DAYTIME FUNCTION AFTER CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) THERAPY FOR THE SLEEP APNOEA/HYPOPNOEA SYNDROME (SAHS)

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Ph.D.
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1995
I declare that this thesis was composed by myself, and is based on studies conducted by myself, with the help detailed within the Acknowledgments, within the Unit of Respiratory Medicine (RIE), University of Edinburgh, and the Scottish National Sleep Laboratory, between 1989 and 1995.

HM Engleman 21st October 1995
Dedicated to my fathers, Steve Engleman and Pat McKim
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ACKNOWLEDGMENTS

My sincere gratitude goes to the supervisors of this project, Professors Neil Douglas and Ian Deary, who provided me with patient guidance and encouragement during the course of this project. I have been fortunate indeed to receive the tutelage of two such skilled and distinguished scientists, who generously communicated some of their wide experience and knowledge of research methods. I am specifically indebted to Professor Douglas for his close involvement in the studies of this thesis, and for a wide-ranging education in clinical and experimental techniques in sleep research. Professor Deary’s explanations of statistical and psychometric methodology were particularly helpful. My supervisors unstintingly made themselves available to discuss all aspects of the research process, often at short notice, and their enthusiasm and integrity in the pursuit of knowledge have made a lasting impression.

Colleagues and collaborators helped throughout the course of this project. Katherine Cheshire performed baseline cognitive testing in some of the early parallel-group patients, and trained me in the administration of tests. Peter Wraith has provided expert computing, programming and statistical skills. Both Ian Smith and Alec Rosie mechanically adapted CPAP units for patients’ use during studies. Ann Chiswick performed auditory evoked potential assessments, while Kathleen Gough arranged for blood pressure equipment to be loaned and downloaded. The help of Nima Asgari-Jirhandeh and Andrew McLeod, medical students on project placement, was invaluable in collating and coding the questionnaire and polysomnographic data collected in the CPAP patient survey, and entering these on computer spreadsheet. The night staff of the laboratory, Carol Hoy, Marjorie Vennelle and Lindsay Agius, used their considerable talents to obtain clinical polysomnography on patients participating in studies, and to perform the skilled task of titrating CPAP pressures. Helen Biernaska, Joyce McPhee, Kristina Stedul and Siân Finch spent long and boring hours scoring sleep records. Both Sascha Martin and Ruth Kingshott provided practical help in performing some patient assessments, the former in particular while I was on maternity leave. The day nurses, Joan MacKenzie and Jane Elder, educated SAHS patients in the mechanisms of CPAP treatment, encouraged patients to comply with CPAP therapy and managed side-effects of therapy. Although the services listed above are material, many of these colleagues have also provided the important but invisible contribution of their good humour, support and friendship.
None of the studies in this thesis could have been performed without the generosity and altruism of their participants, individual patients with SAHS, who consented to undergo long and taxing days of psychometric testing in the laboratory. The contact with SAHS patients that I received during study assessments were among the most pleasurable and indeed educational experiences of this project.

The extended families of which I am privileged to be a member have made this thesis feasible by providing both babysitting and meals during my bouts of typing. My gratitude for these and other services is particularly due to my parents, Kathie and Steve Engleman, my parents-in-law, George and Vivien Venters, my sister-in-law Mhairi Venters and my father Pat McKim, who first showed me that science can be fun. Finally, my dear husband Gavin and son Joe have put up with my physical and attentional absences, and have continued to run a household, provide me with a wonderful family life and keep my world turning.
### Glossary and Abbreviations

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<td>ABP</td>
<td>Ambulatory blood pressure</td>
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<td>AEPs</td>
<td>Auditory evoked potentials</td>
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<td>AHI</td>
<td>Apnoea+hypopnoea index</td>
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<td>AVLT</td>
<td>Auditory-verbal learning test</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<td>BSERs</td>
<td>Brainstem evoked responses</td>
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<td>BVRT</td>
<td>Benton visual retention test</td>
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<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<td>CPAP</td>
<td>Continuous positive airway pressure</td>
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<td>DBP</td>
<td>Diastolic blood pressure</td>
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<td>EEG</td>
<td>Electrocencephalography</td>
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<td>EMG</td>
<td>Electromyography</td>
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<td>EOG</td>
<td>Electro-oculography</td>
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<td>GHQ-28</td>
<td>General health questionnaire-28</td>
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<tr>
<td>HAD</td>
<td>Hospital anxiety and depression</td>
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<td>IQ</td>
<td>Intelligence quotient</td>
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<td>IT</td>
<td>Inspection time</td>
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<td>MAP</td>
<td>Mean arterial pressure</td>
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<td>MMPI</td>
<td>Minnesota multiphasic personality inventory</td>
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<td>MSLT</td>
<td>Multiple sleep latency test</td>
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<td>MWT</td>
<td>Maintenance of wakefulness test</td>
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<td>NART</td>
<td>National adult reading test</td>
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<td>PASAT</td>
<td>Paced auditory serial addition test</td>
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<td>POMS</td>
<td>Profile of mood states</td>
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<tr>
<td>REM</td>
<td>Rapid eye movement (sleep)</td>
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<tr>
<td>RT</td>
<td>Reaction time</td>
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<td>RVIP</td>
<td>Rapid visual information processing</td>
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<td>SAHS</td>
<td>Sleep apnoea/hypopnoea syndrome</td>
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<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
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<tr>
<td>SNSL</td>
<td>Scottish National Sleep Laboratory</td>
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<td>UARS</td>
<td>Upper airway resistance syndrome</td>
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<td>UMAACL</td>
<td>UWIST mood adjective checklist</td>
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<td>UPPP</td>
<td>Uvulopalatopharyngoplasty</td>
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<td>WAIS(-R)</td>
<td>Wechsler adult intelligence scale (revised)</td>
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ABSTRACT OF THESIS

The sleep apnoea/hypopnoea syndrome (SAHS) is characterised by obstruction of the airway during sleep, resulting in repetitive nocturnal breathing pauses, which provoke both oxygen desaturations and arousals from sleep. SAHS is associated with daytime deficits of excessive daytime sleepiness, cognitive impairment and psychological distress, probably as a result of these nocturnal events. The treatment of choice for SAHS is continuous positive airway pressure (CPAP) therapy, a mechanical treatment in which positive airstream pressure is administered to the upper airway through a nasal mask, splinting the airway open and preventing the nocturnal events of SAHS. A limited number of small clinical studies have indicated improvements in daytime function following CPAP therapy, but these have not been well-controlled, particularly in the area of cognitive performance. This thesis contributes controlled studies to the knowledge-base describing CPAP's effects on daytime function. A pilot study employing a parallel-group design in 37 patients showed improvements in objective daytime sleepiness and psychological distress with CPAP, but not cognitive function. This null finding however might have resulted from inter-individual variability. To rectify this, a randomised placebo-controlled crossover study of daytime function on CPAP and on an oral placebo was conducted in 64 patients with a wide range of severity of SAHS. This study showed CPAP-related improvement in symptoms, objective and subjective daytime sleepiness, cognitive performance and well-being. The use of balanced treatment order within a subgroup of 16 patients with mild SAHS (apnoea+hypopnoea index 5 to 14.9) allowed investigation of the minimum illness severity at which daytime benefits from CPAP are observed. Such mild patients demonstrated improvements in symptom score, cognitive performance and psychological distress on CPAP. Although the minimum illness severity meriting CPAP treatment has not been well defined, these data support the efficacy of CPAP at the lowest severity range of SAHS. A randomised study of auditory evoked potentials in 18 patients showed trends only towards improved neurophysiological function after CPAP, and a randomised crossover study of ambulatory blood pressure in 13 patients showed reduced blood pressure on CPAP only in a subgroup of patients who lacked significant dipping of nocturnal blood pressure. The nocturnal determinants of daytime dysfunction in SAHS were explored by correlating factors extracted from polysomnographic and daytime function variables. The principal component extracted from the polysomnographic variables was found to correlate significantly with daytime sleepiness and with intellectual function, corroborating weak or moderate associations between the severity of nocturnal events and daytime deficits. Patients'
perceptions of benefit from CPAP, and their self-reported driving competence, were examined in a survey of 215 CPAP users. Patients reported wide-ranging improvements in nocturnal and daytime symptoms of SAHS, and showed a significant improvement in mileage adjusted rates of road traffic incidents following CPAP. Although side-effects of CPAP were common, these were minor in nature. Thus patients’ reports corroborated the daytime benefits from CPAP documented in the project’s controlled studies. The studies of this thesis demonstrated objective and subjective improvements in symptoms, daytime sleepiness, cognitive performance and well-being in SAHS patients treated with CPAP.
Chapter 1: CLINICAL BACKGROUND OF THE SLEEP APNOEA/HYPOPNOEA SYNDROME (SAHS)

The sleep apnoea/hypopnoea syndrome (SAHS) has been recognised as a clinical entity only in the last 30 years (Gastaut et al 1966), but evidence accumulating since this time has built up a picture of a relatively common illness with significant morbidity and mortality. SAHS may be loosely defined as consisting of restricted airflow during sleep, with resulting symptoms (Gould et al 1988). This introductory chapter provides background on the physiological and clinical features of SAHS. It begins with a description of the primary physiological events typical of SAHS, and the evolution of definitions and measures to describe the syndrome. Literature detailing patients' clinical presentation, physiological mechanisms, morbidity and mortality, epidemiology and treatments in SAHS will be briefly described in order to provide background information on the syndrome, before the specific daytime impairments of SAHS are reviewed in Chapter 2.

1.1 Nocturnal events in SAHS

The central events of SAHS are recurrent episodes of restricted airflow, demonstrated as pauses in breathing known as apnoeas and hypopnoeas, and usually precipitated by obstruction of the upper airway during sleep. These primary events are associated with immediate physiological consequences in the form of oxygen desaturation and sleep fragmentation (Guilleminault et al 1978). Apnoeas and hypopnoeas frequently result in desaturations in arterial oxygen levels (Block et al 1979) and are usually terminated by short-lasting electroencephalographic arousals from sleep (Sullivan and Issa 1980) which allow the recommencement of normal respiration.

Thus SAHS patients experience a triad of nocturnal events, with restricted respiration causing both transient hypoxaemia and sleep disruption. This cycle of events, illustrated in Figure 1.1, can be repeated as many as 100 times during each hour slept (Stradling and Phillipson 1986), provoking significant disruption to oxygenation and sleep quality.
Figure 1.1: One minute of polysomnography in a patient with severe SAHS
Chapter 1: Clinical background of SAHS

Figure 1.1 shows one minute of typical polysomnography in a patient with severe SAHS. The first 3 channels labelled AIRFLOW, THOR RES and ABDO RES show breathing pattern, measured by oronasal airflow, thoracic and abdominal breathing movements respectively. The subsequent 7 channels of polysomnography (EOG, MIX, EEG and EMG) represent neurophysiological recording and reflect sleep quality. The last channel, SaO2, represents arterial oxygen saturation. Three consecutive episodes of flattening of breathing movements are shown as hypopnoeas. The first two hypopnoeas result in dipping of oxygen saturation and are each terminated by a microarousal from sleep, represented in an increase in amplitude and frequency of neurophysiological parameters. These nocturnal events, as described in Chapter 2, may individually or collectively contribute to the daytime problems also associated with the syndrome.

The hypoxaemia of SAHS, measured by ear oximetry, is of a transient but repetitive nature. Nocturnal studies on large groups of mixed severity SAHS patients have shown means of 282 3% oxygen desaturations per night (Roehrs et al 1989) and that an average 18% of the night is spent at less than 90% saturation (Poceta et al 1992, Guilleminault et al 1988). Desaturation events, though short-lasting, can be quite severe, with mean nadirs in saturation from SAHS samples reported in the range 65 to 76% (Greenberg et al 1987, Guilleminault et al 1988, Bédard et al 1991a, Poceta et al 1992, Kribbs et al 1993b), but much lower levels being seen in severe patients, particularly during REM sleep (Sullivan and Issa 1980).

