from 31 accidents to nine accidents per five years. (Haraldsson 1996)

Though some studies (Findley et al 1988, Young et al 1997, George et al 2001) have accessed government databases of accidents, such objective data is available only in a few places in the world. In Scotland, neither the sleepiness and MVA patterns of drivers nor patients with OSAHS have been well investigated. The aim of this study was to use a self-reporting survey to investigate the MVA rate in Scottish OSAHS sufferers before and after treatment and compare these to those of community-acquired controls.

8.2 Study design

This postal based, case-controlled, retrospective questionnaire study investigated the driving history and sleepiness of OSAHS patients and community-acquired controls. The postal survey is included as Appendix 4.

The OSAHS patient surveys were acquired in two groups- those who had been using CPAP treatment (on-CPAP) for at least 2 years, and those recently diagnosed with OSAHS and were waiting to commence CPAP treatment (awaiting-CPAP). Gender and postal-codes were used to match the community-acquired controls to the On-CPAP group.

It was hypothesised that there would be no differences in the subjective ratings of sleepiness, driving ability and accident rate between the on-CPAP group and the community acquired controls, for the previous two years. Further, that the awaiting CPAP group would report higher levels of sleepiness and accident rate and a reduced driving ability compared to the other two groups for the same time period.

The on-CPAP patient group were also asked to report their sleepiness level, driving ability and accident rate for the two year period before commencing CPAP and it was prospectively hypothesised that there would be significant improvement in these features after the commencement of CPAP.

8.3 Statistics

The baseline comparisons for ordinal and continuous data for the three groups were conducted using non-parametric Mann-Whitney U tests with Bonferroni correction for multiple comparisons. Dichotomous and categorical level data were analysed with Chi-square and Fishers exact non-parametric tests. Pre and post CPAP comparisons were conducted using Wilcoxon signed-rank tests.

8.4 Results

8.4.1 Recruitment and Response Rate

On-CPAP patient group

All records for OSAHS patients who had commenced CPAP between February 1999 and March 2000 were reviewed. A total of 452 OSAHS patients had commenced CPAP therapy during this period and of these 162 were initially excluded, as they did not meet the following criteria;

- Aged18-75, holding full drivers licence, AHI ≥20 (AH/hr in bed≥30 if diagnosed on a home based study), ability to complete questionnaire, no record of other sleep disorder in patient case-notes.

290 OSAHS patients were contacted by letter and asked to complete the driving history questionnaire, of these 138 replies were received, giving a response rate of 48%. Five OSAHS patients had died and family members of these patients responded and the Edinburgh sleep centre records were accordingly updated.

The 138 on-CPAP patients (53.6 SD 8.1 years) included in the analysis were significantly older than the 147 on-CPAP non-responders (50.3 SD 9.9 years; p=0.003), but were not significantly older than those initially excluded (54.9 SD 11.9). The on-CPAP patients included in the analysis (AHI 54.7 SD 31.1) had a significantly higher

AHI than those initially excluded (AHI 30.0 SD 25.3; p=0.001) but were not significantly different than the non-responders (AHI 51.2 SD 29.4). Gender differences were found between the 138 On-CPAP patients (16 females) used in the analysis and the OSAHS patients who were excluded from the study (44 females, x^2=10.22, df=1; p=0.001). No gender differences were found between the On-CPAP patients included in the analysis and the non-responders (19 females, x^2=0.076, df=1; ns)

Awaiting-CPAP patient group

Two hundred and five OSAHS patients undergoing CPAP titrations between April and December 2002 were identified. 54 did not meet the inclusion criteria, 151 patients were suitable for inclusion and were contacted to participate in the study (inclusion criteria was the same as for the ON-CPAP group). Of these 151 possible participants, 83 replied giving a response rate of 55%, one person was excluded as they did not hold a driver's license.

The 82 awaiting-CPAP patients (50.5 SD 9.3 years) included in the analysis were not significantly older than those excluded (54.9 SD 26.6 years) or the non-responders. The Awaiting-CPAP patients included in the analysis (AHI 45.1 SD 27.3) had a significantly higher AHI than those initially excluded (AHI 19.6 SD 20.2, p=0.001) but was not significantly different than the non-responders (AHI 43.6 SD 25.1).

Gender differences were found between the 82 on-CPAP patients (11 females) used in the analysis and the 55 awaiting-OSAHS patients who were excluded from the study (16 females, x^2=5.112, df=1; p=0.024). No gender differences were found between the Awaiting-CPAP patients included in the analysis and the non-responders (12 females, x^2=0.513, df=1; ns).

Community acquired control group

The control group comprised of community-acquired volunteers who were randomly selected from the British Telecom telephone directory and were matched to the on-CPAP patient group by gender and postal code. The inclusion criterion was as follows;

- Aged18-75, holds full drivers licence, ability to complete questionnaire.

Two hundred and sixty eight people were contacted (two volunteers were contacted for each ON-CPAP OSAHS patients that was included in the study) of these 127 replies were received giving a response rate of 47%. Under the inclusion criteria 85 controls were used for analysis in the study, 29 were excluded, as they did not hold a driving licence and 13 family members informed us that their family member had died.
Age was only reported by the 85 controls that completed the full questionnaire so it is not possible to determine any age differences in those excluded and non-responders. There were no significant differences in gender between the controls used in the analysis (85, 5 females) and those excluded (37, 5 females, x^2=1.405, df=1;ns) and the non-responders (130, 11 females, x^2=0.297,df=1;ns).
As can be seen from table 8.1, the awaiting CPAP group was 3 years younger and had held their driving license for a shorter time and, as anticipated, reported greater sleepiness than both the on-CPAP and control groups. There were no significant differences between the on-CPAP and control group in age and the length of time they held their driving license, but their subjective sleepiness score (ESS) was trending to significance with the on-CPAP group having a lower score. The on-CPAP group had a significantly higher diagnostic AHI than the awaiting CPAP group.

8.4.2 Subject Demographics

Table 8.1; Subject demographics

	Awaiting CPAP (group1) Mean and SD	On CPAP (group 2) Mean and SD	Controls (group 3) Mean and SD	Group 1 vs 2 p value ¶	Group 1 vs 3 p value ¶	Group 2 vs 3 p value ¶
Age (years)	50.5 (SD 9.3)	53.6 (8.1)	54.1 (10.7)	0.01	0.01	>0.6
ESS	12.8 (4.7)	5.5 (3.9)	6.5 (3.7)	0.002	0.002	0.056
Drivers licence (in years)	28.2 (10.5)	32.5 (9.4)	32.8 (10.5)	0.006	0.006	>0.9
Driving required by occupation*	44y/37n	72y/65n	47y/38n	>0.8	>0.5	>0.4
AHI	45.1 (27.3)	54.7 (31.9)	-	0.028	-	-
Nights using CPAP (mean nights/week)	-	6.7 (0.8)	-	-	-	-
Hours using CPAP (mean hours/night)	-	6.8 (1.3)	-	-	-	-

** Chi square, y=yes, n=no, ¶ Bonferroni correction applied*

8.4.3 Differences in Reported Symptoms

On their recent visit to the Edinburgh Sleep Centre for investigation for OSAHS, the Awaiting-CPAP group completed an in-house sleep/wake questionnaire (see section 3.7), which provided details on symptoms related to the condition. These symptom-related questions were incorporated into the control group questionnaire. The frequencies of these symptoms for the two groups are shown in tables 8.2-8.5.

Table 8.2: OSAHS symptoms- snoring & breathing pauses

	Snoring		Breathing pauses	
Frequency	Awaiting CPAP	Controls	Awaiting CPAP	Controls
Never	0%	16.7%	1.7%	52.4%
Rare	0%	16.7%	5%	8.3%
Occasionally	1.2%	25.0%	5%	9.5%
Often	1.2%	20.2%	31.6%	4.8%
Frequent/ Always	69.5%	17.9%	38.3%	2.4%
Don't know	1.2%	3.6%	18.4%	22.6%
p value	p=0.001		p=0.001	

Table 8.3: OSAHS symptoms- choking & excessive movements

	Choking		Excessive movements	
Frequency	Awaiting CPAP	Controls	Awaiting CPAP	Controls
Never	26.7%	84.5	16.7%	54.8%
Rare	13.3%	13.1	13.3%	26.2%
Occasionally	18.3%	0%	13.3%	8.3%
Often	15.0%	0%	13.3%	3.6%
Frequent/ Always	13.3%	0%	21.7%	4.8%
Don't know	13.3%	2.4%	21.6%	2.4%
p value	p=0.001		p=0.001	

Table 8.4: OSAHS jerking & coughing

	Jerking		Coughing	
Frequency	Awaiting CPAP	Controls	Awaiting CPAP	Controls
Never	16.7%	40.5%	25.0%	58.3%
Rare	10.0%	39.3%	23.3%	33.3%
Occasionally	18.3%	10.7%	15%	4.8%
Often	10.0%	2.4%	11.7%	1.2%
Frequent/ Always	30.0%	6.0%	10%	2.4%
Don't know	15.0%	1.2%	15%	0%
p value	p=0.001		p=0.001	

Table 8.5: OSAHS symptoms- wheezing & wakening to go to toilet

	Wheezing		Frequent wakening to go to toilet	
Frequency	Awaiting CPAP	Controls	Awaiting CPAP	Controls
Never	41.7%	79.8%	25.0%	23.8%
Rare	18.3%	13.1%	11.7%	33.3%
Occasionally	10.0%	3.6%	21.7%	14.3%
Often	8.3%	2.4%	8.3%	14.3%
Frequent/ Always	6.7%	1.2%	31.7%	14.3%
Don't know	15%	0%	1.7%	0%
p value	p=0.001		p=0.05	

The awaiting CPAP group report significantly higher frequencies of each of the eight OSAHS symptoms than the control group.

8.4.4 Perceived driving ability

Each of the three groups were questioned regarding the average number of days per week they drove (1-4 scale), their ability to drive short distances (<75 miles) (1-5 scale), their ability to drive long distances (>75 miles) (1-5 scale) as well as feeling sleepy whilst driving (1-5 scale) and falling asleep whilst driving (1-5 scale). All groups were asked to respond to these questions in regards to the previous two years. Table 8.6 shows the responses of all three groups on the perceived driving ability questions.

Table 8.6; Perceived driving ability

	Awaiting CPAP- Group 1 Mean & SD	On-CPAP- Group 2 Mean & SD	Controls- Group 3 Mean & SD	Group 1 vs 2 p value ¶	Group 1 vs 3 p value ¶	Group 2 vs 3 p value ¶
Driving - days per week	3.6 (0.87)	3.8 (0.52)	3.5 (0.87)	>0.9	>0.6	>0.2
Driving ability –short distances <75 miles	4.5 (0.85)	4.7 (0.72)	4.6 (0.71)	>0.9	>0.9	>0.9
Driving ability - long distances >75	3.5 (1.4)	4.2 (1.0)	4.5 (0.67)	0.002	0.002	>0.2
Feeling sleepy whilst driving	2.2 (0.82)	1.5 (0.58)	1.7 (0.58)	0.002	0.002	0.02
Falling asleep whilst driving	1.2 (0.46)	1.1 (0.30)	1.1 (0.35)	0.05	0.05	>0.9

¶ Bonferroni correction applied

There were no significant differences found between the groups on the average number of days per week they drove, whether driving was required by their occupation, or the self-perceived ability to drive short distances. The awaiting CPAP group did report significantly poorer ability to drive long distances than the on-CPAP and control group. The awaiting CPAP group also reported more frequently feeling sleepy whilst driving and falling asleep more frequently whilst driving than on-CPAP and the controls. The on-CPAP group also reported less frequently feeling sleepy whilst driving as compared the control group.