In SAHS patients, discreet electroencephalographic arousals from sleep have been shown to correspond closely with apnoea (Roth et al 1980, Sullivan and Issa 1980) and apnoea+hypopnoea frequency (Cheshire et al 1992, Poceta et al 1992). These repetitive arousals impair both quantity and quality of sleep, scored according to the averaged, epoch-based system of Rechtschaffen and Kales (1968). Sleep efficiency index, the ratio of wakefulness to sleep, is low in SAHS and is consistently reported in the range 80%-86% (Roehrs et al 1989, Stepanski et al 1984, Greenberg et al 1987, Cheshire et al 1992, Kribbs et al 1993b). Normal sleep quality, as described by Rechtschaffen and Kales' (1968) sleep stage proportions, comprises approximately 5% stage 1, 50% stage 2, 20% slow wave sleep (stages 3+4) and 20-25% stage REM (Erwin et al 1984). In SAHS the sleep stage distribution is shifted towards the light end of the non-REM spectrum, showing 13-69% of stage 1, but only 0-4% slow wave sleep and 9-14% stage REM (Roth et al 1980, Stepanski et al 1984, Roehrs et al
Chapter 1: Clinical background of SAHS


Many patients also show other immediate physiological consequences of increased airway resistance, such as elevations of pulmonary and systemic blood pressure (Schroeder et al 1978), increases in heart rate and cardiac arrhythmias (Schroeder et al 1978, Shepard 1989, Hoffstein and Mateika 1994).

1.2 Diagnosis of SAHS
Disturbances in respiratory pattern in the form of apnoeas and hypopnoeas, as SAHS' name suggests, form the basis for definitions describing the syndrome. The technical definitions describing these nocturnal events, and in turn providing diagnostic criteria, are still evolving.

The original observations of Guilleminault et al (1978) defined an apnoea in adults as 10 seconds or longer of absent airflow signal, and offered as a diagnostic definition of the then 'sleep apnoea syndrome' an apnoea frequency (or apnoea index) of 5 or more apnoeas per hour slept. While this technical definition for apnoea has been universally adopted, subsequent research has demonstrated that Guilleminault et al's early (1978) diagnostic definition may be insufficient.

Apnoeas are conceptualised as the precipitant producing both oxygen desaturations and arousals from sleep within a triad of nocturnal events, so that an index of severity of apnoea should index the severity of desaturation and arousal. However, apnoea frequency has been shown to underrepresent 4% desaturation frequency by a factor of four (Block et al 1979) and to correlate poorly with electroencephalographic arousal from sleep (Gould et al 1988), leaving doubt that apnoea index is the most sensitive overall measure of the nocturnal events of SAHS.

A second problem in early diagnostic descriptions of sleep apnoea syndrome is found in the high incidence within normal subjects of frequent apnoeas during sleep, particularly in the elderly and in men (Block et al 1979). Berry et al (1984) reviewed 13 studies of nocturnal sleep in normals to show that by Guilleminault's definition, up to 72% of healthy subjects, as found in one study, could be diagnosed with sleep apnoea syndrome. These findings of apnoeas in the sleep of normals called into question the discriminability of the diagnostic criterion forwarded by Guilleminault et al (1978) in separating healthy normals from patients. They also emphasised the
importance of supporting symptoms, a prerequisite in any syndrome, in a diagnostic formulation for SAHS.

Subsequent refinement of definitions relating nocturnal breathing abnormalities, their immediate physiological effects and clinical symptoms have been supplied in our group by Gould et al (1988), who has validated measures of nocturnal breathing disruption and formulated diagnostic definitions describing the sleep apnoea/hypopnoea syndrome (SAHS).

The cessation of airflow during an apnoea reflects total occlusion of the airway, but episodes of restriction in the airway with persisting airflow may nevertheless precipitate arterial oxygen desaturations (Block et al 1979, Gould et al 1988, Whyte et al 1992) and arousals from sleep (Gould et al 1988). Such subtotal disturbances in respiration are known as hypopnoeas (Block et al 1979, Gould et al 1988) and have been variously defined as 50% reductions in airflow with (Berry et al 1986, Guilleminault et al 1988, Lamphere et al 1989, Kribbs et al 1993b) or without (Roehrs et al 1989) coincident desaturation, or as 50% reductions in respiratory movement (Gould et al 1988, Douglas 1993, Whyte et al 1992).

In our own group, Gould et al (1988) proposed and validated a technical description of hypopnoeic activity, defined by a 50% or greater reduction in thoracoabdominal movement compared to the preceding stable baseline, measured by the semi-quantitative method of inductance plethysmography. This hypopnoea definition subsumes almost all apnoeas, shows good inter-rater reliability for both number (r=0.98) and duration (r=0.98) of hypopnoeic events (Whyte et al 1992) and correlates better with both desaturation events and with arousals from sleep than 50% reduction in thermistor airflow, which underestimates both types of disruption.

Gould et al (1988) compared the frequency of apnoeas+hypopnoeas by this validated definition in normals and patients with clinical features of SAHS, showing that 50 patients had a minimum apnoea+hypopnoea index (AHI) of 16 and 33 normals had a maximum AHI of 14. Patients subdivided into groups experiencing predominantly apnoeic or hypopnoeic events could not be differentiated in terms of desaturation, arousal frequency or symptoms. In order to reflect the naturally occurring discontinuity between controls and patients, Gould et al (1988) suggested that an AHI of 15 should be used as a clinical diagnostic threshold. The addition to this definition
of SAHS of at least two coexistent clinical symptoms prevented the anomalous diagnosis of healthy normals as suffering from the syndrome.

Recent research may extend the continuum of sleep apnoea syndromes to include a partial variant, ‘upper airway resistance syndrome’ (UARS: Guilleminault et al 1992, 1993), similar to the ‘heavy snorers’ disease’ first proposed by Lugaresi et al (1978). UARS contains no requirement for apnoeas or hypopnoeas or for desaturation during sleep. The central event in UARS is increased resistance in the upper airway, often (Guilleminault et al 1991, Hoffstein et al 1991) but not invariably (Guineminault et al 1992, 1993) associated with snoring, resulting in frequent arousal from sleep. UARS is diagnosed when episodes of high resistance in the upper airway, frequently seen with snoring (Liistro et al 1991, Stoohs and Guilleminault 1991), and arousal from sleep occur with the daytime symptom of excessive daytime sleepiness.

While symptoms are vital in the diagnosis of SAHS, neither these nor physical examination alone are sufficiently reliable predictors of SAHS (Hoffstein and Szalai 1993). The diagnosis of SAHS can be made only with the benefit of overnight monitoring to demonstrate disordered respiratory patterns in sleep. However, as indicated above, the techniques employed for nocturnal recordings and the outcome measures used to diagnose SAHS are not standardised, differing methods providing advantages and disadvantages. The codependence of the triad of nocturnal events allows clinicians to recognise abnormal activity during sleep through a variety of physiological systems.

Diagnostic sleep studies can be accomplished through limited recordings consisting of overnight ear oximetry (Stradling and Crosby 1991) or of monitoring snoring sounds and heart rate (Penzel et al 1990). Such studies offer the advantage of being relatively cheap, portable, and comfortable for subjects, thus facilitating large-scale home-based screening studies (Stradling and Crosby 1991). Many researchers have relied on 4% desaturation frequency as their primary measure of respiratory abnormality (Telakivi et al 1988, Berry et al 1986, Stradling and Crosby 1991). A certain degree of diagnostic accuracy is sacrificed in limited studies, as oximetry alone, scored by computer and thus free from inter- and intra-rater variation, results in false negative diagnosis of SAHS in 15% of patients when defined by >5 4% desaturations per hour in bed, and 28% when defined as >20 4% desaturations per hour in bed (Douglas et al 1992).
Many laboratories use more detailed polysomnography incorporating thermistor measures of oronasal airflow and inductance plethysmography of respiratory movement, to differentiate and resolve apnoeic and hypopnoeic events. Neurophysiological recordings of EEG, EOG and EMG together facilitate the conventional Rechtschaffen and Kales (1968) scoring of sleep state and the monitoring of short arousals from sleep. Studies performed without the benefit of EEG monitoring may miss patients with mild SAHS or UARS, in whom frequent EEG arousals may occur without easily measurable respiratory abnormality. Ear oximetry, as in the limited sleep studies, provides a continuous and reliable evaluation of arterial oxygen saturation. Additional monitoring of ECG to detect arrhythmias associated with breathing restriction, tibialis EMG to detect leg movements typical of periodic leg movement syndrome, snoring-detection microphones and upper airway resistance monitoring are sometimes employed. These more elaborate studies are relatively uncomfortable for subjects, incur high running costs in terms both of equipment and staff labour, but offer greater diagnostic sensitivity and specificity (Douglas et al 1992) and may be particularly valuable for patients with borderline abnormality.

1.3 Physiological mechanisms in SAHS
The breathing irregularities seen in SAHS are almost always a result of constriction or obstruction of the upper airway during sleep, this anatomical area being the final common site for a variety of abnormalities of structure and function causing irregular breathing in sleep (Hudgel 1992, Pépin et al 1992, Douglas and Polo 1994). Snoring sounds occur in many healthy sleeping subjects as a result of high inspiratory pressures acting against narrowing of the pharynx, causing vibrations of the muscles of the upper airway. Many clinicians consider snoring to be precursor to SAHS, forming a link in the continuum from normal respiratory function in sleep to SAHS (Lugaresi et al 1978, Guilleminault et al 1991).

The state of sleep establishes a physiological environment wherein other factors can interact to cause airway obstruction. Sleep causes hypotonia of the musculature supporting patency of the upper airway (Orem and Lydic 1978), the lowest tonic muscle activity occurring in REM sleep when partial paralysis of intercostal muscles may contribute to hypoventilation (Tabachnik et al 1981). The respiratory reflexes concerned with maintaining blood gas balance are also damped by sleep, particularly REM sleep (Douglas et al 1982). It has been noted that many SAHS patients' longest breathing pauses and lowest oxygen saturation dips occur in REM sleep (Guilleminault et al 1978). The supine posture adopted by sleeping humans also
contributes to airway obstruction, as it increases the uvular width and narrows the size of the post-palatal airway space, even in healthy non-snorers (Yildirim et al 1991).

Studies of sleeping SAHS patients identify the site of obstruction during breathing pauses at the level of the pharynx (Chaban et al 1988). A number of anatomical abnormalities of the upper airway may contribute to this airway obstruction. Retrognathism (Riley et al 1983), prognathism (Lyberg et al 1989a), micrognathia (Coccagna et al 1978) and tonsillar hypertrophy (Orr and Martin 1981) have been associated with SAHS. Patients with SAHS, studied while awake, have larger soft palates (Lyberg et al 1989b, Stauffer et al 1989), larger tongues (Lowe et al 1986) and overall smaller pharyngeal spaces (Riley et al 1983, Haponik et al 1983, Rivlin et al 1984, Martin et al 1995a) than normals.

The dynamic function of the upper airway, in addition to its structure, is altered in SAHS. The pharyngeal space is supported by muscle groups whose rigidity affects the collapsibility of the airway. The compliance of the pharyngeal soft tissues has been found to be lower in awake snoring controls than in SAHS patients (Brown et al 1985, Gleadhill et al 1991), predisposing SAHS patients to upper airway collapse in sleep. It has been found that the airways of SAHS patients show greatest compliance in REM sleep (Issa and Sullivan 1984). A recent study using acoustic reflection measurement of the oropharyngeal spaces in waking SAHS patients (Martin et al 1995a) suggested that, in addition to having a smaller cross-sectional area at the oropharyngeal junction than normals, SAHS patients showed smaller reductions in airway area after lying down. This finding may reflect muscular ‘defending’ of the upper airway, at least while awake, in SAHS patients.

SAHS has long been associated with obesity, hence its early name of ‘Pickwickian syndrome’. Obesity is a clinical feature in around two-thirds of patients (Guilleminault et al 1989a). Only 11% of the Edinburgh case series were within 10% of their ideal body weight (Whyte et al 1989) and only 20% of the North American patient series were not overweight (Guilleminault et al 1978).

It is thought that obesity mediates narrowing of the upper airway through mass loading of fat deposits on the pharynx (Davies and Stradling 1990, Hoffstein and Mateika 1992). Magnetic resonance imaging techniques have shown SAHS patients to have greater fat deposits in the pharynx than weight-matched controls (Horner et al 1989). That SAHS patients have fatter necks than normals is corroborated by
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Hoffstein and Mateika (1992) who showed that patients individually matched for body-mass index (BMI) and age to controls had an average 2 cm larger neck circumference. Stepwise multiple regression techniques to evaluate the value of factors in predicting sleeping oxygen saturation dip rates have isolated neck circumference as a more important factor than BMI alone (Davies and Stradling 1990), but desaturation rates may not directly equate with breathing or sleep abnormalities (Douglas et al 1992).

Aside from diet, other "lifestyle" factors exacerbating breathing irregularities in sleep include the ingestion of sedatives (Kales et al 1987) and alcohol (Remmers 1984), which may depress central ventilatory drive or decrease muscle tone and thus upper airway patency.

In summary, the aetiology of SAHS is variable, but abnormalities of anatomy and of neuromuscular control, obesity and posture may all contribute to decreased upper airway calibre during sleep. It is likely that the causes of narrowed airway in any one individual are multifactorial. The wide range of causative mechanisms helps to explain the heterogeneity within SAHS patients, many of whom do not conform to the pickwickian archetype. Familial clustering of the symptoms of SAHS, independent of weight factors, has been noted (Mathur and Douglas 1995, Redline et al 1992). In familial SAHS, inherited morphological features of the upper airway may predispose towards airway obstruction during sleep (Mathur and Douglas 1995), whereas in other patients acquired characteristics such as excess weight or alcohol abuse might be more important.

1.4 Clinical presentation

Surveys of case series of patients diagnosed with SAHS have allowed a number of nocturnal and daytime symptoms to be associated with the syndrome.

1.4.1 Nocturnal features

Heavy snoring is an almost omnipresent feature in patients with SAHS, having been found in 100% of the 50 patients in one early case series (Guilleminault et al 1978) and in 97% of the 80 patients reviewed in another series (Whyte et al 1989). Restless sleep, as a result of excessive motor activity in sleep or frequent awakenings from sleep, is reported by 36% (Whyte et al 1989) to 100% (Guilleminault et al 1978) of SAHS patients. This high frequency of reported disturbed sleep in patients explains why some SAHS patients present to sleep clinics with an initial complaint of
insomnia, rather than excessive sleepiness. In the Edinburgh series, unsatisfying sleep was complained of by 35% of patients (Whyte et al 1989). High frequencies of nocturia or even enuresis are associated with SAHS, ranging from 10% (Whyte et al 1989) to 30% (Guilleminault et al 1978) of patients. Complaints of heavy sweating in the night were found in 66% of a series of 200 patients (Guilleminault 1989). Awareness of nocturnal choking episodes, probably due to a return of consciousness at the termination of apnoeas or hypopnoeas, is a frightening symptom reported by 26% of the Edinburgh series and 11% of the Stanford series (Guilleminault 1989). It seems likely that the absence of a partner to report behaviour in sleep, when memory for events can be impaired, will have an effect on reported rates of snoring, nocturnal choking episodes and restlessness in sleep.

1.4.2 Daytime features
By far the most common daytime symptom of SAHS is excessive daytime sleepiness, found in 87% (Whyte et al 1989) and 78% (Guilleminault et al 1978) of patients in two case series. Excessive daytime sleepiness can range in severity from evening naps in front of the television, a common behaviour with increasing age, to irresistible sleeping in such dangerous situations as driving, reported by at least 6% of one series (Whyte et al 1989). It is likely that the sleep disruption of SAHS contributes to the findings of excessive daytime sleepiness.

SAHS patients often report morning headaches, in frequencies from 24% (Whyte et al 1989) to 36% (Guilleminault et al 1978), perhaps as a result of hypercapnia in sleep. Waking hypertension was found or was being treated in around 32% of two case series (Guilleminault et al 1978, Whyte et al 1989). Ankle oedema was reported by 32% and polycythaemia found in 12% of one series (Whyte et al 1989). Sexual dysfunction has been associated with SAHS, with problems of impotence or loss of libido reported by 6% (Whyte et al 1989) and 42% (Guilleminault et al 1978) of patients in two case series.

In addition to excessive daytime sleepiness, patients with SAHS often complain of less specific neuropsychological features during wakefulness: the nature of these features is the main concern of this thesis. The families of 11% (Whyte et al 1989) to 48% (Guilleminault et al 1978) of SAHS patients report personality changes, including increased irritability and emotional outbursts. A high proportion of patients, 82% in one series (Guilleminault et al 1978), experience difficulties with concentration or memory. Indeed, intellectual deterioration can be the major presenting symptom of
SAHS in some individuals (Scheltens et al 1991). Moreover, SAHS patients have been found to experience high frequencies of minor psychiatric disorders such as depression and anxiety, found in 24% and 26% respectively of patients in one series (Guilleminault et al 1978). These affective problems may be a consequence of the chronic and significantly disabling symptoms of SAHS, as may be the high frequencies of employment problems reported by patients (Guilleminault et al 1978, Kales et al 1985).

In summary, the clinical features of the SAHS are highly variable, often non-specific and common to many disorders, but most frequently include snoring and excessive daytime sleepiness. Diagnosis must thus be made through overnight monitoring to demonstrate disordered respiratory function in sleep (Hoffstein and Szalai 1993).

1.5 Mortality and morbidity in SAHS
The respiratory abnormalities in sleep of SAHS may also produce elevations in systemic blood pressure (Schroeder et al 1978), perhaps contributing to higher-than-expected mortality rates in patients with SAHS (Partinen et al 1988). Untreated SAHS carries a risk of death, which appears to be related to the severity of breathing irregularity in sleep. He et al (1988) found in a retrospective case series that patients with more than 20 apnoeas per hour slept had a significantly lower 8-year survival rate than patients with fewer than 20 apnoeas per hour slept. The mortality risks in SAHS have been evaluated by comparing death rates in patients accepting effective treatments, such as tracheostomy or CPAP, to death rates in conservatively-treated patients. Aggressive therapeutic approaches have been found to significantly improve 5-year mortality rates (He et al 1988). Despite the fact that conservatively-treated patients in another retrospective study (Partinen et al 1988) had fewer breathing abnormalities in sleep and were thinner than aggressively-treated patients, 14 out of 127 died during a 5-year follow-up period, yielding a mortality rate of 11 per 100 per 5 years. None of the 71 aggressively-treated patients died, although the two groups had had similar frequencies of vascular and pulmonary disease before treatment assignment.

A further retrospective study found that untreated SAHS patients were more likely to die at night than their treated counterparts (Thorpy et al 1990), raising the possibility of an association between the nocturnal events of SAHS and sudden death. Sixty to eighty percent of SAHS patients may have daytime hypertension (Kales et al 1984) and patients with SAHS can demonstrate intermittent elevations of arterial blood
pressure up to 200 mmHg (Schroeder et al 1978) as well as sinus arrhythmias (Guilleminault et al 1981) occurring in synchrony with breathing pauses during sleep, in contrast to the normal pattern of lowered blood pressure in sleep (Littler et al 1975). Polysomnographic examinations of identified hypertensives have shown excess frequencies of sleep apnoeic subjects in this group (Kales et al 1984). The causes of the cardiovascular problems associated with SAHS are not well understood, but nevertheless it seems possible that dramatic blood pressure swings may result in myocardial infarctions and strokes in patients with SAHS.

Hung et al (1990), using multiple regression analyses, have shown that apnoea frequencies of greater than 5 per hour slept are an independent risk factor for heart attack. Using snoring as a less severe analogue for SAHS (see Section 1.3), epidemiological research has identified a 2.4 times greater risk of ischaemic heart disease and strokes in habitual snorers than in non-snorers (Koskenvuo et al 1987). The odds of vascular death have been calculated by comparing rates of death from cardiovascular accidents in conservatively- and aggressively-treated SAHS patients. Conservatively treated groups show a death rate from cardiovascular accidents at least 4.7 times that of aggressively treated patients (Partinen et al 1988). Studies comparing the rates of vascular problems in groups of SAHS patients suggest that aggressive treatments may protect against morbidity as well as mortality, as conservatively-treated patients have 2.3 times the odds of vascular problems of tracheostomised patients (Partinen and Guilleminault 1990).

All studies on mortality and morbidity in SAHS have been retrospective, with associated methodological problems (Gonzalez-Rothi and Block 1988) including the absence of control patients or poor control matching, patient selection and response biases and difficulties with handling of missing data. While careful interpretation of retrospective studies is mandatory, it does not seem ethical given the volume of research associating untreated SAHS with increased mortality and morbidity to conduct a prospective, controlled trial comparing treated and untreated mortality rates in SAHS (Schmidt-Nowara and Coultas 1988).

Thus, the retrospective studies that are available for evaluating mortality and morbidity in SAHS suggest that the illness brings to its sufferers an increased risk of sudden death, particularly from cardiovascular causes, and a high incidence of raised blood pressure, myocardial infarctions and strokes. This makes it an illness to be taken
seriously, especially when information relating to its relatively common prevalence is considered.

1.6 Epidemiology of SAHS

SAHS is the most common diagnosis for excessively-sleepy patients studied in sleep laboratories (Coleman et al 1982). Clinical case series show the majority of diagnosed patients with SAHS to be middle-aged, often overweight men. Eighty percent of a patient series studied in the Edinburgh laboratory were men, and the median age at diagnosis was 54 years (Whyte et al 1989). In an American series only 4% of SAHS diagnosed-patients were female and the average age of diagnosed patients was 45 years (Guilleminault et al 1978). Probably for these reasons, many cross-sectional community-based studies estimating the prevalence of SAHS have concentrated on the male population. Such studies estimate the prevalence of SAHS in the community in the range of 0.3% to 4% of adult males, although the prevalence of some degree of disordered respiration in sleep is much higher (Lavie 1983, Franceschi et al 1982, Gislason 1987, Stradling and Crosby 1991, Peter et al 1987, Jennum and Sjøl 1992, Bearpark et al 1993, Young et al 1993, Bearpark et al 1995).

The variation in SAHS prevalence in these international studies may be partly explained by genetic factors in the studied populations, but may also result from local differences in diagnostic thresholds defining pathological frequency of breathing disruption in sleep and in nocturnal recording techniques. There is also variation in the emphasis on corroborating symptoms of SAHS in patients with breathing pauses in sleep. Some studies attempt to estimate the prevalence of SAHS, i.e. frequent apnoeas or hypopnoeas in sleep with coexistent symptoms, while other researchers may be investigating the prevalence of breathing irregularities in sleep per se. However, most researchers attempting to quantify the prevalence of sleep-related respiratory disturbance find a surprisingly high proportion of the population to be affected.

About 1% of a sample of Israeli industrial workers were found to have SAHS, after a subsample reporting symptoms of excessive sleepiness underwent polysomnography (Lavie 1983). A prevalence of 1% for SAHS was also obtained in a study of 2518 Italian hospital in-patients, who were screened with the Stanford Sleepiness Scale, a subjective rating for sleepiness, with subsequent polysomnography in excessively sleepy individuals (Franceschi et al 1982). Both of these studies used 10 apnoeas/hour as a diagnostic threshold for defining SAHS. A similar prevalence estimate of 1.3% was made from a Swedish community-based survey, this time using a AHI threshold
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of >30 per hour slept (Gislason 1987). In a sample of 1001 middle-aged British men, overnight oximetry identified 45 men (4.5% of the target population) with >5 4% dips in oxygen saturation per hour in bed who then underwent full polysomnography. Using criteria of >20 4% dips in arterial oxygen saturation per hour of sleep to define SAHS, 3 men (0.3%) were found to have definite SAHS (Stradling and Crosby 1991). The authors of this study describe the identified SAHS cases as "severe", so it seems likely that this prevalence estimate represents a minimum rate.

Higher prevalence rates have been obtained by German and Australian researchers. Almost 10% of a sample of 95 male German workers showed >10 apnoeas per hour in bed (Peter et al 1987), while 8.5% of a larger Australian community-based series of 294 men had a similar level of respiratory disturbances during sleep (Bearpark et al 1993). The prevalence rate of less severe sleep-disordered breathing is even higher. Nine percent of females and 24% of males (Young et al 1993), or 6% of females and 11% of males (Jennum and Sjøl 1992) show respiratory disturbance indices > 5.

The high obtained prevalence rates above reflect disordered respiration in sleep with or without accompanying symptoms, although some subjects showing disordered breathing in sleep might be asymptomatic. The more recent epidemiological studies (Jennum and Sjøl 1992, Young et al 1993, Bearpark et al 1995) have incorporated symptom questionnaires to corroborate the presence of symptoms with disordered breathing patterns in sleep, to better estimate the true prevalence of SAHS.

Both Danish (Jennum and Sjøl 1992) and American (Young et al 1993) research groups have examined nocturnal breathing patterns and symptoms in large samples of more than 600 men and women, aged 30 to 60 years. Frequent sleepiness in addition to >5 respiratory pauses in sleep was reported by 1% of females and 2% of males in the Danish study and 2% of females and 4% of males in the American sample. A similar prevalence rate for suspected SAHS was found with the application of a symptom criterion to the large Australian cohort (Bearpark et al 1995). Three percent of the subjects in that study, all male, complained of frequent daytime sleepiness and showed a respiratory disturbance index > 5.