8.4.5 Reported Motor Vehicle Accidents

As well as responding to questions regarding perceived driving ability and sleepiness, the three groups were asked to report the number of MVAs they had been involved with in the previous two years and to indicate the number of these associated with sleepiness and at what time of day these accidents had occurred on.

Accidents were classified thus:

Near Miss Accident, almost had a collision but avoided at last moment

Minor Accident, collided with property or person, but no people injured

Major Accident, collided with property or person, people injured

Reported MVAs for the previous two years

Table 8.7 shows the responses of all three groups on the reported motor vehicle accident questions. As can be seen from table 8.7, the Awaiting group reported more minor accidents than the On-CPAP and more sleep related near miss accidents than both other groups. The On-CPAP groups also reported significantly fewer near misses and minor accidents than the control group; there were no differences between these two groups in relation to sleep-related accidents.

Table 8.7; MVAs by accident type

	Awaiting CPAP Group 1 Mean & SD	On-CPAP Group 2 Mean & SD	Controls Group 3 Mean & SD	Group 1 vs 2 p value ¶	Group 1 vs 3 p value ¶	Group 2 vs 3 p value ¶
Near miss incidents	1.77 (6.93)	0.41 (1.2)	0.90 (1.6)	0.07	0.4	0.002
Sleep related near miss incidents	1.23 (5.3)	0.13 (0.61)	0.04 (0.19)	0.02	0.006	0.6
Minor accidents	0.30 (0.68)	0.07 (0.29)	0.19 (0.45)	0.002	0.6	0.03
Sleep related minor accidents	0.11 (0.57)	0	0	0.02	0.08	0.9
Major accidents	0	0.01 (0.09)	0.01 (0.11)	0.4	06	9
Sleep related major accidents	0	0.01 (0.09)	0	0.4	0.9	0.8
Total number of accidents	2.07 (7.37)	0.49 (1.24)	1.11 (1.67)	0.002	0.9	0.002
Sleep related total number of accidents	1.34 (5.74)	0.14 (0.62)	0.04 (0.19)	0.008	0.004	0.6

¶ *Bonferroni correction applied*

Table 8.8 shows the frequency and percentages of number of participants in each group reporting accidents. Fewer participants in the On-CPAP group reported having minor/major accidents than the Awaiting CPAP group (p=0.002). There were also fewer On-CPAP patients reporting near miss accidents than both other groups. When near miss and actual accidents were analysed together, significantly fewer of the On CPAP patients were involved than both other groups. On analysis of the numbers of participants in each group reporting sleepiness related accidents, more participants in the awaiting group reported sleep related near miss incidents than the other two groups. However there were no differences in the three groups in the number of participants reporting minor/major sleep related accidents.

Table 8.8; Number of participants in each group reporting accidents

	Awaiting CPAP- number of group having accidents and %	On-CPAP - number of group having accidents and %	Controls - number of group having accidents and %	1 vs 2 p level*	1 vs 3 p level*	2 vs 3 p level*
Near miss incidents	23 (28%)	24 (17%)	32 (38%)	0.01	0.2	0.02
Minor and Major accidents	19 (23%)	9 (6%)	8 (9%)	0.002	0.03	0.4
Total number of accidents	33 (40%)	29 (21%)	40 (47%)	0.04	0.4	0.002
Near miss incidents associated with sleepiness	14 (17%)	9 (6.5%)	3 (3.5%)	0.002	0.002	0.4
Minor and Major accidents associated with sleepiness	4 (5%)	1 (0.7%)	0	0.1	0.2	0.9
Total number of accidents associated with sleepiness	18 (22%)	10 (7%)	4 (6.5%)	0.004	0.002	0.4

**Chi square with Bonferroni correction*

8.4.6 Dose response relationship between AHI and MVAs in the Awaiting group

An analysis of AHI and MVA prevalence was undertaken. Table 8.9 shows the AHI cut off values and corresponding number of patients in the Awaiting-CPAP group reporting a MVA or near miss incident. There were no dose response relationships between AHI and driving incidents detected from the awaiting CPAP sample. Table 8.10 shows no dose response relationship between the control group and the three AHI sub-groups of awaiting CPAP group for near miss, minor and major accidents. All three of the AHI groups reported more near miss incidents associated with sleepiness than the control groups.

Table 8.9; Awaiting CPAP group - Dose response for AHI and MVAs

	Number of group having incidents	Number of group not having incidents	
AHI 20-27/hour	10	18	p>0.9
AHI 28-41/hour	12	14	
AHI 42+/hour	11	17	

Table 8.10; Differences between the AHI sub groups of the Awaiting CPAP group and control group

	AHI 20-27/h vs Controls p value	AHI 28-41/h vs Controls P value	AHI 42+/h vs Controls p value
Near Miss accidents	0.93	0.93	0.93
Near Miss accidents associated with sleepiness	0.01	0.03	0.03
Minor accidents	0.87	0.84	0.84
Minor accidents associated with sleepiness	0.08	1.0	1.0
Major accidents	0.57	0.58	0.58
Major accidents associated with sleepiness	1.0	1.0	1.0

8.4.7 Secondary measures of measurement time of MVAs

MVA rate by time of day shows variability in the three groups. Analysis including the near miss incidents indicates that there was no difference between the accident rates in the awaiting CPAP and the control group at any time of day or night. The On-CPAP group has fewer MVAs than the awaiting-CPAP group between the hours of 9am and midday, and fewer MVAs than both the awaiting CPAP and controls between the hours of midday and 6pm. Table 8.11 displays the differences of MVAs by time of day.

Table 8.11 Total numbers of MVAs (including near miss incidents) by time of day in three hour blocks

	Awaiting CPAP Group 1 Mean & SD	On-CPAP Group 2 Mean & SD	Controls Group 3 Mean & SD	1 vs 2 p value ¶	1 vs 3 p value ¶	2 vs 3 p value ¶
Total number of accidents 6am+	0.18 (0.71)	0.04 (0.22)	0.05 (0.26)	>0.2	>0.5	>0.9
Total number of accidents 9am+	0.32 (1.20)	0.04 (0.22)	0.14 (0.56)	0.012	>0.8	>0.9
Total number of accidents 12pm+	0.40 (1.41)	0.01 (0.12)	0.24 (0.68)	0.002	>0.9	0.002
Total number of accidents 3pm+	0.65 (2.60)	0.07 (0.25)	0.22 (0.54)	0.008	>0.9	0.02
Total number of accidents 6pm+	0.11 (0.42)	0.09 (0.48)	0.08 (0.32)	>0.9	>0.9	>0.9
Total number of accidents 9pm+	0.35 (2.68)	0.01 (0.12)	0.01 (0.12)	>0.6	>0.6	>0.9
Total number of accidents 12am+	0.01 (0.11)	0.01 (0.09)	0	>0.9	>0.6	<0.9
Total number of accidents 3am+	0	0.01 (0.12)	0.01 (0.12)	>0.6	>0.6	>0.9

¶ *Bonferroni correction applied*

Table 8.12:Percentage of MVAs across the day in three-hour blocks

	6am+	9am+	12pm+	3pm+	6pm+	9pm+	12am+	3am+
MVA by time of day (%)	7.6%	16.3%	20.8%	30.7%	10.6%	12.1%	0.8%	1.1%

When all incidents were grouped together by time of day 50% of these occurred between 12pm and 6pm.

8.5 Changes in perceived driving ability and MVA rates with CPAP

As well as providing information on subjective sleepiness, perceived driving ability and MVA rates in the previous two years, the On-CPAP group were also asked to provide information on these areas for a period of two years before they commenced CPAP.

Tables 8.13 displays the changes in the On-CPAP group from before and after the commencement of CPAP.

Table 8.13; Changes in sleepiness, driving ability and MVA rate with CPAP

	ON-CPAP Pre-treatment mean & SD	On-CPAP Post-treatment mean & SD	p value
ESS	14.9 (5.2)	5.5 (3.9)	0.001
Driving –days per week	3.8 (0.60)	3.8 (0.52)	0.4
Driving ability –short distances <75 miles	4.1 (1.07)	4.7 (0.72)	0.001
Driving ability – long distances >75	3.2 (1.29)	4.2 (1.00)	0.001
Feeling sleepy whilst driving	2.7 (1.0)	1.5 (0.58)	0.001
Falling asleep whilst driving	1.5 (0.66)	1.1 (0.30)	0.001
Near miss incidents	2.5 (6.07)	0.41 (1.2)	0.001
Sleep related near miss incidents	2.1 (5.88)	0.13 (0.61)	0.001
Minor accidents	0.2 (0.57)	0.07 (0.29)	0.05
Sleep related minor accidents	0.7 (0.37)	0	0.02
Major accidents	0.02 (0.57)	0.01 (0.09)	0.3
Sleep related major accidents	0.01 (0.08)	0.01 (0.09)	0.9
Total number of accidents (including near misses)	2.7 (6.14)	0.49 (1.24)	0.001
Sleep related total number of accidents (including near misses)	2.1 (5.95)	0.14 (0.62)	0.001
Total number of accidents (not including near misses)	0.22 (0.59)	0.08 (0.32)	0.003
Sleep related total number of accidents (not including near misses)	0.08 (0.36)	0.01 (0.09)	0.03
Number of patients reporting minor or major MVA	0.15 (0.36)	0.07 (0.25)	0.014
Number of patients reporting near miss incident	0.43 (0.49)	0.17 (0.38)	0.001

Table 8.14 Changes in sleepiness after the commencement of CPAP

	Percent of responses
Much more sleepy	0.7%
More sleepy	0.7%
About the same	8.7%
Less sleepy	34.1%
Much less sleepy	52.9%
Didn't respond	2.9%

Tables 8.13 shows that there was no change in the average days per week the group drove and there were also no significant differences in the number of major and sleep related major accidents reported. However the On-CPAP group reported significantly improved subjective sleepiness (ESS) and on a five-point scale questioning CPAPs effect on sleepiness 87% reported feeling less sleepy (table 8.14). Since the commencement of CPAP the group reported improved ability to drive both short and long distances, a reduction in near miss and minor accidents and a reduction in the number of these accidents attributed to sleepiness. The On CPAP group also reported a reduction in the frequency of feeling sleepy and falling asleep whilst driving.

8.6 Discussion

The hypothesis that the awaiting-CPAP group would report significantly higher subjective sleepiness, reduced ability to drive long distances and higher frequencies of symptoms of OSAHS than controls was supported by the results of the study. The hypothesis that the awaiting-CPAP group would report higher numbers of motor vehicle incidents (including near-miss incidents) was only supported for higher rates of sleep-related near miss accidents than the control group and for more minor accidents compared to the On-CPAP group. Also, the awaiting CPAP group reported higher subjective daytime sleepiness, reduced ability to drive long distances and a higher total number of accidents (including near miss incidents) than the on-CPAP group. The On-CPAP and control groups showed no significant differences in subjective daytime sleepiness, self-rated ability to drive long distances, or sleep-related driving incidents, confirming the null hypothesis. However the On-CPAP group reported significantly

fewer total numbers of motor vehicle incidents (which included both near miss incidents and minor accidents) compared to the control group.

On analysis of the number of participants in each group reporting accidents, fewer On-CPAP participants reported near miss incidents and being involved in a minor/major accident than participants in the awaiting CPAP group. Further, fewer of the on-CPAP participants reported near misses than the control group. Sleep associated incidents were reported by more participants in the awaiting-CPAP group than either other group, but there were no differences between the on-CPAP and control group for the percentage of participants reporting sleep related accidents.