The epidemiological studies performed yield a wide range of prevalence estimates for SAHS, probably due to differences in sampling methods and diagnostic criteria, but all confirm that SAHS is a common condition. Those studies providing the best documentation of accompanying symptoms of SAHS, despite differences in nocturnal
measurements used, are consistent in indicating that 1-2% of middle-aged females and 2-4% of middle-aged males may suffer from SAHS.

1.7 Treatments for SAHS
1.7.1 Tracheostomy
The sites of upper airway obstructions during sleep can be bypassed by the surgical construction of a tracheostomy. This invasive surgical option was among the earlier treatments used in SAHS, and was offered to patients with severe obstructive SAHS, disabling symptoms of excessive daytime sleepiness, associated cardiac arrhythmias in sleep and extreme nocturnal oxygen desaturations (<40% SaO2) (Guilleminault et al 1981). There is no doubt that tracheostomy prevents respiratory pauses in sleep and associated abnormalities of sleep architecture, improves some nocturnal symptoms such as snoring and restless sleep, and alleviates daytime symptoms such as excessive daytime sleepiness and personality changes (Guilleminault et al 1981). This treatment may also prevent some of the cardiovascular sequelae of SAHS, as long-term vascular morbidity in SAHS patients treated with tracheostomy is lower than that of conservatively-treated patients (Partinen and Guilleminault 1990).

However, tracheostomy carries with it its own substantial morbidity risk. Immediate post-operative complications include excessive wound bleeding and sepsis at the wound site or in the lower respiratory tract. These can lead to a requirement for total tracheostomy revision, which occurred in 16% of patients in one series (Guilleminault et al 1981). Longer-term problems such as chronic infection, granulomatous or position-dependent obstructions of the tracheostomy tube (these sometimes requiring a total tracheostomy revision) and problems with managing secretions, occurred in at least 60% of tracheostomised patients in two series (Guilleminault et al 1981, Conway et al 1981). Psychosocial problems in adjusting to the long-term management of a permanent stoma are common (Guilleminault et al 1981). Therefore, tracheostomy is now a superseded treatment and is reserved only for severe cases of SAHS refractory to other treatments (Guilleminault et al 1989).

1.7.2 Uvulopalatopharyngoplasty (UPPP)
UPPP involves the surgical removal of excess tissue from the oropharynx (Fujita et al 1981), a procedure which may be effective in preventing snoring (Gislason et al 1988) but which has a high failure rate for treating SAHS (Walker et al 1988, Gislason et al 1988, Wetmore et al 1986, Fujita et al 1985). The most common criterion used to assess the success of UPPP is a post-surgical reduction of 50% in apnoea and
hypopnoea frequency in sleep. Using this criterion, success rates for UPPP vary from 9% to 65% (Walker et al 1988, Gislason et al 1988, Wetmore et al 1986, Fujita et al 1985). It may be more pertinent to consider the effectiveness of UPPP in reducing the apnoea/hypopnoea index to below 15 per hour, and in the studies where data presentation allows this, close reading of papers yield success rates of 9% (Walker et al 1988), 33% (Wetmore et al 1986) and 62% (Gislason et al 1988). The comparatively high success rate for the last study is in part due to a less severe patient group (mean AHI 27), 6% of whom had AHIs below 15 before surgery. There appears to be a marked inter-individual variation in the response to UPPP, which may be influenced by preoperative severity of breathing irregularities in sleep (Gislason et al 1988) or by the site of upper airway obstruction (Fujita et al 1985). In addition to inconsistent patient response to the surgery, UPPP involves considerable post-surgical discomfort and the risks of complications such as dysphagia, nasal regurgitation of food, nasal speech and infection (Guilleminault et al 1989).

1.7.3 Drug treatments
A number of drug treatments for SAHS are prescribed, although none has been markedly successful in reducing breathing irregularities in sleep.

Protriptyline:
Protriptyline, a tricyclic anti-depressant, reduces REM sleep duration (Hollister 1978) and increases airway muscle tone (Bonora et al 1985). Conway et al (1982) treated a small sample of 9 patients with protriptyline for 2 to 18 months and found improved measures of breathing irregularity in sleep in 4 of these patients. However, this study provided no control for the effects of weight loss, which may have been a significant factor in the clinical improvement of at least 2 of the 4 successfully-treated cases. A similar study assessing 14 SAHS patients also found improved duration of apnoeas after 1 to 15 months of protriptyline, but again employed no control for potential weight loss during the long follow-up period (Clark et al 1979). In another study, 12 patients were given repeat sleep studies after an average 4 months on protriptyline (Smith et al 1983), during which time the patient group showed a significant loss in weight, but no significant difference in AHI after treatment. Two better-quality studies found no improvement in AHI when the effects of weight loss were limited by a shorter treatment duration of 2 weeks (Brownell et al 1982, Whyte et al 1988).

Likewise, some researchers have documented subjective improvements in daytime symptoms of patients receiving protriptyline (Conway et al 1982), but this response
has not been documented in a patient-blind study, where the expectation of improvement was controlled by employing a placebo limb (Whyte et al 1988). The other study which provided a placebo limb reported in passing improvements in subjective daytime sleepiness, but provided no measurements to corroborate this impression (Brownell et al 1982). Smith et al (1983) assessed daytime sleepiness objectively with a modified multiple sleep latency test and found a significant lengthening of median sleep onset latency, but this patient group's significant weight loss over the treatment period remains a confounding factor when interpreting these results.

Anti-cholinergic side-effects of protriptyline treatment, such as dry mouth, urinary hesitancy and impotence, are relatively common (Brownell et al 1983), and confusional states (Conway et al 1982) and cardiac complications (Clark et al 1979) have also been reported. It is notable that in Conway et al's study (1982), 3 of the 9 patients treated with protriptyline suffered intolerable side-effects and that 6 of the 14 patients in Clark et al's study (1979) experienced complications during protriptyline treatment.

Acetazolamide:
Acetazolamide, a diuretic, may stimulate respiratory responses to hypoxia by inducing metabolic acidosis (Kales et al 1987). In a placebo-controlled, double-blind trial, acetazolamide halved apnoea+hypopnoea frequency in sleep, but daytime symptoms persisted and paraesthesiac side-effects occurred in 8 of 10 patients (Whyte et al 1988). Though the improvement of polysomnographic features was statistically significant, a reduction in AHI from 50 to 26 per hour slept would not normally be considered a clinical success. Another study also found a significant reduction in apnoea, but not hypopnoea, index (Tojima et al 1988), but again the clinical benefit of a drop in mean apnoea index from 25 to 18 per hour slept is dubious. Although the authors of this study reported subjective improvements in daytime and nighttime symptoms of SAHS, the lack of a placebo control in their study weakens the force of this statement.

Medroxyprogesterone:
Drug treatment with medroxyprogesterone, a progesterone derivative, has been advocated in SAHS cases where daytime hypoventilation is a feature (Kryger 1989, Sutton et al 1975), but has not proven effective in other patients (Strohl et al 1981, Rajagopal et al 1986, Cook et al 1989, Orr et al 1979).
Sutton et al (1975) found significant improvements in daytime blood gas values in an uncontrolled study of 10 'Pickwickian' patients, but sleep studies to evaluate the severity of nocturnal events before and after progesterone treatment were not performed. The 9 patients studied by Strohl et al (1981) underwent sleep studies before and after treatment which showed no significant improvement in mean apnoea frequency. However, the authors stated that a subgroup of patients exhibiting daytime hypercapnia had reduced levels of breathing irregularity in sleep during progesterone treatment. The study by Orr et al (1979) also included a subgroup of SAHS patients with pre-progesterone daytime hypercapnia, but technical failures prevented the re-evaluation of most of these patients' blood gases after treatment. However, in contrast to Sutton et al (1975), Orr et al (1979) performed sleep studies before and after treatment, which showed no significant improvement in the frequency of obstructive apnoeas during progesterone treatment. The patients in the studies by Orr et al (1979) and Strohl et al (1975) reported improvements in daytime symptoms such as hypersomnolence, but in the absence of a placebo control the value of subjective impressions of improvement are doubtful. Neither the placebo-controlled crossover trial of Cook et al (1989) nor the withdrawal phase-controlled study of Rajagopal et al (1986), both of which employed short treatment durations which reduced the influence of weight changes, showed improved measures of breathing irregularity in sleep on progesterone.

Steroid-type side-effects of medroxyprogesterone include weight gain, hair loss, gynaeomastia and impotence (Kales et al 1987), with patients' testosterone levels reduced by 75% (Cook et al 1989). In an overwhelmingly male patient population, these feminising side-effects may be unacceptable.

In summary, the available drug treatments for SAHS do not offer proven benefits in terms of improved respiration in sleep and all carry a high risk of unpleasant side-effects.

1.7.4 Weight loss

Weight reduction in obese patients, in whom excess fat on the upper airway may be an important factor in generating respiratory pauses, has been shown to be effective in reducing respiratory abnormalities in sleep (Browman et al 1984, Smith et al 1985). In a single case, a weight loss of 26 kg resulted in a reduction in apnoea index from 60 to 3 per hour slept (Browman et al 1984). A larger sample of 15 overweight patients
losing an average of 10 kg over about 5 months showed a mean fall in apnoea frequency from 55 to 29 per hour (Smith et al 1985). There remains a question as to the sustainability of dietary weight loss in many patients. Some surgeons have recommended gastric bypass surgery in grossly overweight patients as a treatment for SAHS, this method of weight reduction being perhaps more permanent than dietary weight loss. Apnoea indices in a group of 15 patients dropped from an average of 82 to 15 after gastric bypass surgery (Peiser et al 1984), but long-term outcomes from this drastic surgery have yet to be assessed. These studies of weight reduction in SAHS show that breathing irregularities may be reduced by weight loss, but that the magnitude of reduction in breathing irregularities may not be optimal.

1.7.5 Continuous positive airway pressure (CPAP)
Continuous positive airway pressure (CPAP) was developed by Sullivan in the early 1980's (Sullivan et al 1981) and has become the treatment of choice for SAHS, due to its success in reversing respiratory irregularities in sleep and its non-invasive nature (Sullivan and Grunstein 1989, Polo et al 1994). The CPAP apparatus (for an illustration, see Figure 4.4) consists of an electrically-driven blower unit connected to a nasal mask via a flexible hose. The nasal mask is worn in sleep and delivers to the patient a gentle airstream that mechanically "splints" open the upper airway. The pharyngeal space is enlarged under CPAP (Abbey et al 1989) and pharyngeal compliance is reduced (Issa and Sullivan 1984), thereby preventing a collapse of the upper airway during sleep.

CPAP has been demonstrated to be highly effective in abolishing respiratory pauses in sleep, reducing breathing irregularities in 5 patients from an average of 63 apnoeas per hour slept to zero (Sullivan et al 1981), and in 18 patients from an average of 53 apnoeas per hour slept to 3 (Sanders 1984). Arterial oxygen saturation is also improved subsequent to the normalisation of breathing pattern (McEvoy and Thornton 1984). In addition, sleep quality is enhanced by CPAP (Lamphere et al 1989), becoming less fragmented by multiple apnoea-related arousals and resulting in a lengthened total sleep time. Because sleep disruption is minimised, CPAP facilitates the return of normal sleep architecture, including percentages of slow wave sleep and REM. Effective nasal CPAP also eliminates snoring (Berry and Block 1984, Guilleminault et al 1992) and has been shown to significantly improve EEG-arousal index in snorers (Guilleminault et al 1992) and EEG-arousal index, objective daytime sleepiness and slow-wave sleep percentage in non-snorers (Guilleminault et al 1993) with suspected UARS.
Whereas CPAP is an effective treatment for SAHS, its short-term use does not effect a cure for breathing irregularity in sleep, so patients must use CPAP for the foreseeable future. CPAP use has not been found to have carry-over effects after withdrawal on breathing patterns, sleep quality or pharyngeal volume (Collop et al 1991).

As was implied earlier in this chapter, retrospective studies suggest that CPAP may significantly improve survival rates of SAHS patients, although the limited time that CPAP has been in use as a treatment for SAHS reduces the availability of information available on cumulative mortality rates. In a 5-year follow-up study, CPAP treated patients had a significantly better mortality rate that untreated patients (He et al 1988).


Side-effects such as nasal obstruction, airstream-associated conjunctivitis and problems with mask comfort or airstream pressure tolerance are common in CPAP-treated SAHS patients (Nino-Murcia et al 1989) and have been found in around 40% of CPAP-treated patients in a follow-up study (McEvoy and Thornton 1984). However, the side-effects of CPAP are relatively trivial and can be managed effectively with adequate aftercare (Sullivan and Grunstein 1989).

Recent international studies have found that SAHS patients' average CPAP use rates are lower than the 7 or 8 hours per night recommended by clinicians, and are frequently overestimated by patients (Rauscher et al 1993b, Kribbs et al 1993a). Studies in CPAP clinic populations, which include a cross-section of recent and established CPAP users, document average objective compliance rates of approximately 5 hours per night (Krieger 1992, Pépin et al 1995). In other samples, objectively monitored CPAP use has ranged from 3.2 (Kribbs et al 1993a) to 6.7 hours per night (Fleury et al 1994), with early CPAP use being associated with poorest use rates. The higher use rates in selected long-term users (Meurice et al 1994,
Chapter 1: Clinical background of SAHS

Fleury et al 1994) are likely to reflect self-selection on the part of patients, who frequently reject CPAP therapy (Waldhorn et al 1990, Rauscher et al 1991, Fleury et al 1994). Because nightly CPAP treatment requires constant patient effort in remembering to use treatment, motivational factors such as the extent of daytime sleepiness may play a significant role in the take-up rates of CPAP treatment (Rauscher et al 1991).

1.8 Summary

In SAHS, respiratory pauses precipitated by obstructions of the upper airway result in frequent arterial oxygen desaturations and arousals from sleep. The syndrome may be as prevalent as 4% in middle-aged males and is associated with significant mortality and morbidity from cardiovascular causes. The most common symptoms of SAHS are heavy snoring and excessive daytime sleepiness, but positive diagnosis requires nighttime sleep studies with direct or indirect monitoring of respiratory patterns. Surgical treatments have limited usefulness due in the case of tracheostomy to a high independent risk of morbidity and in the case of UPPP to a restricted success in alleviating apnoeas and hypopnoeas. Pharmacological treatments are not of proven benefit and dietary weight loss may not be sustainable in those obese patients for whom it is effective. CPAP, a mechanical therapy that prevents airway obstructions in sleep, has become the treatment of choice for SAHS due to its efficacy in relieving daytime and nighttime features of the illness and due to the benign nature of its side-effects. CPAP's effects on daytime function will be dealt with in more depth in Chapter 3.
Chapter 2:
DAYTIME NEUROPSYCHOLOGICAL FUNCTION IN SAHS

Patients with SAHS, as outlined in Chapter 1, experience a constellation of daytime features in addition to nocturnal events. Three broad areas of neuropsychological function are known to be compromised in SAHS, with patients complaining frequently of excessive daytime sleepiness, cognitive deficit and degrees of psychological distress. These daytime problems can contribute to reduced functioning in a variety of domains, including work efficiency, road safety and psychosocial adjustment. In this chapter I will seek to provide an overview of research studies documenting the daytime problems of SAHS patients, their possible causes and potential reversibility.

The subjective complaint of excessive daytime sleepiness is second only to snoring in frequency as a presenting symptom of SAHS, occurring in 78% (Guilleminault et al 1978) to 87% (Whyte et al 1989) of patients. Patients with SAHS very commonly fall asleep in situations of minimal stimulation, such as watching television or reading, but may also fall asleep under conditions when wakefulness is essential, such as whilst driving (Guilleminault et al 1989). Patients may also report intellectual deterioration. All of the patients reporting daytime sleepiness in one case series (78% of the total sample) complained also of inadequate concentration skills or memory (Guilleminault et al 1978). In one case report, a dementia-like cognitive deterioration was the major presenting symptom (Scheltens et al 1991). Mood problems are common in SAHS, with 48% of the American case series reporting personality changes and 11% of the Scottish SAHS patients or their family members admitting to irritability. It is easy to imagine how these daytime problems can adversely affect a wide range of everyday activity, including social interaction and work achievement.

Patients state that the daytime symptoms of SAHS are more frequently the spur precipitating medical consultation than are nocturnal symptoms. Eighty percent of SAHS patients in one case series sought medical help primarily because of excessive daytime sleepiness or clouded mental states, while only 20% were seen as a result of their own or their spouses' complaints of nocturnal events such as snoring or choking (Guilleminault et al 1978). SAHS patients' bias in reporting daytime problems to medical professionals may reflect individuals' lack of awareness of their breathing pauses during sleep, particularly when a partner is not present to witness these events, or a degree of ignorance of the long-term repercussions of disordered breathing in
sleep. But patients' emphasis on daytime symptoms may also reflect their importance in reducing overall quality-of-life.

Research into the daytime problems of SAHS draws from historically divergent scientific fields, which have evolved distinctive batteries of assessment tools. The study of sleepiness has relied primarily on electrophysiological techniques of measurement, while cognitive function is typically assessed using paper and pen or computer-administered performance testing and psychological distress by self-rated questionnaire. For this reason it is expedient to deal with the three broad areas of daytime deficit in SAHS separately, but the distinction is at least partially artificial because the domains of sleepiness, cognitive performance and psychological wellbeing are interrelated. For instance, sleepiness produces measurable decrements in cognitive performance (Wilkinson et al 1966) and may provoke depression as a result of lowered quality-of-life (Isaac et al 1992), while mood and cognitive performance are highly interrelated (Matthews 1992). Detailed below are primarily case-control studies documenting daytime impairments in the form of sleepiness, cognitive dysfunction and psychological distress.

2.1 Excessive daytime sleepiness
While the great majority of SAHS patients complain of excessive daytime sleepiness, subjective accounts of degree of sleepiness are neither sufficiently specific nor sensitive for research purposes. Because of problems associated with some subjective assessments of sleepiness (Dement et al 1978, Roth et al 1980, Browman and Mitler 1988), a variety of objective instruments for evaluating sleep tendency have been developed, all based on polysomnographic measurements of the latency to sleep during daytime nap opportunities. These instruments have shown that SAHS patients are significantly more sleepy than normals.

The most commonly used objective tool for evaluating daytime sleepiness is the multiple sleep latency test (MSLT; Carskadon et al 1986; Thorpy 1992), which assesses sleep tendency by measuring the actual ability to fall asleep. The test consists of five 20-minute daytime nap opportunities with concurrent polysomnography, spaced at 2 hour intervals starting at 10 am and with the final test at 6 pm. Patients are asked to try to fall asleep in a darkened, quiet room while the latency from lights-out to the first epoch of any sleep stage is measured. The nap duration is limited to a maximum of 20 minutes so that sleep debt will not be eradicated.
The wide use of the MSLT within sleep research has allowed a large database of measurements from individuals of different age-groups and health status to be built up, facilitating the establishment of norms for the primary measure obtained from the MSLT, the mean sleep onset latency of the five naps. A mean sleep onset latency of 5 minutes or less corresponds to a level of sleepiness associated with decrements in performance and irresistible sleep episodes (Carskadon and Dement 1981), so this range is said to indicate pathological sleepiness (Carskadon et al 1986). While most normals have mean sleep latencies greater than 10 minutes (Richardson et al 1982), the range from 5 to 10 minutes represents a 'diagnostic grey zone' of moderate sleepiness (Van den Hoed et al 1981). Case-control studies verify the validity of the MSLT in discriminating between hypersomnolent and normal subjects. In an early study, Dement et al (1978) matched six healthy control subjects for age, sex and weight to 10 SAHS patients, whose mean sleep latency was significantly lower at 3.4 minutes than the controls' 10.8 minutes. In a similar study, 10 patients with a mean apnoea frequency of 57 per hour slept had a mean sleep onset latency of 2.6 minutes, while age-matched healthy controls averaged 12.9 minutes (Roth et al 1980).


An alternative, objective test of daytime sleepiness exists in the form of the maintenance of wakefulness test (MWT), wherein subjects are asked to try to stay awake in a sleep-conducive environment (Mitler et al 1982). Norms have yet to be established for the MWT, but this objective sleepiness test has also been shown to discriminate between normals and hypersomnolent patients. Early studies using the MWT paradigm in small samples of SAHS patients documented mean sleep onset latencies of approximately 11 minutes, significantly lower than the mean 19 minutes found in normals (Mitler et al 1982, Browman and Mitler 1988). Later studies on much larger numbers of SAHS patients (Sangal et al 1992a, Poceta et al 1992) have found mean MWT latencies of 24 and 26 minutes respectively, but do not present control values for comparison.
Patients with SAHS also show elevated scores on a subjective rating of recent napping behaviour, the Epworth sleepiness scale (Johns 1991, 1992, 1993, 1994), which has been reported as showing close correlation with the ‘gold-standard’ MSLT (Johns 1993, 1994). SAHS patients’ average Epworth score was 11 on a 24-point scale, and significantly higher than those of healthy controls, who averaged 6 points (Johns 1991). Similarly elevated Epworth scores averaging 14 (Johns 1992) and 12 (Johns 1993) have been reported in subsequent SAHS samples.

Thus, both objective and subjective assessments of daytime sleepiness show that SAHS patients are excessively sleepy, and the objective polysomnographic instruments indicate that the sleepiness seen in SAHS is of a severe or moderate nature.

2.2 Cognitive dysfunction

As many patients in the American case series complained of mental deterioration as of excessive daytime sleepiness (Guilleminault et al 1978). Epidemiological studies have found that subjects with symptoms of SAHS, such as heavy snoring and tiredness, complain more of subjective problems with concentration and memory than do non-snorers (Jennnum and Hein 1988).

From the mid-1980s, case-control studies appeared which attempted to specify and quantify the cognitive deficits reported to clinicians by their patients (Kales et al 1985, Findley et al 1986, Greenberg et al 1987, Klonoff et al 1987, Bédard et al 1991a, 1991b, 1993). In these studies (Table 2.1), descriptions of the cognitive dysfunction in SAHS were made by comparing neuropsychological test performance in SAHS patient samples to that of normals, sometimes individually matched for sex, age, education and socioeconomic level, as these variables are known to affect cognitive performance (Lezak 1983). Many studies have evident methodological problems as a result of control-matching problems, but nevertheless they hint at the nature and severity of cognitive dysfunction in SAHS.

In an early case series, Kales et al (1985) obtained Bender gestalt and Wechsler adult intelligence scale (WAIS) or Wechsler memory scale data from 50 patients with SAHS severe enough to warrant a recommendation of tracheostomy. Only 24% of the subjects showed no sign of organic impairment on reproduction of the Bender designs, and 24% scored sufficient errors to show mild to severe impairment.
## Table 2.1: Case-control studies of cognitive function in SAHS

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Study design</th>
<th>Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kales et al 1985</td>
<td>50 severe SAHS pts</td>
<td>Uncontrolled case series-compared to norms</td>
<td>Bender, WAIS IQ, WMS</td>
<td>40% of pts 'impaired' in intelligence and/or memory</td>
</tr>
<tr>
<td>Greenberg et al 1987</td>
<td>14 SAHS pts, 24 mixed sleepy/healthy controls</td>
<td>Controlled</td>
<td>WAIS-R IQ, PWA, Bender, PB, TM, LC, WMS</td>
<td>Pts &lt; Controls in BD, Bender, LC, PB</td>
</tr>
<tr>
<td>Klonoff et al 1987</td>
<td>11 SAHS pts, 11 coronary bypass pts</td>
<td>Controlled</td>
<td>WAIS-R, BVRT, VF, TM, SP, SR, Category, FT</td>
<td>No differences</td>
</tr>
<tr>
<td>Findley et al 1986</td>
<td>26 SAHS pts; 17 hypoxaemic and 9 non-hypoxaemic</td>
<td>Hypoxaemic compared to non-hypoxaemic pts</td>
<td>WAIS IQ, RT, TM, PASAT, WMS</td>
<td>Hypoxaemic &lt; non-hypoxaemic in TM, RT, PASAT, immediate WMS, delayed WMS</td>
</tr>
<tr>
<td>Pitson et al 1993</td>
<td>87 snorers, 96 SAHS pts and 39 healthy controls</td>
<td>Controlled</td>
<td>Median, simple RT</td>
<td>Both snorers and SAHS pts slower than controls</td>
</tr>
<tr>
<td>Bédard et al 1993</td>
<td>10 SAHS pts, 10 controls</td>
<td>Controlled</td>
<td>RT, WAIS-R, WMS, LC, PB, TM, PM, VF</td>
<td>Pts &lt; Controls in Perf IQ, LC, PB, TM, PM, VF, delayed WMS</td>
</tr>
<tr>
<td>Naëgelé et al 1995</td>
<td>17 SAHS patients, 17 controls</td>
<td>Controlled</td>
<td>TM, LC, Stroop, memory, WISC, VF, Tower</td>
<td>Pts &lt; Controls in Stroop, memory, perseverative responses</td>
</tr>
</tbody>
</table>

**Key:**
- WAIS- Wechsler Adult Intelligence Scale
- WMS- Wechsler Memory Scale
- TM- TrailMaking
- LC- Letter cancellation
- BVRT- Benton visual retention test
- Tower- Tower of Toronto task
- PASAT- Paced auditory serial addition test
- WISC- Wisconsin card sorting test
- RT- Reaction time
- PB- Pegboard
- BD- Block design
- PM- Porteous mazes
- FT- Finger tapping
- SR- Seashore rhythm
- SP- Speech perception
- VF- Verbal fluency
Cognitive impairment was judged to be present when the differential between obtained performance and verbal IQ scores exceeded 15 points, a condition met by 39% of the patients who underwent the WAIS battery. Forty-six percent of patients were judged to have impaired short-term memory and 32% deficits in long-term memory. This study included no control beyond the age-scaled norms obtained when standardising the tests, leaving the possibility that some other sampling bias besides age in the patient sample might have interacted in their apparently depressed performance. Loading towards lower educational level and socioeconomic status might then have contributed towards the high rates of impairment in the SAHS patients, but this study suggested a high incidence of cognitive impairment in SAHS.