In comparison with the MVA prevalence reported in section 7.1 (9% Shiomi 2002), 12% Hortsmann 2000, 33% Barbe 1998, Yamamoto 44%, Cassell 1996, 43% in a heterogeneous sample of symptomatic snorers Haraldsson 1995b) for untreated OSAHS, this current study reports MVA prevalence of 23% for actual accidents, rising to 33% when near miss incidents are included. Meanwhile the prevalence of sleep related MVAs in untreated OSAHS in this study is 5% for actual accidents and 22% for all driving incidents. This 5% for sleep-related MVAs is lower than the estimates of Lloberes and Wu respectively. The current study also found fewer near miss accident reports in OSAHS patients (28%) than the case series of Noda (1998), where near misses reportedly affected 50%.

Sleepiness and driving ability of the On-CPAP group in this study were congruent with those observed by Minemura (1993) George (1995) and Engleman (1996) all of whom report subjective improvement in EDS, ability to drive long distances and lower rates of MVAs than untreated patients. Direct comparison to the prevalence reported by Cassell (1996), Yamamoto (2000) and Haraldsson (1996) on reduction of MVA rates is complicated due to the differences in study design. But this Scottish series showed a higher percentage of participants reporting MVAs (6% major and minor, 21% for all accidents types over 2 years) than the Yamomoto study (over two years). The awaiting CPAP group also reported a higher actual collision rate than the on CPAP group, the mean rates falling three-fold. The post-CPAP driving incident rate was lower than that of the Cassell study, and Cassell's time window for reports was one year of CPAP use, as

compared to two years in the present study. Haraldsson found that only nine accidents occurred in sample of 56 patients over a five-year period, compared to the current results of 11 accidents from 138 patients over a two-year period.

The community control group data in the present study were similar to that of Wu et al (1996), in which 12 of 80 controls had had an MVA, compared to 8 of 85 patients in the current study. However Wu et al do not report the time scale for the accidents. McCartt (1995) reported that 2% of their respondents had reported an MVA associated with sleepiness over their lifetime, a figure slightly lower than in our sample (3.5% reporting that in the previous two years they had or nearly had and MVA due to sleepiness).

Unlike previous studies, there was no dose-response relationship by mean AHI level detected in this Scottish series of untreated OSAHS patients. This may stem from the small sample size available in the present study. Each of the studies cited in section 8.1 had sample sizes which ranged from 100+ (Aldrich 1988, Teran-Santos et al 1999 7) 400+ (Shiomi 2002) to 900+ (Young 1997) participants, except that of Findley which had only 44 OSAHS which were spilt into mild (16) moderate (17) and severe (13). However, Findley et al had the benefit of database information on driving accident rates for the state of Virginia, and it was in comparison to these controls that the severe OSAHS patients showed increased MVA rate.

A dose-response analysis in this Scottish series was undertaken retrospectively with the cut off levels for disease severity determined by calculating three AHI bands to produce similar number of participants in each group.

As there was a minimal level of AHI required for inclusion for the study, the lowest AHI band spanned 20-27/h, while the Young study included AHI >5 as clinically relevant. Thus the lack of a dose response may also be attributed to the differences in AHI criteria as compared to the previously cited studies.

The secondary outcomes of the study, by time of day, also showed differences between the three groups. The awaiting group reported more motor incidents than the on-CPAP group in three-hour bands at 9am+, 12pm+ and 3pm+ when all accident types were

included. The On-CPAP group also reported fewer total driving incidents than the control group at 12pm+ and 3pm+.

Research on sleep related MVAs in the general population in England has provided evidence that three peak times for sleep related accidents occur around 2-3am, 6-7am and 4-5pm (Horne and Reyner 1995). The pattern of MVAs over time in the current study do not reflect this, with only 8.7% of all the MVAs reported occurring during 3-9am. This almost certainly reflects the lower traffic densities at those times (Horne and Reyner 1995), and may in part be due to the differing age of the two study populations. The Horne and Reyner study had a predominantly younger sample as compared to the middle aged sample in the current study, and these age differences will most likely produce differing driving habits.

However, as no previous normative values have been established for OSAHS related motor vehicle accidents in terms of time of accident, and as limited data was gathered on this, it is not possible to completely attribute reasons for these differences between the patient and volunteer groups. However in a study investigating MVAs by road type in the general population on 15 roads of varying classification in England, Flately et al (2004) report that MVAs and sleep related MVAs show variation by road type, lighting, time of year and by changes in traffic density. Sleep related MVAs increased as traffic volume increased on non-motorway roads. However on motorways as traffic density increased sleep related MVAs showed a negative correlation with traffic density. As the detail of information obtained regarding the time and place of accidents is limited in the present study, it is not useful to speculate if any of these variables could have been factors in the MVA rate.

The current study does highlight differences between the three groups for time of accident and further investigation with more rigorous data collection of this areas are required to establish if these differences between the three groups are sleep related.

A possible reason for the lack of significant differences between the awaiting CPAP and control group in reported MVAs may stem from the lack of demographic and anthropometric data for the control group, and a consequent inability to control for these

factors. Questionnaire based studies must balance information requested against length of questionnaire, leading inevitably to compromises on data comprehensiveness. Unlike the patient group who would be aware of the role of sleepiness in driving, it is very likely that the majority of the controls would not, and so it was prospectively decided to request the minimum amount of personal information to try to maximise the response rate of this group. Another factor in this lack of difference between the awaiting CPAP group and the controls in accident rates may be the unwillingness of OSAHS patients to accurately report accident rates prior to starting on effective treatment, probably for fear of losing their licence (Engleman 1997 24).

The lack of personal data, especially that of previous medical history to some extent may explain the higher MVA rate found in the control group (as compared to the On-CPAP group). Conditions such as diabetes mellitus and cardiac problems, as well as use of sedating drugs (i.e. antihistamines) or being male or younger than 25, have all been associated with increased MVA rate. Also despite questions regarding OSAHS symptoms and whether controls had been diagnosed with a sleep disorder, there is no way to rule out possible sleep disordered breathing in the control group. This may mean that MVAs in this particular group would be higher than a control group selected for an absence of serious illness and SDB. Further, information regarding occupation and lifestyle, for example shift work and self-induced sleep restriction, were not sought and these factors are also linked with increased MVA.

Conversely, the differences in driving incidents reported by the control group, the awaiting CPAP and on-CPAP patient groups may also be influenced by volunteer bias in the patient group. Previous research has documented that responders to questionnaire studies tend to be healthier than the non-responders (Altman 1991) and so there is no way to exclude the possibility that only the patients who felt less affected by OSAHS symptoms (in the awaiting group) or the patients who perceive better benefits from CPAP responded self selecting themselves as responders.

However it has been documented previously that OSAHS patients often under-report their involvement in MVAs both before commencing treatment (Engleman 1997) and after treatment initiation (Findley 2000). Hence, the differences (and lack of

differences) found between the three groups may in part be due to under-reporting from the patient groups. Also participants were not questioned whether the accidents they reported were their fault, hence it is not possible to rule out that an increased MVA rate in any of the groups could have been due to them being involved in an accident which was the fault of someone else. This information was not sought due to the dubiety as to its validity.

A further possible methodological issue in the current study is the lack of an estimate of annual mileage. Increased mileage is a known risk factor for MVAs, and this study did not request an estimate of yearly mileage, precluding an ability to control for mileage. However during the AusEd driving simulator study, patients and controls were asked to supply this data, and a majority initially left this question unanswered. As it would not be possible to contact each person responding to the questionnaire who left this blank it was decided instead to employ as an estimate of driving exposure the average days per week that subjects drove. Although this does not allow for controlling of mileage, this data allowed us to compare a measure of driving exposure, unlike other studies including Aldrich (1898) George (1999) Shiomi (2000) and Wu (1996). Driving exposure in days per week was not significantly different in the three groups of the Scottish survey.

These issues in part restrict the conclusions that can be drawn from this current study. Nevertheless these issues are not limited to this study alone but are a by-product of retrospective self-report methods of data collection.

Overall this study confirms earlier findings suggesting elevated self-reported MVA incident rates and prevalence in untreated OSAHS patients, and that the prevalence of sleep-related driving incidents are significantly higher than in community controls. Further this study provides useful evidence that OSAHS patients, once on CPAP therapy, pose no increased risk of road accidents.

Chapter 9: Conclusions and future research

The AusEd driving simulator is a laboratory based task, designed as a tool to assess fitness to drive in the obstructive sleep apnoea/hypopnoea syndrome (OSAHS). Results from the treatment effect trial indicate that the AusEd simulator could not discriminate driving performance; measured by steering deviation, lane position, speed control, reaction time and driving incidents in treated and untreated OSAHS. In the case-controlled study only reaction time was significantly poorer in the untreated OSAHS patient group compared to the control group, and this difference was abolished with CPAP therapy. However this difference in performance was not mirrored in the other task components, further suggesting a lack of sensitivity of the simulator. It is possible that differences in performance were not found because the OSAHS patient group were too mildly affected or not impaired in their ability to drive. However as other research groups (Risser et al 2000, Juniper et al 2000) have found differences in driving performance in OSAHS patients with similar disease severity as those in the current study, this seems unlikely.

EEG traces recorded during the AusEd driving task which were subjected to FFT analysis indicated an increase in the spectral power density of the faster theta and alpha bands from a baseline level. This provides some support for the hypothesis that driving incidents may be a consequence of increasing sleepiness rather than driver inattention or overt sleep. The second physiological measure of eye blinking during the task was not a sensitive measure to discriminate between OSAHS patients (pre- or post-treatment) and controls. Time-on-task increases in blink rate were seen in all three groups, and these increases were not mirrored by the distribution of driving incidents (i.e. crashes), leading one to speculate that blink rate may not be the best method of assessing sleepiness.

Results from the driving questionnaire study were congruent with previous research, suggesting that as a population untreated OSAHS patients are at increased MVA risk

compared to treated OSAHS patients. This Scottish self reported accident and driving ability study, shows similar results to surveys from other countries.

Although the AusEd simulator was unable to advance understanding of which aspects of driving performance may be impaired in OSAHS patients, the study has highlighted potential methodological issues with the use of PC based driving simulators as a tool for assessing driving. The AusEd simulator was designed to assess three areas of driving performance (tracking, visual search and speed control) important to maintaining safe control of the vehicle. The lack of differences in performance between the patients and control groups is most likely as a result of the insensitivity of the simulator, and demonstrates that any simulator should undergo extensive research and validation to adequately assess its ability to accurately mimic real driving. Although there were programming problems with the AusEd simulator, the program was sound in theoretical design and provides evidence that not every computer based driving program could mimic real life driving. However, one can speculate that a PC based simulator will never truly emulate a real-life driving task. Although PC simulators like the AusEd are designed as 'safe' and economical methods of assessing performance, they do not replicate the full driving experience. There is no restriction of seat belts, no manoeuvre procedure (i.e. checking over ones shoulder before crossing lanes), no ability to measure a person's use of the rear view mirror and indeed no measure of a person's ability to assess changes in driving condition (i.e. turning on head lights or wind screen wipers), all aspects which are tested for (either on road or in a written test) in the DVLA driving test. Further, there is a lack of proprioceptive, vestibular and peripheral vision cues of the motion of the car. When this is coupled with the fact that the consequences of a crash or off-road event on the simulator does not have the same consequences as in real life, the overall 'simulation' of driving is imperfect.