Findley et al (1986) assessed cognitive performance in 26 SAHS patients and compared age-scaled scores from 9 hypoxaemic SAHS patients to those of 17 non-hypoxaemic patients. A comprehensive psychometric battery included the WAIS-R subtests of block design and vocabulary, TrailMaking B, 4-choice reaction time, short-term and delayed elements from the Wechsler memory scale and the paced auditory serial addition task (PASAT), a test of sustained concentration. The hypoxaemic group’s mean score lay in the impaired range for TrailMaking, PASAT and delayed recall, while the non-hypoxaemic group’s average score was in the normal range for all tests. The hypoxaemic group’s scores in TrailMaking, reaction time and recall, were significantly poorer than the non-hypoxaemic group’s. The study was designed to evaluate the impact of hypoxaemia on psychometric function, rather than to discriminate particular deficits associated with SAHS. However, because the hypoxaemic patients also had significantly worse measures of severity of SAHS, a comparison of their scores to those of the less severely hypoxaemic patients provides valuable information. The study implies that frequency of nocturnal apnoeas may be related to degree of cognitive deficit, as the hypoxaemic group showed twice as many nocturnal desaturations as the less hypoxaemic group. A correspondingly more severe level of waking hypoxaemia in the more hypoxaemic group, whose PaO2 averaged 63 mmHg, may have influenced the findings of more severe cognitive deficit in this group.

Greenberg et al (1987) administered a psychometric battery to 14 SAHS patients with a mean frequency of 34 apnoeas per hour in bed, to 10 sleepy controls with other disorders of excessive sleepiness (narcolepsy [n=5], periodic leg movement syndrome [n=4] and idiopathic hypersomnia [n=1]) and to 14 healthy controls, whose mean age and education approximated that of the SAHS group. The battery administered
Chapter 2: Daytime function in SAHS

included performance and verbal subtests from the WAIS-R scale, a letter cancellation test, the Bender gestalt test, the TrailMaking B task, pegboard test, controlled word association test and the Wechsler memory scale, and thus covered a wide range of executive neuropsychological function. A clinical neuropsychologist produced a blind impression of the overall global impairment rating based on each subject's test scores. One-way ANOVA showed that the SAHS group performed significantly worse than both control groups on the block design WAIS-R subtest, the letter cancellation test, the Bender design reproduction, pegboard test and the global impairment rating, leading authors to conclude that SAHS produces impairment in visuomotor skills, concentration ability, visuographic ability, motor efficiency and overall level of function respectively. The use of a sleepy control group allowed the authors to assess the influence of sleepiness per se on neuropsychological performance, when it was found that the sleepy controls scored nearer to the range of the healthy controls than to that of the SAHS patients. The level of cognitive impairment found was judged moderate in severity, as SAHS patients' scores lay half a standard deviation below that of the controls.

This study provides useful evidence of the specific impairments of SAHS and in addition makes a methodological allowance for the impact of sleepiness itself on performance, but the control groups used were not ideal. Both control groups had a non-significant excess of years of education compared to the SAHS group, which could affect test performance (Lezak 1983), and in addition both control groups had non-significantly higher scores on the Vocabulary and Information subtests from the WAIS-R battery. These subtests were used by Greenberg et al (1987) to estimate pre-morbid performance as part of the control-matching procedure, yet both control groups' mean scores lay roughly half a standard deviation higher than those of the SAHS group. This decrement in SAHS patients' performance on pre-morbid estimates of function mirrors the half a standard deviation deficit in current performance found by Greenberg et al (1987), so it must be questioned whether the lower performance in SAHS patients is a function of lower pre-morbid ability.

Klonoff et al (1987) compared the performance of a group of 11 SAHS patients (mean apnoea frequency 49 per hour slept) on the WAIS-R battery, the Benton visual retention test, verbal fluency test and several subtests from the Halstead-Reitan battery including the TrailMaking, speech perception, category, finger-tapping and seashore rhythm tests to that of a group of patients awaiting coronary bypass surgery. T-tests comparing the performance on these tests in the two untreated patient groups found no
differences, but the authors were careful to draw no concrete conclusions from this study concerning cognitive impairment in SAHS. Their discussion centred on the longitudinal changes in cognitive and psychological function after treatment in the two groups, rather than on the baseline characteristics of each patient group. The patient groups were not matched for education or occupational status, with the SAHS patients showing a generally less well-educated but higher socioeconomic profile. Further, poor cardiovascular function in the bypass group may have independently affected their neuropsychological performance, so a conclusion that this study showed no cognitive deficit in patients with SAHS cannot be drawn.

Simple reaction time testing was employed by Pitson et al (1993) to compare the response speed of 37 controls, 96 patients complaining of snoring but with less than 5 4% desaturations per hour in bed, and 87 symptomatic SAHS patients showing >5 4% desaturations per hour in bed. Despite the fact that the controls were on average older than either patient groups (J Partlett, personal communication), their reaction times (mean 307 ms) were significantly shorter than both the snorers (350 ms) and the SAHS patients (358 ms). These results indicated that patients with permutations of SAHS may suffer impaired vigilance.

Two further case-control studies were published towards the end of the period covered in this thesis. Bédard et al (1993) matched 10 healthy control subjects for sex, age and education with 10 moderate and severe SAHS patients. His psychometric battery included Wilkinson-type four-choice reaction time, the WAIS-R tests, Wechsler memory scale, the complex figures test, a verbal fluency test, WISC-R mazes, a letter cancellation task, the pegboard test motor speed and dexterity and the TrailMaking tasks A and B. Although the patients scored only 4 IQ points lower on WAIS-R verbal tests, their performance IQ was significantly lower by 13 points. The patients performed significantly more poorly than the controls on the digit symbol substitution, object assembly and picture arrangement subtests of the WAIS-R, as well as on the letter cancellation test, delayed memory of the Wechsler scale, TrailMaking task B, WISC mazes, verbal fluency and pegboard proficiency. The data were obtained in a small sample where outlying scores can have profound effects, but suggest compromise of executive functions and decreased vigilance in SAHS patients.

Naégelé et al (1995) used a similar case-control design, this time with 17 patients (AHI > 10) and 17 age-matched controls, and administered a cognitive battery including the Stroop and TrailMaking tasks of mental flexibility; a digit-cancellation
test to assess attention; WAIS-R digit span, Corsi blocks, verbal and visual learning tests to test learning and memory; and tasks thought to index frontal lobe function, the Wisconsin card sorting test, verbal fluency test and the Tower of Toronto task of forward planning. Patients showed poorer performance on the Stroop test, in verbal and visual learning and retrieval, and in perseverative responses on the Tower and card-sorting tasks. Logistic regression analysis suggested that Stroop and Tower tests showed the best discrimination between patients and controls, suggesting that mental set shifting and planning abilities are most compromised in SAHS.

These studies using neuropsychological testing yield an impression of mild and moderate deficits across a wide range of cognitive function in patients with SAHS. Impairment has been noted in attention skills, visuomotor coordination, memory, abstract reasoning and planning ability.

2.3 Evoked responses
An alternative approach to the study of both cognitive function and sleepiness in SAHS is provided by electrophysiological studies of nervous system activity in the form of evoked responses (Walsleben et al 1989, Mosko et al 1981, Stockard 1982, Wetmore et al 1988, Snyderman et al 1982, Rumbach et al 1991). Neurophysiological activity is evoked during the response to stimuli, typically auditory tones, which can be presented under different paradigms in order to enhance the resolution of certain components of the waveform. The conformation of the waveform, the latency and amplitude to its peaks and troughs, indexes underlying neuronal activity (Callaway et al 1978). Typically, the longer the expected latency of a particular wave component, the higher and more specialised is its hypothesised function (Goodin et al 1978).

Brainstem evoked responses (BSERs) are extremely short latency waveforms, recorded in the first 10 msecs after auditory stimuli, that appear to reflect sensory input processes (Walsleben et al 1989). Their conformation is unaffected by level of consciousness or attention (Amadeo and Shagass 1973), but is dependent on the function of the primary auditory pathway from cochlear nerve to brainstem (Mosko et al 1981). Case-control studies of BSERs in SAHS have yielded mixed results, most showing no differences between patients and normals (Mosko et al 1981, Stockard 1982, Wetmore et al 1988) but others showing slower central conduction times (Walsleben et al 1989) or prolonged peak latencies (Snyderman et al 1982) in patients.
The longer latency auditory evoked potentials (AEPs) appear to reflect higher cognitive function (Blackwood et al 1987), indexing storage and retrieval of information and discrimination of stimuli (Figure 2.1). The P3 and N2 wave components of evoked auditory potentials appear to be delayed and often smaller in amplitude in brain dysfunction (Blackwood et al 1987). P3 latency is highly correlated with measures of cognitive function such as reaction time (McCarthy and Donchin 1981) and WAIS IQ scores from both brain-damaged (Blackwood et al 1987) and healthy subjects (Pelosi et al 1992). P3 latency is a sensitive index not only of the cognitive deficit associated with dementia and organic brain damage (St Clair et al 1985, 1988) but also of the more subtle, diffuse deterioration of ageing (Goodin et al 1978).

![Figure 2.1: Auditory evoked potential waveform](image)

Deficits of SAHS apparent on cognitive testing and sleepiness assessments are also found by AEP measurements. 14 sleep apnoeics had significantly slower N2 and P3 latencies than matched normals (Walsleben et al 1989), and P2, N2 and P3 components were delayed in 47 SAHS patients compared to age-matched controls (Rumbach et al 1991).

Evoked cognitive potentials, like neuropsychological performance, may vary with level of attention and sleepiness, as well as with cognitive ability. Researchers have found decreasing amplitudes in the wave components with drowsiness, but then
increasing amplitudes and latencies with increasing depth of NREM sleep (Weitzman and Kremen 1965). Broughton et al (1982) found decreased amplitudes in N1, P2 and N2 in awake narcoleptics compared to controls. The waking P3 amplitude was found to be significantly smaller in a group of narcoleptics, also shown to be sleepier on the MSLT, than that in controls (Aguirre and Broughton 1987). Thus, as in cognitive performance testing, evoked potentials may not discriminate between the effects of organic brain damage and sleep disruption in SAHS. This link between cognitive deficit and sleepiness is discussed in greater detail in a later section. The above evidence, however, from studies both of evoked responses and cognitive performance point to measurable cognitive deficits in SAHS patients.

Thus research using neurophysiological techniques indicates disturbances of higher cortical function and perhaps sensory activity in patients with SAHS, corroborating other evidence of both of impaired cognitive performance and alertness in SAHS.

2.4 Psychological well-being

Early characterisations of SAHS noted a high incidence of altered personality and poor mood in patients with the syndrome. Guilleminault et al (1978) reported that families had noted personality changes in almost half of SAHS patients, who were described as showing increased irritability and a greater propensity for emotional outbursts. Later studies employing quantitative methods to describe the personality profiles, mood and affect of SAHS patients document a higher frequency of minor psychiatric morbidity and psychopathology in SAHS patients than in normals.