However, the gold standard of testing would be a real-world driving test and as noted in section 2.10.1 this would be prohibitively expensive and possibly dangerous, hence the need for exploration of driving simulators. It is my opinion that if driving simulators are to be used as a tool to assess fitness to drive, a degree of realism is required. Therefore simulators of the standard of the Swedish transportation simulator or the Loughborough University simulator should be utilised. Simulators of these standards offer larger viewing screens, moving bases, and steering wheel and pedal

configurations of actual cars, giving a far more 'realistic' simulation of driving than one which is PC based. However, the advantages these simulators have in design, technology and sophistication are counterbalanced by their expense and the fact that they are not portable. As a tool for fitness to drive is desirable due to the expanding number of patients being investigated for OSAHS, and consequently the increasing number of patients awaiting treatment, it seems unlikely that funding would be available to purchase and maintain the number of these simulators required to assess large number of patients.

However, even simulators of this realistic calibre have theoretical and practical issues. The question regarding which aspects of driving performance represent impairment, and at what level, is still unclear. Further, little evidence exists to show the correlation between simulated driving performance and real life driving performance. Despite evidence that simulators can discriminate *en masse* driving performance between OSAHS patients, controls and non-sleep-disordered, sleep-deprived young adults, one can speculate that PC based driving simulators are not currently valid tools for assessing fitness to drive. Further, although others (Turkington 2003, Hack 2000, George 1997) have shown that CPAP therapy reduces steering deviation and RT, further research must be undertaken to investigate if these improvements in performance may be maintained over long periods of time.

Due to the lack of correlations between simulated driving and real driving, and the lack of understanding as to why some OSAHS patients are more susceptible than others to MVAs, simulators are not yet sufficiently validated to be used as tools to discriminate driving safety in individual OSAHS patients. Perhaps an intermediate approach could be to implement a restricted drivers license scheme, which has been shown to be effective in America for newly qualified drivers (McKnight and Peck 2003, Lin and Fearn 2003) who have recently passed their driving test. One could limit OSAHS patients driving at night, by themselves or even on motorways, which is a restriction of the provisional driver's licence in Britain. Further, as during simulated driving, evidence of cumulative deleterious effects on driving performance in sleep-deprived adults and after alcohol have been shown (Horne et al 2003, Arnedt et al 2000), perhaps more emphasis should be placed on untreated OSAHS patients avoiding alcohol. Of course,

the issue of which drivers are at risk is still unanswered and a blanket restriction on all OSAHS drivers until treatment is undesirable as this could have serious consequences socially and financially to the subpopulation who have normal driving performance and no increased risks of MVAs.

One of the main features of OSAHS is the increased level of daytime sleepiness. As reported in the EEG data in chapter 7, increases in power in the theta and alpha band prior to an off road event or crash suggest a slowing of the EEG may cause accidents. This coupled with significantly higher numbers of MVAs and near misses associated with sleepiness, as reported by the untreated OSAHS patients reported in chapter 8, further suggests that it is sleepiness that causes MVAs. However, as it has been suggested that individuals may not be aware of their own level of sleepiness (Kecklund and Kerstedt 1994) or how imminent sleep may be (Horne and Reyner 1995), simply telling OSAHS patients not to drive while sleepy may not be sufficient.

Perhaps a restricted license should be given to only those OSAHS patients determined to be hypersomnolent, but of course this debate is circular in nature, as the need for an objective test for fitness to drive arose from the fact that the MWT was not an tailored test for driving fitness.

Research into the OSAHS is in its infancy. Although large advances in understanding of the condition have been made in the last few decades, our understanding of the mechanisms and in turn the insults to the physiology of the body from this condition are still evolving. Research is required to determine which physiological aspects of the condition are responsible for the daytime sequelae of the condition, including sleepiness, cognitive and motor deficits seen in OSAHS patients. This will allow a better understanding of the condition and allow further research to be directed into which aspects of the condition could impair driving. Although CPAP seems to treat OSAHS adequately in tolerant users, ongoing research for a cure for the condition would be the gold standard. As levels of sleepiness and MVAs seem to reduce with CPAP, one would assume a cure would also reverse the increased levels of MVAs found in some OSAHS patients. Until this time, untreated OSAHS patients and their families must be

advised they should not drive if they feel or appear sleepy, as with any other driver, even if healthy.

Unfortunately, although one might assume it would be OSAHS patients who perform poorly on a driving simulator who also perform poorly in real life, the evidence to support this is still lacking. Hence, simulators are not ready to be used as an objective tool to assess fitness to drive in the patients with OSAHS.

In the future, studies with greater statistical power, more severe disease (either by respiratory or sleepiness criteria) and more realistic simulators might, after adequate validation, provide the research tools to discriminate drivers at excess risk of accidents from those who have normal performance. Currently, the best indicator of accident propensity in OSAHS patients remains their own self-reports of episodes of sleepiness while driving.

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APPENDIX 1

CONTENTS:

Edinburgh Sleep Centre,
Ward 48, Royal Infirmary of Edinburgh
1 Lauriston place
Edinburgh
EH3 9YW

Dear

Our records show that you will shortly attend the Sleep Laboratory for investigation of the obstructive sleep apnoea/hypopnoea syndrome (OSAHS). This is an illness that can be successfully treated by wearing a nasal mask during sleep, in a treatment called continuous positive airway pressure (CPAP) therapy. We would also like to assess the effects of an experimental capsule treatment, taken by mouth for OSAHS.

As a suspected sufferer of this condition, we would like to ask you whether you might be willing to help us with research into the effects of these two treatments for OSAHS on sleep quality, driving ability and daytime sleepiness on concentration tests. The study would involve a full day of testing the day after your overnight stay, finishing around 5pm. You would then be asked to return at a later date for an overnight CPAP trial, to take for one month either the capsule treatment or CPAP treatment, returning a month later for a further half-day of daytime testing. Neither of these treatments has been associated with any serious side effects.

Further information about the study is contained within the enclosed information sheet and consent form. Please phone Miss Lynne Anderson on 0131 536 4192 if you have other unanswered queries about the study, or impartial advice can be obtained from Dr. Tom Mackay of the Sleep Centre on 0131 536 2355.

We would be most grateful if you could complete the attached response form and return it in the enclosed SAE to let us know if you might be interested. If you already feel happy to take part in the study, having read the information sheet, please also sign and return the consent form.

Yours sincerely,

L Anderson, MA, Research Associate
Professor N J Douglas, Consultant Physician, FRCPE
Dr TW Mackay, Consultant, MRCPE

INFORMATION SHEET

LABORATORY-BASED DRIVING TASK STUDY

The study

You have been asked to participate in a study of driving ability, sleepiness and concentration before and after treatment for the obstructive sleep apnoea/hypopnoea syndrome (OSAHS), a condition that causes breathing pauses during sleep. The results of this study will be used to improve knowledge of the effects of OSAHS on daytime performance and the management of other patients with this syndrome. The study is funded by the Chest, Heart and Stroke Scotland charity.
You will be asked to have tests before and after 1 month of treatment with either a capsule, taken by mouth, or continuous positive airway pressure (CPAP). A computer program will decide which one treatment you will be asked to take, with a 50:50 chance of getting each.

The study treatments

1. **CAPSULES** that may ease your breathing problems during sleep by increasing the muscle tone in your throat. Patients taking these have reported occasional headaches, rashes and nausea.

2. **CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)** which may prevent your throat blocking during sleep by blowing a gentle stream of air into your airway through a nasal mask. This treatment is the current standard treatment for OSAHS, and may cause minor stuffiness of the nose or drying of the throat.

In the event of side effects or other adverse events related to treatments, please contact Dr. HM Engleman of the Edinburgh Sleep Centre on 0131 536 2360/ 2355 or the respiratory registrar on call 0131 536 1000.

The procedures

Before you start treatment, you'll be asked to attend for monitoring over a full night and day. The tests will involve being 'wired up' with skin sensors that detect brainwaves, breathing and oxygen levels. Only the scalp and face sensors will be left on for the daytime tests. The daytime tests will involve 4 assessments of sleepiness, during which you'll be asked to stay awake for periods in a dimly lit room. In between these, you'll be asked to complete questionnaires about your everyday sleepiness level, and concentration tests resembling puzzles and computer games. You will be asked to come back for a second night to try the CPAP treatment and then start your one-month of treatment at home thereafter, and to return in one month for an appointment to perform again a driving-based concentration test. At the end of the study, depending on your local health authorities approval, you will be offered the standard treatment for OSAHS, CPAP. If CPAP is not available at this time you will be placed on a waiting list.

Further information

Impartial advice can be obtained from Dr. TW Mackay, Edinburgh Sleep Centre, Wd 48, Royal Infirmary (tel. 0131 536 2355).

If you agree to take part in this study, we will contact your GP and keep them informed of any clinically relevant results. It is understood that you can withdraw at any time without prejudice to the quality of your treatment for SAHS. If you understand the requirements and procedures of the study and agree to take part, please sign the consent form.

CONSENT FORM

Title of proposed research: Laboratory-based driving task

Name of investigators: L Anderson, HM Engleman and NJ Douglas

Address: Edinburgh Sleep Centre, Ward 48, Royal Infirmary of Edinburgh

Further information is available from: Miss Lynne Anderson, Edinburgh Sleep Centre, Ward 48, Royal Infirmary of Edinburgh. Impartial advice can be gained from Dr. TW Mackay, Edinburgh Sleep Centre.

In this study, funded by the Chest Heart and Stroke Scotland charity, you will be asked to have an overnight sleep study and a daytime assessment in the Edinburgh Sleep Centre. During these, you will be 'wired up' with skin sensors to detect physiological activity, and will be asked to sleep during the night, and then undergo sleepiness tests, questionnaires and concentration tests the next day. You will subsequently be asked to take for one month either a capsule taken by mouth or to use continuous positive airway pressure (CPAP) treatment, and return for a driving-based concentration test at the end of the month's treatment.

Either of these two treatments may be effective in reducing the breathing pauses in sleep which are seen in the sleep apnoea/hypopnoea syndrome. The capsule may alter muscle activity in the upper airway. CPAP treatment works by keeping the airway open during sleep with a gentle stream of air blown through a nasal mask. Each of these treatments may produce minor side effects, which resolve with simple measures or with the discontinuation of treatment. Occasional rashes, headaches and nausea have been associated with the capsule treatment, but no serious side effects have been seen. CPAP treatment can cause a runny nose or a dry throat in some users.

AS YOUR CONSULTANT TOLD YOU, PLEASE DO NOT DRIVE IF YOU FEEL SLEEPY OR TIRED

- I agree to participate in this study.
- I have read this consent form and Patient/Subject Information Sheet and had the opportunity to ask questions about them.
- I agree for notice to be sent to my General Practitioner about my participation in this study.
- I agree to the provision of any clinically significant information to be sent to my General Practitioner.
- I understand that I am under no obligation to take part in this study and that a decision not to participate will not alter the treatment that I would normally receive.
- I understand that I have the right to withdraw from this study at any stage and that to do so will not affect my treatment.
- I understand that this is non-therapeutic research from which I cannot expect to derive any benefit.

Name of Patient: Signature of Patient: Date:
Signature of Investigator: Date:

Edinburgh Sleep Centre,
Ward 48, Royal Infirmary of
Edinburgh
1 Lauriston place
Edinburgh
EH3 9YW

Dear

RE:

The above named patient has, as you know, been attending my sleep clinic and is currently under diagnosis for the obstructive sleep apnoea/hypopnoea syndrome (OSAHS). Your patient has kindly agreed to enter a randomised controlled trial of sleepiness and daytime performance, involving a sleep study and two daytime testing sessions at the Edinburgh Sleep Centre. Your patient will be randomised to receive one month of treatment with the continuous positive airway pressure (CPAP) device or one month of an oral treatment, and will be offered the standard treatment for OSAHS, CPAP therapy, at completion of or withdrawal from the study. Participation in this study will not delay treatment even for capsule-treated patients, as only patients awaiting CPAP treatment have been approached.

The study has the approval of the Lothian Health Board Medical Ethics Committee. It is important that the nature of the tablet therapy is not divulged to the patient, but equally I recognise that it is important that you have immediate access to information about the capsules if this is required in an emergency. I thus enclose a sealed envelope containing information about the capsules. I would be grateful if you can let me know if you need to open this envelope during the study. After the end of the study the envelope and its contents can be destroyed.

I can assure you that the capsules being used are unlikely to cause significant side effects. Please do not hesitate to contact me if you require any further information.

Yours sincerely,

NEIL J. DOUGLAS

Professor of Respiratory & Sleep Medicine

APPENDIX 2

CONTENTS:


STOP
STOP
VOLUNTEERS WANTED
CAN YOU SPARE FOUR HOURS OF YOUR TIME TO HELP WITH A RESEARCH PROJECT IN THE ROYAL INFIRMARY OF EDINBURGH?
WE ARE CONDUCTING RESEARCH ON A NEW PC BASED DRIVING SIMULATOR AND ARE LOOKING FOR MALES AGED 30 to 60 TO HELP.
THE STUDY IS NON INVASIVE. NO NEEDLES OR DRUGS INVOLVED.
IF YOU SPEAK ENGLISH AS YOUR FIRST LANGUAGE, AND YOU ARE NOT AN ENROLLED STUDENT THEN PLEASE CONTACT LYNNE ANDERSON BY PHONING:
0131 536 4192
OR E-MAILING:
Lynne.Anderson@ed.ac.uk

Edinburgh Sleep Centre,
Ward 48, Royal Infirmary of
Edinburgh
1 Lauriston place
Edinburgh
EH3 9YW

Dear

Further to our recent conversation we write to ask you whether you would be kind enough to help with a medical research project assessing performance on a driving simulator.

Chest, Heart and Stroke Scotland, has funded a three-year project based in the Edinburgh Sleep Centre, Royal Infirmary of Edinburgh, to evaluate whether performance on a driving simulator accurately reflects 'real life' driving. We are studying the performance of people with the sleep apnoea/hypopnoea syndrome (SAHS), a condition known to affect driving ability, and need to compare their results with members of the normal healthy population of identical age and sex. We can assure you that the research is not painful and will involve you attending the Edinburgh sleep Centre for one half day.

Further information about the study is contained within the enclosed information sheet and consent form. Please phone Miss Lynne Anderson on 0131 536 4192 if you have other unanswered queries about the study, or impartial advice can be obtained from Dr. Tom Mackay of the Sleep Centre on 0131 536 2355.

We would be most grateful if you could complete the attached response form and return it in the enclosed SAE to let us know if you might be interested. If you already feel happy to take part in the study, having read the information sheet, please also sign and return the consent form. We also ask that you complete the enclosed questionnaire and return it with your response form, so we can determine if you fit the criteria for the study.

Yours sincerely,

L Anderson, MA, Research Associate
Dr TW Mackay, Consultant, MRCPE
Professor N J Douglas, Consultant Physician, FRCPE

INFORMATION SHEET

LABORATORY-BASED DRIVING TASK STUDY

The study

You have been asked to participate in a study looking at driving performance on a PC based driving simulator. In this study we are comparing the performance of people suffering from the obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and normal healthy people who are identical in age and sex.
The results of this study will be used to improve our knowledge about how driving performance differs between sufferers and non-sufferers of OSAHS and will help in the management of patients with this syndrome.
The study is funded by the Chest, Heart and Stroke Scotland charity.

The procedures

Once we have received the questionnaire back, if you still fit the criteria and match up with a OSAHS sufferer, a time will be arranged for you to attended the Edinburgh Sleep Centre for a half day.

You will be asked to complete questionnaires about your everyday health, and complete concentration tests resembling puzzles, in addition to 'driving' on the simulator. The tests will involve being 'wired up' with skin sensors that detect brainwaves, and being video recorded whilst on the driving simulator.
We can assure you that none of the tests are invasive or painful. The tests should be able to be completed in around 4 hours.

Further information

Impartial advice can be obtained from Dr. TW Mackay, Edinburgh Sleep Centre, WD 48, Royal Infirmary (tel. 0131 536 2355).

If you agree to take part in this study it is understood that you can withdraw at any time. If you understand the requirements and procedures of the study and agree to take part, please sign the consent form.

Edinburgh Sleep Centre,
Ward 48, Royal Infirmary of
Edinburgh
1 Lauriston place
Edinburgh
EH3 9YW

Dear Sir or Madam:

I am a research associate for the University of Edinburgh currently based in the Edinburgh Sleep Centre in the Royal Infirmary of Edinburgh, and I am writing to ask if you would please consider placing the enclosed advert on your notice board.

Here at the Sleep Centre we conduct research in a condition called the sleep apnoea/hypopnoea syndrome, which causes sleepiness and is known to affect driving performance in sufferers before treatment is established.

We are currently conducting research with a PC based driving simulator to investigate whether the driving simulator can detect differences in driving performance before and after treatment in sufferers of this condition.

However, we require healthy volunteers to act as control subjects for our study so that we can determine if the simulator can also detect differences in performance between sufferers and non-sufferers.

We are writing to a variety of places in and around Edinburgh and would be most grateful for your help.
If you have any questions or queries about the advert please do not hesitate to contact me on 0131 536 4192 or by e-mailing me at Lynne.Anderson@ed.ac.uk

Yours faithfully,

Lynne Anderson
Research Associate to Professor N.J. Douglas

Name:..... Date of Birth: .....

SLEEP/ WAKE QUESTIONNAIRE

Please find enclosed a questionnaire for you to fill in and return.

For most questions several options are available, please circle the answer that is most appropriate.

All answers will remain confidential.

Thank you for your co-operation.

Are you a student? YES NO

Is English your first Language? YES NO

ABOUT YOU

Name: ..... Date of Birth : .....

Address : ..... Tel No: .....

..... Gender : Male / Female

..... Number of Children: .....

Height:..... ft and inches/ metres Weight:.....stones / kg

Collar Size : ..... inches / cm Age: .....years

Marital Status: single / married / divorced / widowed

Do you have regular bedpartner? Yes / No

Occupation:
current ..... for..... years
previous ..... for..... years
previous ..... for..... years
previous ..... for..... years

Do you perform shift-work or night work? Yes / No

If so, please specify shift rotation pattern and how long you are on each shift

.....

.....

.....

Are you a: smoker / non-smoker / ex-smoker for ..... years

Tobacco use:

cigarettes Number per day ..... tea
cigars Number per day .....
tobacco (own rolled) Oz. per week ..... beer
tobacco (pipe) Oz. per week ..... wine

Caffeinated and alcoholic drinks:

cups per week .....
coffee cups per week .....
pints per week .....
glasses per week .....
spirits drinks per week .....
sherry/port glasses per week .....

Please list below all medications, including sleeping pills and inhalers, which you are currently taking

Name of medicine	**Dose**	**Name of medicine**	**Dose**
1.....	.....	6.....	.....
2.....	.....	7.....	.....
3.....	.....	8.....	.....

Have you ever had any of the following conditions or operations?
Please circle those applicable to you.

Asthma *Chronic bronchitis* *Emphysema* *Hay fever*

High blood pressure *Stroke* *Heart attack* *Angina*

Nasal congestion *Nose operations* *Throat operations* *Broken nose*

Kidney/ Liver problems *Diabetes* *Thyroid problems* *Epilepsy*

Depression/ Anxiety *M.E./ Chronic fatigue syndrome* *Nervous breakdown*

Have you any other health problems, which might be relevant? If so, please give details below.

.....

.....

.....

YOUR SLEEP PATTERN

Please give a single 'best guess' answer to the following:	**Weeknights**	**Weekends**
1. What time do you usually go to bed at night?	.....	.....
2. How long does it usually take you to fall asleep at night?	.....	.....
3. What time do you usually get up in the morning?	.....	.....
3. How many hours of *actual sleep* do you usually get at night (This may be different than the number of hours you spend in bed).....		.....
4. Do you usually have problems with awakenings from sleep (Excluding visits to the toilet)?	Yes / No	Yes / No
5. How long do you usually spend asleep during the day and evening?	.....	.....

EVENTS DURING SLEEP

Please tick one column for each question to let us know about the presence and frequency of the following sleep-related problems in the recent past. Your bedpartner, if applicable, may be a helpful witness for these.

	Never	Rare (1-3 nights per month)	Occasional (1-2 night per week)	Often (3-4 nights per week)	Frequent or Always (5-7 nights per week)	Don't Know
6. Snoring						
7. Breathing pauses						
8.Choking, gasping or suffocating attacks						
9. Excessive Movements						
10. Jerking of legs or arms						
11. Coughing						
12. Wheezing						
13. Frequent awakenings to use the toilet						

Snoring

14. If you snore, is the volume level: Quiet / Moderate / Heavy
(heard in bedroom only) (heard outside bedroom)

15. If you snore, is this: When on back only / On back and side / all positions

DAYTIME EVENTS

16. How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose ***the most appropriate number*** for each situation.

Scale

0 = would **never** doze
1 = **slight** chance of dozing
2 = **moderate** chance of dozing
3 = **high** chance of dozing

Situation	Chance of Dozing
Sitting and reading	.....
Watching TV	.....
Sitting, inactive in a public place (e.g. a theatre or a meeting)	.....
As a passenger in a car for an hour without a break	.....
Lying down to rest in the afternoon when circumstances permit	.....
Sitting and talking to someone	.....
Sitting quietly after a lunch without alcohol	.....
In a car, while stopped for a few minutes in traffic	.....
TOTAL	.....

Please tick one column for each question to let us know about the presence and frequency of the following daytime events in the recent past, after a normal nights sleep.

	Never	**Rare (1-3 days per month)**	**Occasional (1-2 days per week)**	**Often (3-4 days per week)**	**Frequent or Always (5-7 days per week)**	**Don't Know**
17. Unrefreshed by sleep in the morning						
18. Sleepiness in day or evening						
19. Disruption to working (inc. housework) activities from sleepiness						
20. Disruption to social or family activities from sleepiness						
21. Physical tiredness or exhaustion						
22. Problems in concentrating						
23. Problems with memory						

Please circle the one most appropriate answer, below:

24. During a typical week, how often do you struggle to resist sleep during the day or evening?

Never / rarely / 1-2 times per week / 3-6 times per week / Every day / More than once per day

25. During a typical week, how often do you actually fall asleep during the daytime (9 am to 5 pm)?

Never / rarely / 1-2 times per week / 3-6 times per week / Every day / More than once per day

26. During a typical week, how many times might you have a nap during the evening (5 to 11 pm)?
Never / rarely/ 1-2 times per week/ 3-6 times per week/ Every evening/ More than once per evening

Driving

27. Do you hold a driving licence? Yes / No

28. If yes, is this licence: Car / HGV / PSV
(circle all that apply)

29. Do you drive to and from work? Yes / No

30. Is driving essential for your job? Yes / No

33. How many miles do you drive annually (include business and personal driving)?

0 – 500 / 501 – 5,000 / 5,001 – 15,000 / more than 15,000 miles

34. Over the past year, how frequently have you experienced the following problems whilst driving? Please tick one column for each question.