Psychological health in SAHS has been investigated using measures of personality, mood, psychiatric distress and quality-of-life. While these instruments contain differing biases towards trait, state or functional assessment, all contain information on psychological wellbeing. Most measures of well-being consist of self-rated questionnaires, which are vulnerable to manipulation by subjects who may feel that complaints of significant psychological distress might precipitate more rapid or effective treatment. Additional methodological problems are posed by the lack of distinction (both in patients' perceptions and in the formulation of psychological instruments) between physical and mental symptoms of psychological distress. Many instruments cannot discriminate between a lack of vigour caused by excessive daytime sleepiness and the anergia of clinical depression (Lee 1990).
Trait assessment of personality in SAHS (Beutler et al 1981, Kales et al 1985, Klonoff et al 1987, Platon and Sierra 1992) has most commonly been conducted with the Minnesota Multiphasic Personality Inventory (MMPI: Dahlstrohm et al 1972, 1975). The MMPI, which is considered a relatively stable measure of persistent personality and psychopathology (Beutler et al 1981), consists of a self-rated questionnaire comprising more than 500 questions, resolving into ten clinical subscales measuring hypochondriasis, depression, conversion hysteria, psychopathy, masculinity-femininity, paranoia, psychaesthenia, schizophrenia, hypomania and social introversion. It has been used with remarkably consistent results in samples of patients with SAHS.

Beutler et al (1981) found that 20 SAHS patients scored significantly higher than 10 age- and socioeconomic status-matched normals on the scales for hysteria and depression. High point pattern analysis characterised the apneics as having relatively high hysteria and hypochondriasis scores, reflecting a tendency to dependency on physical symptoms. In a larger sample of 48 patients with severe SAHS, Kales et al (1985) found significantly higher scores for hypochondriasis, depression, hysteria, schizophrenia and psychaesthenia than for 78 age- and sex-matched healthy controls. 65% of the patients had at least one scale score in the elevated range, versus 29% in the control group. The SAHS patients studied by Kales et al (1985) were severe enough to warrant treatment with tracheostomy, so the increased intensity and range of psychopathological MMPI scores in this sample compared to that of Beutler et al (1981) is likely to be related to differences in SAHS severity in the two patient groups. The personality profiles of 69% of Kales' patients were coded as somatic-neurotic in type, describing "a reactive type of psychopathology in response to a major medical illness" (Kales et al 1985). Thus Kales et al (1985) suggest that the disturbances in psychological well-being in SAHS patients may be secondary to functional limitations imposed by SAHS.

Because of impairment in daytime respiratory function, chronic obstructive pulmonary disease (COPD) produces severe physical limitations on behaviour and function, producing an objectively poor quality-of-life (McSweeny et al 1982). It is therefore notable that an even greater proportion of SAHS patients show MMPI characteristics of reactive depression than do COPD patients, suggesting that limitations to daytime function are at least as great in SAHS as in COPD (Kales et al 1985).
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A further, more recent study of MMPI scores in 23 SAHS patients and 17 healthy control subjects group-matched for age, sex and educational level has showed the familiar profile of significantly higher scores in the apnoeics than in controls on scales for depression, hypochondriasis, hysteria, schizophrenia and psychasthenia (Platon and Sierra 1992). High point pattern analysis in this sample characterise the apnoeic group as showing relatively high scores for hypochondriasis, schizophrenia and depression.

Thus MMPI-based studies of personality show a consistent, long-term somatic-neurotic coping strategy in SAHS patients. Longitudinal studies (discussed in Chapter 3) have shown normalisation of MMPI-measured psychopathology after successful treatment of SAHS, implying that disordered respiration in sleep, or one of its sequelae in the form of daytime symptoms, are most likely the cause of the typical apnoeic MMPI pattern.

Studies of more transient mood state in SAHS patients (Beutler et al 1981, Derderian et al 1988, Mosko et al 1989, Kribbs et al 1993b) have been performed almost exclusively with the Profile of Mood States (POMS: McNair et al 1981). Subjects are presented with 65 adjectives and are asked to rate the applicability of each of the adjectives to their state that day, using a five-point scale. The POMS yields scores for 6 affective states: depression-dejection, anger-hostility, vigour-activity, fatigue-inertia, confusion-bewilderment and tension-anxiety, as well as a total mood disturbance score. As might be expected, SAHS patients show high POMS scores for fatigue and low POMS scores for vigour.

In Beutler's study, which compared apnoeics' and control subjects' POMS scores, the patient group had significantly lower scores on the vigour and fatigue scales, reflecting lower energetic levels in the patient group. The studies by Derderian et al (1988), Mosko et al (1989) and Kribbs et al (1993b) were primarily concerned with monitoring change in mood after treatment for SAHS, and contained no direct comparison of POMS scores in SAHS cases and healthy controls. While there is a large variability in the mean POMS scores of SAHS patients reported by these researchers, rough comparisons show untreated patients' fatigue scores to be at least 2 standard deviations outside of Beutler's healthy controls' scores, in the direction of greater inertia, in all three studies. Derderian's small sample of 7 patients were in Beutler's normal range on all other POMS scales, while Mosko's large group of 73
SAHS patients appeared to score outside the normal range on all scales except the confusion-bewilderment measure.

Structured psychiatric interview techniques provide further evidence of psychiatric morbidity in SAHS. Reynolds et al (1984) found that 10 of 25 SAHS patients met research diagnostic criteria for a past or present psychiatric illness, most diagnosed with depressive or alcohol abuse disorders. Mosko et al (1989) employed a questionnaire based on standard psychiatric criteria (DSM-III) to catalogue the number of depressive symptoms suffered by patients in the preceding 5 years. 58% of the apnoeic patient sample had more than four symptoms of depression for 2 weeks or longer, fulfilling DSM-III criteria for a major depressive episode. The Zung self-rating depression scale classified 45% of 55 SAHS patients as depressed, using a threshold score of 50 or more as diagnostic (Millman et al 1989), although reservations might be expressed concerning the inclusion of items in this scale that relate equally to symptoms of depression and sleep apnoea, such as sleep disruption, task performance deficits and decreased libido. Cheshire et al (1992) refined psychiatric screening in SAHS by using the Hospital Anxiety and Depression (HAD) scale to assess symptoms of dysphoria. The HAD scale (Zigmond and Snaith 1983) was designed for use in patients with physical illness and thus deliberately excludes questioning that may confound somatic symptoms of physical and mental illness instead concentrating on the anhedonic state specific to affective disorder. Cheshire et al (1992) found 12 of 29 patients scored in the clinically suspicious range for anxiety and/or depression.

A few preliminary and recent reports have directly attempted to measure the functional impact of SAHS on quality-of-life, although it can be assumed that many of the assessments described above indirectly measure satisfaction with and participation in daily activities. Isaac et al (1992) compared scores on the Sickness Impact Profile (Bergner et al 1976) from patients with documented mild SAHS (AHI< 20) to a group of referred patients who had symptoms of SAHS (excessive daytime sleepiness and/or snoring) but too few respiratory events to permit diagnosis of SAHS. While the two groups could not be discriminated using the POMS scale, the diagnosed patients showed significantly poorer social, work, marital and family functioning than those with symptoms only. In a recent report, 44 sleep clinic patients completed the SF-36 rating of quality-of-life (Stewart et al 1988) before undergoing polysomnography and an MSLT (Briones et al 1995). The extent of daytime sleepiness in these subjects, many of whom had SAHS, was moderately correlated with the degree of impairment in mental health and social function, and both sleep...
onset latency and respiratory disturbance index were associated with limitations due to emotional and physical problems and to tiredness.

As these quality-of-life studies document, the daytime problems associated with SAHS have wide-ranging effects on everyday life for sleep apnoeics. Interpersonal relationships and work efficiency are further areas which appear to be compromised in SAHS.

A questionnaire administered to a consecutive series of SAHS patients with illness severe enough to warrant tracheostomy found a high incidence of psychosocial problems (Kales et al 1985). 66% of this series believed their relationships to be adversely affected by their illness, and 64% attributed marital and family problems to SAHS.

In a study evaluating the psychosocial function of married male apnoeics and their partners, Carter and Knight (1987) used the Social Adjustment Scale to show disturbed function for both patients and spouses in marital and social/leisure areas. In the Marital Satisfaction Inventory, the SAHS patients' wives rated themselves higher for global distress and conflict over child-rearing than normals.

In Kales et al's series (1985), 89% of severe SAHS patients reported experiencing problems in the workplace as a result of their illness. Within this adversely affected subgroup, 79% found that their work capacity was limited, 62% had fallen asleep at work on several occasions and 13% reported leaving employment as a direct consequence of their symptoms. These self-reports remain the only source of information on productivity and safety in the workplace in SAHS.

Thus, the various state, trait and functional measures of psychological health so far used in the assessment of patients SAHS have provided evidence showing significant psychological dysfunction. Sleep apnoeics show higher mean scores for personality-based trait assessments of psychopathology than do normals, have typically tired and anergic mood state profiles compared to normals, show a high incidence of suspected psychiatric illness and a poorer quality-of-life than controls.

2.5 Road safety

Much effort has been channelled into study of the road safety risks associated with impaired daytime functioning in SAHS (Guilleminault et al 1978, Parsons 1986,
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Most of these studies investigating the incidence of car accidents use self-reports from SAHS patients, who may fear the loss of their driving licenses, and thus are likely to under-report the scale of their problem. Nevertheless, the available evidence points clearly to a greatly increased rate of automobile accidents in patients with SAHS. Many of these accidents occur due to frank falling asleep while driving (Aldrich 1987), but impairment of more subtle perceptuo-motor ability may also contribute to the high accident rates in SAHS patients (Horne 1992). Findley et al (1989a) demonstrated that SAHS patients perform worse than controls on a 30-minute driving-based vigilance task, but was unable to document electroencephalographic episodes of sleep during performance (Findley et al 1993).

Probably one half of SAHS patients fall asleep at the wheel of their car. Uncontrolled studies have found that 54% (Guilleminault et al 1978) and 56% (Cassell et al 1990) of SAHS patients fall asleep whilst driving, while controlled studies show that the incidence of sleeping whilst driving is far higher in sleep apnoeics than in the normal population (Findley et al 1988, Haraldsson 1990b). Twenty-four percent of Findley's (1988a) sample of polysomnographically-diagnosed SAHS patients fell asleep at the wheel at least once per week, against 3% of a control group who demonstrated a clinically insignificant frequency of apnoeas during sleep. Haraldsson et al (1990b) compared responses on a questionnaire of driving experiences from 73 patients with symptoms highly suggestive of SAHS and 142 controls, recruited from a pool of ENT patients with no symptoms of SAHS. Fifty-two percent of the probable SAHS sufferers reported habitual sleeping whilst driving, against less than 1% of the control group. These figures on sleeping at the wheel correlate well with other studies of near-miss car accidents, which find frequencies in SAHS patients of 32% (Gonzalez-Rothi et al 1988) and 66% (Aldrich 1989).

Driving skills of SAHS patients have been evaluated in the laboratory using long, monotonous driving simulators. Findley et al (1989a) administered several types of driving simulator to a small number of severe SAHS patients and to age- and sex-matched normals, and found significantly poorer performance in the patients on all of the three simulators employed. The SAHS patients scored a modestly lower number of correct responses during film-projection simulations of both highway and urban
roads, each simulation lasting 22 minutes, than the controls. But more dramatic differences in performance were found with the SteerClear computer driving simulation, when patients averaged 44 errors versus the controls' score of 9. SteerClear is a 30-minute vigilance task presenting subjects with a view of a two-lane road on which cows periodically appear. Because the only response required from the subject is to change lanes and avoid cows by pressing a computer key, it cannot be termed a true driving simulation: but it nevertheless contains elements of response speed and visuomotor co-ordination that contribute to driving skill. A slightly larger group of 15 patients with the symptoms of SAHS showed significantly poorer performance during a more sophisticated driving simulation than 10 matched controls (Haraldsson et al 1990a). After 10 minutes practice at the task, subjects drove at 55 mph for between 30 and 90 minutes in a realistic interactive simulation, during which braking speed, steering precision and off-road incidents were monitored. The SAHS patients' mean and 90th centile scores for both braking speed and steering deviation were significantly poorer than the controls', and patients had a significantly greater number of off-road incidents, corresponding to a car crash scenario.

Empirical evidence of truly poorer driving performance is gained from retrospective studies comparing car accident rates in SAHS patients and the larger population. Findley et al (1988a) found that the 5-year accident rate of 29 diagnosed sleep apnoeics was 7 times greater than that of 32 patients who showed no significant abnormality on sleep study. The SAHS patients' accident rate was more than twice that of all 3.7 million Virginian drivers. The patients' high accident rate was not attributable to a few highly dangerous drivers in the patient group, as the frequency of drivers reporting accidents was also significantly higher in the patient group. Seven of the 29 SAHS patients reported at least one accident, while only 1 of the 35 the non-SAHS patients had had an accident in the last 5 years. The odds of SAHS patients being the driver at fault in their reported accidents was 8 times higher than in the non-SAHS patients. In another study, George et al (1987) used centralised governmental computer records to match 10 control subjects to each of 27 sleep apnoeics, and found a lifetime accident rate more than twice as high in patients than in controls. Around half of the randomly selected controls had had an accident, against 93% of the patients. These retrospective studies provide convincing evidence that SAHS patients represent a risk on the road.