	Never	Rarely	Occasionally	Frequently	Always
Feeling sleepy on long journeys (more than 1 hour)					
Feeling sleepy on short journeys (less than 1 hour)					

35. Have you ever nodded off whilst driving? Yes / No

36. Please tell us below of any driving incidents, by filling in the number of events you have experienced over the last year, within each box

	Caused by sleepiness	Unrelated to sleepiness
Pulled off the road because of sleepiness		Not applicable
Near-miss accidents (e.g. veering out of lane, running a red traffic light or failing to give way at a junction, running off the road)		
Collisions		

OTHER PROBLEMS

Please circle any of the following events that you have ever experienced:

Hallucinations or vivid dreams whilst still conscious, occurring at sleep onset or on awakening

Paralysis or inability to move, occurring at sleep onset or on awakening

Muscular weakness or collapse whilst laughing or during strong emotions

Sensation of restlessness or crawling in legs, relieved by standing or walking

Bed-wetting (as an adult)

Sleepwalking

37. If you are an adult, have you experienced any changes in your sex drive or sexual function?

Increased / Unchanged / Decreased

38. Have you experienced any recent changes in weight?

Increased / Unchanged / Decreased by ..... kg / lbs over .....years

39. Are you excessively irritable or short tempered? Yes / No

40. Do you feel depressed or 'low'? Yes / No

THANK YOU FOR YOUR HELP

APPENDIX 3

CONTENTS:

SF-36 HEALTH SURVEY

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general would you say your health is:

(Circle one)

Excellent.....1

Very good.....2

Good.....3

Fair.....4

Poor.....5

2. Compared to one year ago, how would you rate your health in general now?

(circle one)

Much better now than one year ago.....1

Somewhat better now than one year ago.....2

About the same as one year ago.....3

Somewhat worse now than one year ago.....4

Much worse now than one year ago.....5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking **more than a mile**	1	2	3
h. Walking **half a mile**	1	2	3
i. Walking **one hundred yards**	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

		YES	NO
a.	Cut down on the **amount of time** you spent on work or other activities	1	2
b.	**Accomplished less** than you would like	1	2
c.	Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(circle one)

Not at all.....1

Slightly.....2

Moderately.....3

Quite a bit.....4

Extremely.....5

7. How much bodily pain have you had during the past 4 weeks?

(circle one)

None.....1

Very mild.....2

Mild.....3

Moderate.....4

Severe.....5

Very severe.....6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

Not at all.....1

A little bit.....2

Moderately.....3

Quite a bit.....4

Extremely.....5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks –

(circle one number on each line)

	All of the Time	Most of the Time	A good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of life?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and low?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks , how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc)?

(circle one)

All of the time.....1

Most if the time.....2

Some of the time.....3

A little of the time.....4

None of the time.....5

11. How TRUE or FALSE is each of the following statements for you?

(circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get ill more easily than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Name: Date:

FUNCTIONAL OUTCOMES OF THE SLEEP QUESTIONAIRE (FOSQ)

Some people have difficulty performing everyday activities when they feel tired or sleepy. The purpose of this questionnaire is to find out if you generally have difficulty carrying out certain activities because you are too sleepy or tired. In this questionnaire, when the words "sleepy" or "tired" are used, it means the feeling that you can't keep your eyes open, your head is droopy, that you want to "nod off", or that you feel the urge to take a nap. The words do not refer to the tired or fatigued feeling you may have after you have exercised.

DIRECTIONS: Please put a tick (3) in the box for your answer to each question. Select only one answer for each question. Please try to be as accurate as possible. All information will be kept confidential.

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
1 Do you have difficulty concentrating on the things you do because you are sleepy or tired?		☐	☐	☐	☐
2 Do you generally have difficulty remembering things, because you are sleepy or tired?		☐	☐	☐	☐
3 Do you have difficulty finishing a meal because you become sleepy or tired?		☐	☐	☐	☐
4 Do you have difficulty working on a hobby (for example, sewing, collecting, gardening) because you are sleepy or tired?	☐	☐	☐	☐	☐

		(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
5	Do you have difficulty doing work around the house (for example, cleaning the house, doing laundry, taking out the rubbish, repair work) because you are sleepy or tired?	☐	☐	☐	☐	☐
6	Do you have difficulty operating a motor vehicle for short distances (less than 100 miles) because your sleepy or tired?	☐	☐	☐	☐	☐
7	Do you have difficulty operating a motor vehicle for long distances (greater than 100 miles) because your sleepy or tired?	☐	☐	☐	☐	☐
8	Do you have difficulty getting things done because you are too sleepy or tired to drive or take public transportation?	☐	☐	☐	☐	☐
9	Do you have difficulty taking care of financial affairs and doing paperwork (for example, writing cheques, paying bills, keeping financial records, filling out tax forms, etc) because you are sleepy or tired?	☐	☐	☐	☐	☐
10	Do you have difficulty performing paid or volunteer work because you are sleepy or tired?	☐	☐	☐	☐	☐
11	Do you have difficulty maintaining a telephone conversation because you become sleepy or tired?	☐	☐	☐	☐	☐

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
12 Do you have difficulty visiting with your family or friends in <u>your</u> home because you become sleepy or tired?	☐	☐	☐	☐	☐
13 Do you have difficulty visiting with your family or friends in <u>their</u> home because you become sleepy or tired?	☐	☐	☐	☐	☐
14 Do you have difficulty doing things for your family or friends because you are too sleepy or tired?	☐	☐	☐	☐	☐

	(4) No	(3) Yes, a little	(4) Yes, moderately	(5) Yes, extremely
15 Has your relationship with family, friends or work colleagues been affected because you are sleepy or tired?	☐	☐	☐	☐

In what way has your relationship been affected?

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
16 Do you have difficulty exercising or participating in a sporting activity because you are too sleepy or tired?	☐	☐	☐	☐	☐
17 Do you have difficulty watching a film or videotape because you become sleepy or tired?	☐	☐	☐	☐	☐

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
18 Do you have difficulty enjoying the theatre or a lecture because you become sleepy or tired?	☐	☐	☐	☐	☐
19 Do you have difficulty enjoying a concert because you become sleepy or tired?	☐	☐	☐	☐	☐
20 Do you have difficulty watching TV because you are sleepy or tired?	☐	☐	☐	☐	☐
21 Do you have difficulty participating in religious services, meetings or a group or a club because you are sleepy or tired?	☐	☐	☐	☐	☐
22 Do you have difficulty being as active as you want to be in the evening because you are sleepy or tired?		☐	☐	☐	☐

23 Do you have difficulty being as active as you want to be in the morning because you are sleepy or tired? ☐ ☐ ☐ ☐

24 Do you have difficulty being as active is you want to be in the afternoon because you are sleepy or tired? ☐ ☐ ☐ ☐

24 Do you have difficulty keeping pace with others your own age because you are sleepy or tired? ☐ ☐ ☐ ☐

	(1) Very low	(2) Low	(3) Medium	(4) High
26 How would you rate your general level of activity?	☐	☐	☐	☐

Functional Outcomes of Sleep Questionnaire (FOSQ)

EPWORTH SLEEPINESS SCALE

MW Johns. Sleep 1991, 14(6), 540-5.

Name: Study:

Date:

How likely are you to doze of or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way if life in recent times. Even if you have not done some of these things try to work out how they would have effected you. Use the following scale to choose the most appropriate number for each situation.

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

SITUATION	Chance of dozing
Sitting reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car, when stopped for a few minutes in the traffic	

Thank you for your co-operation

SYMPTOM QUESTIONNAIRE

Name:
Date:

We would like to know which, if any, night time or daytime symptoms associated with sleep apnoea you have experienced in the last month.

Please tick a column for each symptom to let us know if it is present and how severe it has been for you.

(The don't know column will be useful for some symptoms if you have no partner to witness night-time events, if you are unemployed or retired).

	Not present	**An infrequent problem**	**A frequent problem**	**A Constant problem**	**Don't know or N/A**
Snoring in sleep					
Breathing pauses in sleep					
Choking attacks in sleep					
Unrefreshed by night time sleep					
Falling asleep in the daytime					
Falling asleep in the evening					
Tiredness					
Feeling sleepy whilst driving					
Falling asleep when driving					
Feeling depressed and 'low'					
Low sex drive					
Excessive irritability with friends, colleagues or family					
Concentration problems					
Forgetfulness					
Falling asleep at work					
Poor performance at work					
Other					

DRIVING HISTORY QUESTIONNAIRE 1

We would like to know about your experience of driving in the **past 5 years**. This information is entirely confidential and will not be passed to insurers, police or other authorities. Please complete all of this section.

1. How many years have you been able to drive? _____

2. Approximately how many miles per year do you drive? _____miles

3. Is driving required by your occupation? Please tick ☐ YES ☐ NO

4. In an average week how many days do you drive? Please tick ☐ 5+ ☐ 3-4 ☐ 1-2 ☐ Less frequently

5. We would like to know about your ability to drive long distances (>75 miles) in the **last five** years, compared to other drivers. Please tick a single column

	VERY GOOD	GOOD	AVERAGE	POOR	VERY POOR
ABILITY TO DRIVE LONG DISTANCES SAFELY					

6. We would like to investigate how sleepiness is related to road accidents. The definitions of accident types are as follows:

Near Miss Accident-	Almost had a collision but avoided at last moment
Minor Accident -	Collided with property or person, but no people injured
Major Accident-	Collided with property or person, and people were hurt

In the past **5 years** how many of each of the following events happened to you?

	NEAR MISS ACCIDENT	MINOR ACCIDENT	MAJOR ACCIDENT
NUMBER OF EVENTS IN ALL			
NUMBER OF THESE CAUSED BY SLEEPINESS			

Please follow the example given below, to give a short description of all the accidents you have had in the last **5 years.**

Date of accident	Time of accident	Road type	Weather conditions	How long had you been driving when accident happened	Were other cars involved	Was anyone hurt
1.2.99	About 10.00am	Motor-way	Snowing and windy	About 20 mins	Yes	No
Please give a brief description I was driving to work, and slid on some black ice and I hit the car in front.						

Date	Time of accident	Road type	Weather conditions	How long had you been driving when accident happened	Were other cars involved	Was anyone hurt
Please give a brief description						

Date	Time of accident	Road type	Weather conditions	How long had you been driving when accident happened	Were other cars involved	Was anyone hurt
Please give a brief description						

Date	Time of accident	Road type	Weather conditions	How long had you been driving when accident happened	Were other cars involved	Was anyone hurt
Please give a brief description						

DRIVING HISTORY QUESTIONNAIRE 2

We would like to know about your experience of driving in the **last month**. This information is entirely confidential and will not be passed to insurers, police or other authorities. Please complete all of this section.

1. How many years have you been able to drive? _____

2. Approximately how many miles per year do you drive? _____Miles

3. Is driving required by your occupation? Please tick □ YES □ NO

4. In an average week how many days do you drive? Please tick □5+ □ 3-4 □ 1-2 □ Less frequently

5. We would like to know about your ability to drive long distances (>75 miles) in the **last month**, as compared to other drivers. Please tick a single column

	VERY GOOD	GOOD	AVERAGE	POOR	VERY POOR
ABILITY TO DRIVE LONG DISTANCES SAFELY					

6. We would like to investigate how sleepiness is related to road accidents. The definitions of accident types are as follows:

Near Miss Accident- Almost had a collision but avoided at last moment
Minor Accident - Collided with property or person, but no people injured
Major Accident- Collided with property or person, and people were hurt

In the **past month** how many of each of the following events happened to you?

	NEAR MISS ACCIDENT	MINOR ACCIDENT	MAJOR ACCIDENT
NUMBER OF EVENTS IN ALL			
NUMBER OF THESE CAUSED BY SLEEPINESS			

In the **past 5 years** how many of each of the following events happened to you?

	NEAR MISS ACCIDENT	MINOR ACCIDENT	MAJOR ACCIDENT
NUMBER OF EVENTS IN ALL			
NUMBER OF THESE CAUSED BY SLEEPINESS			

Please follow the example given below, to give a short description of all the accidents you have had in the last **5 years.**

Date of accident	Time of accident	Road type	Weather conditions	How long had you been driving when accident happened	Were other cars involved	Was anyone hurt
1.2.99	About 10.00am	Motor-way	Snowing and windy	About 20 mins	Yes	No
Please give a brief description I was driving to work, and slid on some black ice and I hit the car in-front.						
Date	Time of accident	Road type	Weather conditions	How long had you been driving when accident happened	Were other cars involved	Was anyone hurt
Please give a brief description						
Date	Time of accident	Road type	Weather conditions	How long had you been driving when accident happened	Were other cars involved	Was anyone hurt
Please give a brief description						

Name: **DOB:** **Date:** **Study:**

COMPUTER QUESTIONNAIRE

Please read the questions below and circle the appropriate answer(s).

1. Do you use a computer in your place of work?

   Yes No Not applicable

2. In an average week how many days do you use a computer for work?

   5+ 3-4 1-2 Less frequently

3. Do you have access to a computer at home?

   Yes No

4. In an average week how many days do you use a computer for leisure purposes?

   5+ 3-4 1-2 Less frequently

5. If you use a computer what do you use it for, please circle all that apply:

   Word processing Spreadsheets Home Finances Games

   Internet E-mail Other please specify

6. Do you use your computer to play games?

   Yes No

7. In an average week how many days do you use a computer for playing games?

   5+ 3-4 1-2 Less frequently Don't play games

8. Other than a computer do you have any computer consoles?

   Yes, please specify

   No

THANK YOU

KAROLINSKA SLEEPINESS SCALE

Please circle the number below that best describes how you feel right now.

1	2	3	4	5	6	7	8	9
Extremely alert		Alert		Neither alert nor sleepy		Sleepy – but no difficulty remaining awake		Extremely sleepy – fighting sleep

CPAP SIDE EFFECTS QUESTIONNAIRE

Name:
Date:

1. **In the last month, have you had any problems associated with using CPAP**
   (Please circle) Yes / No

2. **Please tick a box for each of the following problems to let us know how severe the problems are for you.**

	Problem not present	Problem present, but not affecting CPAP use	Problem present, limiting CPAP use	Problem present, stopping CPAP use	Problem present, even before CPAP use
Nasal stuffiness/nose bleeds					
Dry throat					
Wake up with mask off					
Red or soar eyes					
Difficulty in falling asleep or frequent wakenings					
Stomach bloating or 'wind'					
Chest Wheeze					
Difficulty in exhaling with mask					
Sore or rubbing mask					
Leaking of air from mask					
Unpleasant appearance of CPAP equipment					
Excessive noise from CPAP unit (for you or your partner)					
Inconvenience not worth the benefits					
Other (please specify any other problem and it's severity)					

PLEASE CHECK THAT ALL APPROPRIATE SECTIONS OF THIS FORM ARE FILLED IN

CAPSULE SIDE EFFECT QUESTIONNAIRE

Name:
Date:

3. In the last month, have you had any problems associated with taking the capsule?
(Please circle) Yes / No

4. Please tick a column for each of the following problems to let us know how severe the problems are for you.

	Problem not present	Problem present, but not affecting taking of capsule	Problem present, capsule not taken every night	Problem present, stopping capsule intake	Problem present, even before capsule treatment
Dry throat					
Difficulty in falling asleep or Frequent wakenings					
Nausea					
Headaches					
Dizziness					
OTHERS, please specify any other problems and there severity					

THANK YOU FOR YOUR HELP

TREATMENT SATISFACTION QUESTIONNAIRE

NAME:

DATE:

We would like to know how useful and how convenient you have found your current treatment. Please circle a number from 1 to 10 on the scale below to indicate your experience.

1. How effective is your current treatment at improving your symptoms?

U s e l e s s
completely ineffective

Extremely effective

1 2 3 4 5 6 7 8 9 10

2. How acceptable do you find your treatment?

U s e l e s s
completely ineffective

Extremely effective

1 2 3 4 5 6 7 8 9 10

3. How satisfied overall are you with your current treatment?

U s e l e s s a n d
completely ineffective

Extremely effective

1 2 3 4 5 6 7 8 9 10

4. How much have you been able to use your current treatment over the last month? Please indicate an average number of nights per week, and an average number of hours on the nights when treatment has been used.

Nights per week _____nights

Hours per nights_____hours

5. For how long did you use your treatment for last night?

_____ hours

National Adult Reading Test (NART)

CHORD	SUPERFLUOUS
ACHE	SIMILE
DEPOT	BANAL
AISLE	QUADRUPED
BOUQUET	CELLIST
PSALM	FACADE
CAPON	ZEALOT
DENY	DRACHM
NAUSEA	AEON
DEBT	PLACEBO
COURTEOUS	ABSTEMIOUS
RAREFY	DETENTE
EQUIVOCAL	IDYLL
NAÏVE	PUERPERAL
CATACOMB	AVER
GOALED	GAUCHE
THYME	TOPIARY
HEIR	LEVIATHAN
RADIX	BEATIFY
ASSIGNATE	PRELATE
HIATUS	SIDEREAL
SUBTLE	DEMESNE
PROCREATE	SYNCOPE
GIST	LABILE
GOUGE	CAMPANILE

APPENDIX 4

CONTENTS:

Edinburgh Sleep Centre,
Ward 48, Royal Infirmary of
Edinburgh
1 Lauriston place
Edinburgh
EH3 9YW

Dear

We write to ask you whether you would be kind enough to help with a research study which is investigating how sleepiness is associated with road traffic accidents.

As a sufferer of the sleep apnoea/hypopnoea syndrome we would appreciate it if you could take 15 minutes of your time to complete the enclosed *'Driving Survey'* asking about your driving history in the last few years. Even if you do not drive we would appreciate if you could fill in the first question. All information that you give us will remain **completely confidential** and will not be passed on to the police, insurers or other authorities and we can assure you it will **not** affect the treatment you receive in any way.

By helping us with this Survey Study, we will be better able to understand how sleepiness affects driving.

Please return the survey to us in the self addressed envelope.

If you have any questions regarding the survey please call Miss Lynne Anderson on 0131 536 4192.

Thank you very much for your help it is greatly appreciated.

Yours sincerely,

Miss L Anderson, MA, Research Associate
Dr TW Mackay, Consultant, MRCPE
Professor N J Douglas, Consultant Physician, FRCPE

Edinburgh Sleep Centre,
Ward 48, Royal Infirmary of
Edinburgh
1 Lauriston place
Edinburgh
EH3 9YW

Dear

We are randomly writing to people in Scotland to ask you whether you would be kind enough to help with a research study which is investigating how sleepiness is associated with road traffic accidents.

At the Edinburgh Sleep Centre in the Royal Infirmary of Edinburgh, we conduct research in a condition called the sleep apnoea/hypopnoea syndrome, which causes sleepiness and is known to affect driving performance in suffers before treatment is established. We are currently investigating how driving history compares between sufferers and other people in the community. We hope you will help us by being a community normal subject.

We would appreciate it if you could take 10 minutes of your time to help this medical research by completing the enclosed *'Community Sample Driving Survey'* asking about your driving history in the last few years. Even if you do not drive we would appreciate if you could fill in the first question. All information that you give us will remain **completely confidential** and will not be passed on to anyone out with the sleep centre and we can assure you the information will be used only to help us better understand how sleepiness is associated with driving performance and road traffic accidents.

If you have any questions concerning this survey, please call Miss Lynne Anderson on 0131 536 4192, or impartial advice can be obtained from Dr. Tom Mackay of the Sleep Centre on 0131 536 2355.

We would be most grateful if you could complete the questionnaire and return it in the enclosed self-addressed envelope.

Yours sincerely,

L Anderson, MA, Research Associate
Dr TW Mackay, Consultant, MRCPE
Professor N J Douglas, Consultant Physician, FRCPE

Driving Survey

This questionnaire should take 10-15 minutes to complete; all the answers will remain completely confidential and will not be passed on to insurers or the police, and will not affect your treatment in any way. Please try and answer all the questions as accurately as possible, however if you are unsure of the exact answer to any of the questions please answer as best as you can.

Your time and help are greatly appreciated

THANK YOU.

Do you hold a Full drivers Licence? NO YES

If NO please return the survey now. If YES please complete the rest of the survey.

YOU AND CPAP

1. Are you still using your CPAP machine? Please Circle

NO YES

2. If you are not using your CPAP machine when did you stop? _____month _____year

3. Apart from CPAP are you currently using any other treatment for your snoring/sleep apnoea?
Please Circle

Y E S p l e a s eN O s p e c i f y
_____

4. How many nights a week do you currently use your CPAP machine?
Please circle one number
0 1 2 3 4 5 6 7

5. When you use your machine, how many hours do you sleep with it?.....hrs

6. Have you been diagnosed with any other sleep disorders? Please circle

N O Y E S p l e a s e specify_____

SLEEPINESS

7. How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? Even if you have not done some of these things, try to work out how they would affect you both NOW you are using CPAP and BEFORE you started CPAP therapy.

Use the following scale to choose the most appropriate number for each situation.

Scale		
0	=	would never doze
1	=	slight chance of dozing
2	=	moderate chance of dozing
3	=	high chance of dozing

Try to think how you would have been affected in these situations both now and before you started CPAP therapy

SITUATION	Chance of dozing NOW	BEFORE CPAP
Sitting reading		
Watching TV		
Sitting, inactive in a public place (e.g. a theatre or a meeting)		
As a passenger in a car for an hour without a break		
Lying down to rest in the afternoon when circumstances permit		
Sitting and talking to someone		
Sitting quietly after lunch without alcohol		
In a car, when stopped for a few minutes in the traffic		

8. Since starting CPAP are you:
Please Circle one answer

Much more sleepy / More sleepy / About the same / Less sleepy / Much less sleepy

DRIVING HISTORY

We would like to investigate how sleepiness is related to road accidents. In the following sections we will ask you questions concerning your driving performance both before you started using CPAP and now that you are on treatment. This information is entirely confidential and will not be passed to insurers, police or other authorities.

9. How long have you held a full drivers license.....yrs.

BEFORE STARTING CPAP THERAPY

The following questions are referring to your driving experiences in the 2 years before you started on CPAP therapy. Although you may not remember exactly, please try your best to answer the questions.

10. Was driving required by your occupation? Please circle

YES NO

11. In an average week how many days did you drive? Please circle

5+ 3-4 1-2 Less frequently

12. Before you started CPAP therapy had you ever felt sleepy while driving? Please circle

Never / Occasionally / Often / Daily / Every Journey

13. Before you started CPAP therapy how many times did you feel sleepy while driving?

times ☐

14. Before you started CPAP therapy did you ever fall asleep while driving? Please circle

Never / Occasionally / Often / Daily / Every Journey

15. Before you started CPAP therapy how many times have you fallen asleep while driving?

times ☐

16. We would like to know about your ability to drive SHORT distances (less than 75 miles), and LONG distances (more than 75 miles) in the 2 years before you started CPAP therapy, compared to other drivers.

Please tick one box each for short and long.

	VERY GOOD	GOOD	AVERAGE	POOR	VERY POOR
Ability to drive short distances safely	☐	☐	☐	☐	☐
Ability to drive long distances safely	☐	☐	☐	☐	☐

17. The definitions of accident types are as follows:

Near Miss Accident- Almost had a collision but avoided at last moment
Minor Accident - Collided with property or person, but no people injured
Major Accident- Collided with property or person, and people were hurt

In the 2 years before you started using CPAP therapy how many of each of the above events have happened to you? Please write the numbers in all boxes.

	NEAR MISS ACCIDENT	MINOR ACCIDENT	MAJOR ACCIDENT
NUMBER OF THESE			
NUMBER OF THESE CAUSED BY SLEEPINESS			

18. Before starting CPAP therapy if you had any accidents we would also like to know at what time approximately, the accidents you entered in the table above happened. Please enter the number of accidents you have had in the different time bands. Please write the number in each box.

	6am +	9am +	12pm+	3pm+	6pm+	9pm+	12am+	3am +
Near miss accidents								
Minor accidents								
Major accidents								

If you did not have any accidents please tick ☐

19. Again if you had any accidents in the 2 years before starting CPAP therapy we would like to know the number of accidents that occurred on each of the following types of road.
Please write the number in each of the boxes.

	Motor Way/ Dual Carriageway	A class single carriageway	B class country road	Built-up / Urban road	Other –please state
Near miss accidents					
Minor accidents					
Major accidents					

If you did not have any accidents please tick ☐

DRIVING HISTORY SINCE STARTING CPAP THERAPY

The following questions are referring to your driving experiences in the last 2 years that you have been using CPAP. Although you may not remember exactly, please try your best to answer the questions.

20. Is driving required by your occupation? Please circle

YES NO

21. In an average week how many days do you drive? Please circle

5+ 3-4 1-2 Less frequently

22. When you use CPAP do you ever feel sleepy while driving? Please circle

Never / Occasionally / Often / Daily / Every Journey

23. When you use CPAP how many times have you felt sleepy while driving?

times ☐

24. When you use CPAP do you ever fall asleep while driving? Please Circle

Never / Occasionally / Often / Daily / Every Journey

25. When you use CPAP how many times have you fallen asleep while driving?

times ☐

26. We would like to know about your ability to drive SHORT distances (less than 75 miles), and LONG distances (more than 75 miles) in the last 2 years that you have been using CPAP, compared to other drivers.

Please tick one box each for short and long.

	VERY GOOD	GOOD	AVERAGE	POOR	VERY POOR
ABILITY TO DRIVE SHORT DISTANCES SAFELY	☐	☐	☐	☐	☐
ABILITY TO DRIVE LONG DISTANCES SAFELY	☐	☐	☐	☐	☐

27. The definitions of accident types are as follows

Near Miss Accident-	Almost had a collision but avoided at last moment
Minor Accident -	Collided with property or person, but no people injured
Major Accident-	Collided with property or person, and people were hurt

In the last 2 years that you have been using CPAP how many of each of the above events have happened to you? Please write the number in all boxes.

	NEAR MISS ACCIDENT	MINOR ACCIDENT	MAJOR ACCIDENT
NUMBER OF THESE			
NUMBER OF THESE CAUSED BY SLEEPINESS			

28. After starting CPAP therapy if you had any accidents we would also like to know at what time approximately, the accidents you entered in the table above happened. Please enter the number of accidents you have had in the different time bands. Please write the number in each box.

	6am +	9am +	12pm +	3pm+	6pm+	9pm+	12am +	3am +
Near miss accidents								
Minor accidents								
Major accidents								

If you have not had any accidents please tick ☐

29. Again if you had any accidents in the 2 years since starting CPAP therapy we would like to know the number of accidents that occurred on each of the following types of road.
Please write the number in each of the boxes.

	Motor Way/ Dual Carriageway	A class single carriageway	B class Country Road	Built-up / urban road	Other – please specify
Near miss accidents					
Minor accidents					
Major accidents					

If you have not had any accidents please tick ☐

THANK YOU FOR YOUR CO-OPERATION

Driving Survey

The questionnaire should take 10-15 minutes to complete, all the answers will remain completely confidential and will not be passed on to insurers or the police, and will not affect your treatment in any way. Please try and answer all the questions as accurately as possible, however if you are unsure of the exact answer to any of the questions please answer as best as you can.

Your time and help are greatly appreciated

THANK YOU.

Do you hold a Full drivers Licence? YES NO

If NO please return the survey now. If YES please complete the rest of the survey.

SLEEPINESS

1. How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? Even if you have not done some of these things, try to work out how they would affect you.

Use the following scale to choose the most appropriate number for each situation.

Scale

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Try to think how you would have been affected in these situations.

SITUATION	Chance of dozing
Sitting reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car, when stopped for a few minutes in the traffic	

DRIVING HISTORY

We would like to investigate how sleepiness is related to road accidents. In this section we will ask you questions concerning your driving. This information is entirely confidential and will not be passed to insurers, police or other authorities.

2. How long have you held a full drivers license.....yrs.

The following questions are referring to your driving experiences in the last 2 years. Although you may not remember exactly, please try your best to answer the questions.

3. Is driving required by your occupation? Please circle

YES NO

4. In an average week how many days do you drive? Please circle

5+ 3-4 1-2 Less frequently

5. In the last two years have you ever felt sleepy while driving? Please circle

Never / Occasionally / Often / Daily / Every Journey

In the last two years how many times have you felt sleepy while driving?

☐ times

7. In the last two years have you ever fallen asleep while driving?

Never / Occasionally / Often / Daily / Every Journey

In the last two tears how many times have you fallen asleep while driving?

☐ times

9. We would like to know about your ability to drive SHORT distances (less than 75 miles), and LONG distances (more than 75 miles) in the last two years, compared to other drivers.

Please tick one box each for short and long.

	VERY GOOD	GOOD	AVERAGE	POOR	VERY POOR
ABILITY TO DRIVE SHORT DISTANCES SAFELY	☐	☐	☐	☐	☐
ABILITY TO DRIVE LONG DISTANCES SAFELY	☐	☐	☐	☐	☐

10. The definitions of accident types are as follows:

Near Miss Accident-	Almost had a collision but avoided at last moment
Minor Accident -	Collided with property or person, but no people injured
Major Accident-	Collided with property or person, and people were hurt

In the last two years how many of each of the above events have happened to you? Please write the numbers in all boxes.

	NEAR MISS ACCIDENT	MINOR ACCIDENT	MAJOR ACCIDENT
NUMBER OF THESE			
NUMBER OF THESE CAUSED BY SLEEPINESS			

11. If you had any accidents in the last two years we would also like to know at what time approximately, the accidents you entered in the table above happened. Please enter the number of accidents you have had in the different time bands. Please write the number in each box.

	6am +	9am +	12pm+	3pm+	6pm+	9pm+	12am+	3am +
Near miss accidents								
Minor accidents								
Major accidents								

12. Again if you had any accidents in the last two years we would like to know the number of accidents that occurred on each of the following types of road.
Please write the number in each of the boxes.

	Motor Way/ Dual Carriageway	A class single carriageway	B class country road	Built-up / Urban road	Other – Please state
Near miss accidents					
Minor accidents					
Major accidents					

THANK YOU FOR YOUR CO-OPERATION

Personal Information

Year of birth: _____

SEX: MALE FEMALE

Community Sample Driving Survey

This questionnaire should take 10-15 minutes to complete, all the answers will remain completely confidential and will not be passed on to insurers or the police. Please try and answer all the questions as accurately as possible, however if you are unsure of the exact answer to any of the questions please answer as best as you can.

Your time and help are greatly appreciated

THANK YOU.

Do you hold a Full drivers Licence? YES NO

If NO please return the survey now. If YES please complete the rest of the survey.

SLEEPINESS

1. How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? Even if you have not done some of these things, try to work out how they would have affected you in the last 2 years

Use the following scale to choose the most appropriate number for each situation.

Scale

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Try to think how you would have been affected in these situations.
Chance of dozing

SITUATION	In the last 2 years
Sitting reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car, when stopped for a few minutes in the traffic	

EVENTS DURING SLEEP

Please tick one column for each question to let us know about the presence and frequency of the following sleep-related problems in the recent past. Your bedpartner, if applicable, may be a helpful witness for these.

	Never	Rare (1-3 nights per month)	Occasional (1-2 night per week)	Often (3-4 nights per week)	Frequent or Always (5-7 nights per week)	Don't Know
2. Snoring						
3. Breathing pauses						
4. Choking, gasping or suffocating attacks						
5. Excessive movements						
6. Jerking of legs or arms						
7. Coughing						
8. Wheezing						
9. Frequent awakenings to use the toilet						

10. If you snore, is the volume level: Quiet / Moderate / Heavy (he

bedroom)

11. If you snore, is this: When on back only / On back and side / all positions

12. Have you ever been diagnosed with a sleep disorder? Please circle

NO YES please specify_____

Are you currently using any treatment for a diagnosed sleep disorder? Please circle

NO YES please specify

_____

DRIVING HISTORY

We would like to investigate how sleepiness is related to road accidents. In this section we will ask you questions concerning your driving. This information is entirely confidential and will not be passed to insurers, police or other authorities.

14. How long have you held a full drivers license.....years.

The following questions are referring to your driving experiences in the last 2 years. Although you may not remember exactly, please try your best to answer the questions.

15. Is driving required by your occupation? Please circle

YES NO

16. In an average week how many days do you drive? Please circle

5+ 3-4 1-2 Less frequently

17. In the last 2 years have you ever felt sleepy when driving? Please circle

Never / Occasionally / Often / Daily / Every Journey

18. In the last 2 years how many times have you felt sleepy while driving?

☐ times

19. In the last 2 years have you ever fallen asleep when driving? Please circle

Never / Occasionally / Often / Daily / Every Journey

20. In the last 2 years how many times have you fallen asleep while driving?

☐ times

21. We would like to know about your ability to drive SHORT distances (less than 75 miles), and LONG distances (more than 75 miles) in the last 2 years, compared to other drivers.

Please tick one box each for short and long.

	VERY GOOD	GOOD	AVERAGE	POOR	VERY POOR
ABILITY TO DRIVE SHORT DISTANCES SAFELY	☐	☐	☐	☐	☐
ABILITY TO DRIVE LONG DISTANCES SAFELY	☐	☐	☐	☐	☐

22. The definitions of accident types are as follows:

Near Miss Accident- Almost had a collision but avoided at last moment
Minor Accident- Collided with property or person, but no people injured
Major Accident- Collided with property or person, and people were hurt

In the last 2 years how many of each of the above events have happened to you? Please write the numbers in all boxes.

	NEAR MISS ACCIDENT	MINOR ACCIDENT	MAJOR ACCIDENT
NUMBER OF THESE			
NUMBER OF THESE CAUSED BY SLEEPINESS			

23. In the last 2 years if you had any accidents we would also like to know at what time approximately, the accidents you entered in the table above happened. Please enter the number of accidents you have had in the different time bands. Please write the number in each box.

	6am +	9am +	12pm+	3pm+	6pm+	9pm+	12am+	3am +
Near miss accidents								
Minor accidents								
Major accidents								

If you have not had any accidents please tick ☐

24. Again if you had any accidents in the last 2 years we would like to know the number of accidents that occurred on each of the following types of road.
Please write the number in each of the boxes.

	Motor Way/ Dual Carriageway	A class single carriageway	B class Country Road	Built-up / urban road	Other – please specify
Near miss accidents					
Minor accidents					
Major accidents					

If you have not had any accidents please tick ☐

THANK YOU FOR YOUR CO-OPERATION

APPENDIX 5

Poster presentation:

Anderson L, Vennelle M, MacKay TW, Engleman HM, Douglas NJ.

Controlled study of reported driving impairment in patients with the sleep apnoea/ hypopnoea syndrome

A174; American Thoracic Society 99th Annual Meeting, Seattle, 2003