Sleep-related accidents, which are appear to be frequent in SAHS patients, may pose an even greater safety risk than accidents caused by other driving errors. Sleep-related accidents may be difficult to identify, particularly in fatal crashes, but three studies
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have attempted to assess the relative safety risks imposed by accidents caused by sleeping. In an analysis of casualty and mortality rates in accidents thought to be caused by falling asleep, by fits or by heart attacks, sleep-related accidents accounted for 27% of accidents but 83% of deaths (Parsons 1986). Zomer and Lavie (1990) employed centralised records of accidents and coroners' verdicts to identify sleep-related accidents and found that such accidents claimed 50% more casualties and almost 3 times more fatalities than expected. Horne and Reyner (1995), in a recent British survey of road traffic accidents, have also indicated that sleep-related accidents more often resulted in death or serious injury than those with another cause.

If, as these studies suggest, sleep-related accidents are more serious than crashes from other causes, untreated drivers with SAHS present an additional risk to the public.

Part of this additional risk from sleep-related accidents may relate to the conditions under which these particular accidents occur. Zomer and Lavie (1990) found that the great majority of their sleep-related accidents, 75%, occurred outside of an urban setting. Seventeen of the 38 press reports (45%) collated by Parsons (1986) described accidents occurring on a motorway, and in Horne and Reyner's study (1995), 75% of suspected sleep-related accidents occurred on motorways or major roads. It is notable too that the driving simulation task that best discriminated SAHS patients from normals was the highly monotonous SteerClear (Findley et al 1989a). The stimulation provided by traffic lights, road junctions, pedestrians and stop-go traffic in a town environment thus may aid vigilance in sleepy drivers. With a paucity of alerting stimuli against which to measure one's performance, the dangerous monotony of the motorway environment may provoke a loss of awareness of conscious state (Horne 1992), with potentially high costs. Despite the high accident risks documented in the above research studies, even sleepy SAHS patients do not appear to alter their driving behaviour to reduce hazards to themselves and others (Cassel et al 1990).

2.6 Severity of SAHS and daytime function

Many authors have documented significant correlations between the severity of nocturnal events in SAHS and their daytime sequelae, suggesting that the severity of SAHS determines the extent of daytime impairment.

Studies in SAHS patients show significant correlations between objective daytime sleepiness measured by the MSLT and MWT and nocturnal events in the form of apnoeic ($r=0.5$, Roth et al 1980) and apnoeic+hypopnoeic frequency ($r=0.3$; Roehrs et
al 1989, Poceta et al 1992), as well as hypoxaemic variables (r=0.3-0.5; Roehrs et al 1989, Bédard et al 1991a, Poceta et al 1992) and sleep quality measured by the averaged procedure of Rechtschaffen and Kales (1968) (r=0.3-0.8; Stepanski et al 1984, Guilleminault et al 1988, Roehrs et al 1989) or by more sensitive event-scored arousals (r=0.4-0.7; Roehrs et al 1989, Poceta et al 1992, Roth et al 1980). Post-hoc splitting of a large sample of apnoeic patients by Guilleminault et al (1988) showed significantly higher indices of respiratory abnormality and sleep disruption in patients with greater objective excessive daytime sleepiness, measured by the MSLT.

Subjective sleepiness evaluated by the Epworth sleepiness scale correlates with both AHI and nocturnal hypoxaemia (r=0.4, Johns 1993). However, others have found no nocturnal correlate of MSLT score from a large array of variables indexing breathing disruption, sleep fragmentation and hypoxaemia (Cheshire et al 1992).

Cognitive performance correlates significantly with AI (r=0.5, Bédard et al 1991a) and AHI (r=0.4-0.6, Cheshire et al 1992) in SAHS patients, in heavy snorers (r=0.3, Berry et al 1986) and in an elderly subject sample, some of whom had significant AHIs and sleepiness (r=0.3-0.5, Yesavage et al 1985). Hypoxaemia has also been significantly correlated with cognitive impairment in SAHS patients (r=0.4-0.8; Cheshire et al 1992; Bédard et al 1991a, Greenberg et al 1987, Findley et al 1986) and in heavy snorers (r=0.3-0.5; Berry et al 1986, Telakivi et al 1988), as has event-scored arousal frequency (r=0.5-0.6, Cheshire et al 1992) and Rechtschaffen and Kales' (1968) sleep quality (r=0.5, Bédard et al 1991a). Findley et al's (1986) split-sample study of hypoxaemic vs. non-hypoxaemic SAHS patients implies that the frequency and severity of oxygen desaturation during sleep is related to the degree of cognitive impairment.

An unexpected positive correlation between AHI and Beck depression self-rating (Watson et al 1985), reflecting less distress with more severe SAHS, is the only evidence linking severity of SAHS with psychological distress, but studies are few in this area.

The severity of SAHS is also associated with the degree of impairment of driving performance in correlational and split-group studies (Haraldsson et al 1990a, Aldrich 1989, Cassel et al 1990, Findley et al 1989b). Haraldsson et al (1990a) found the relative risk of having had an accident in the preceding 5 years grew with the intensity of symptoms of SAHS. Heavy snorers who did report subjective excessive daytime sleepiness had an accident rate 1.4 times that of normals, while patients with
symptoms more suggestive of SAHS, but with no subjective sleepiness whilst driving, had accident rates 2.3 times that of controls. Sleepy drivers in a symptomatically-defined SAHS group were 3 times as likely to have had an accident than the controls. Aldrich (1989) demonstrated a higher frequency of SAHS patients admitting sleep-related accidents when AHI was greater than 60 (30%) than in less severe patients with indices less than 60, 15% of whom reported sleep-related crashes. Cassell et al (1990) published a dose-response relationship between apnoea index and the incidence of once-weekly sleeping at the wheel in patients assessed for sleep apnoea. While less than 10% of patients with fewer than 5 apnoeas per hour slept reported this behaviour, around half of patients with apnoea indices from 5 to 20 per hour dozed at the wheel and almost 70% of those with indices greater than 20 dozed weekly while driving. A similar dose-response relationship was seen in mild, moderate and severe SAHS patients’ self-reported accident rates, which were 82%, 150% and 290% respectively of that expected from the Virginian population (Findley et al 1989b).

These studies document associations between the nocturnal features of SAHS and consequent daytime function, and provide evidence that the degree of nocturnal disruption experienced by patients is reflected in their waking state.

2.7 Aetiology of daytime impairment in SAHS

The correlational findings presented above suggest that overall severity of breathing disruption in SAHS is related to subsequent magnitude of daytime impairment. But these studies do not provide a detailed information on the separate contributions of individual nocturnal events to individual daytime deficits of SAHS. Repetitive airway restriction in sleep has immediate physiological consequences in both hypoxaemia and sleep disruption. These two secondary events are the putative causative agents for the daytime neuropsychological impairment of SAHS.

The issue of the aetiology of daytime impairment in SAHS is pertinent, and impinges on the primary investigation of this thesis, the reversibility of daytime deficits of SAHS by CPAP therapy. The determinants of daytime deficit in SAHS can be investigated by examining models of the effects on daytime function of hypoxaemia and sleep disruption, and by assessing clinical studies conducted to explore this issue.
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2.7.1 Models of sleep fragmentation and hypoxaemia

Studies examining the daytime effects of sleep loss and chronic obstructive pulmonary disease (COPD) provide approximate models for the impairments associated with sleep fragmentation and hypoxaemia respectively.

The types of daytime deficits documented by these two models show overlap in effects, particularly for cognitive impairment, but the literature attaches rather different prognoses to daytime deficits mediated primarily through sleep fragmentation and hypoxaemia, the former being temporary and remediable by the restoration of quality and quantity of sleep, while the latter’s effects are associated with only partial reversal of deficits with treatment.

2.7.1.1 Experimental sleep loss


Human studies show that experimental partial and total sleep loss provoke measurable deficits in daytime alertness, cognitive performance and mood very similar to those observed in SAHS.

The most noticeable effect of sleep loss is to induce sleepiness (Horne 1988). A clear association between prior sleep quality and both objective (Carskadon and Dement 1979, Bonnet 1987, Philip et al 1992) and subjective (Bonnet 1985) daytime sleepiness has been demonstrated. Both sleep fragmentation (Bonnet 1985, Bonnet 1987, Philip et al 1992) and sleep deprivation (Carskadon and Dement 1979) in healthy normals produce measurable decreases in sleep onset latency during daytime naps. Sleep reduction studies show correlations of 0.5 to 0.6 between prior night’s total sleep time and objective daytime sleepiness evaluated by the multiple sleep latency test (Carskadon and Dement 1979).

Impaired alertness may be reflected in altered daytime waking EEG activity. Brunner et al (1993) found altered EEG spectra, with power increases in the high delta frequency range and decreases in the alpha range, after 4 nights’ partial sleep deprivation of normals. Such slowing of EEG is typical of the lapse into drowsiness
(Rechtschaffen and Kales 1968), and has been also been found, coinciding with behavioural wakefulness, during total sleep deprivation (Horne 1978).

An association between sleep loss and daytime sleepiness is documented in the above studies, some of which closely mimic the sleep fragmentation seen in SAHS. These findings provide circumstantial evidence that the chronic and continuous sleep disruption seen in SAHS may provoke excessive daytime sleepiness.


Experimentally-produced sleep fragmentation in normals, more closely simulating that of SAHS, results in impairment of cognitive performance. The elegant series of studies performed by Bonnet and colleagues (Bonnet 1985, Bonnet 1987, Downey and Bonnet 1987) documented objective decrements in performance on arithmetical vigilance tasks (Bonnet 1985), oddball auditory tone detection tasks (Bonnet 1987), reaction times (Bonnet 1985, Downey and Bonnet 1987) and digit symbol coding efficiency (Bonnet 1985) after 2 nights of sleep fragmentation at 1 (Bonnet 1985) and 2 (Bonnett 1987) minute frequencies.

Bonnet (1985) compared his findings of cognitive impairment under conditions of sleep fragmentation against those obtained under the same duration of total sleep deprivation, commenting that the decrease in addition efficiency after 2 nights of sleep fragmentation approximated that seen after 1 night of total sleep deprivation, thus showing a surprisingly large impact of sleep fragmentation on performance. His 1987 study explored the effects of different intensities of arousal from sleep, showing that short, EEG-only arousals were not less damaging to performance than fuller awakenings from sleep. Downey and Bonnet (1987) showed that performance is worse affected by fragmentation than restriction of sleep. Reaction time to an arithmetic problem was slower during fragmentation at 10 minute intervals than after 2.5 hours of continuous sleep, and worst when sleep was disrupted at 1 minute frequencies. These data suggest that sleep continuity, rather than quality of sleep architecture or total quantity of sleep, may be extremely important in maintaining
cognitive function. This then implies that SAHS-mediated sleep fragmentation may be even worse for daytime cognitive performance than restricted but continuous sleep.

It has been hypothesised that cognitive deficits after sleep loss may be due to changes in the state of consciousness, representing drifts into sleep (Williams et al 1959, Horne 1988, Horne 1992). Such a "lapse" hypothesis, proposing that performance fall-off occurs during microsleep episodes, is supported by the subanalysis of mean and median reaction times obtained during sleep deprivation, presented by Williams et al (1959). While median reaction time increased approximately 20% after 78 hours of sleep deprivation, mean reaction time doubled, suggesting that a few outlying, long latency responses skewed the mean score. However, Williams et al (1959) later discarded the lapse hypothesis of cognitive impairment when they showed that lapses in memory with a word-learning list task were worst in the delayed recall of the word list, rather than on immediate recall. The lapse hypothesis proposed that microsleeps during the word list presentation would impair information acquisition such that immediate recall should have been as poor as delayed recall. However, word learning is a relatively short and stimulating task, and the loss of word recall might be attributable to motivational deficits after sleep deprivation. Certainly the lapse hypothesis fits with Williams et al's (1959) reaction time data.

Studies showing altered neurophysiological state during wakefulness after sleep loss (Bjerner 1949, Naitoh et al 1969, Williams et al 1959, Brunner et al 1993), like those documenting altered evoked potential conformation in hypersomnia (Weizman and Kremen 1965, Aguirre and Broughton 1987, Broughton et al 1982) may support the lapse hypothesis of cognitive dysfunction in SAHS.

The EEG correlates of sleep deprivation were investigated as far back as 1949, when Bjerner observed that delayed responses on serial RT tasks after sleep deprivation were associated with depressed alpha EEG amplitudes (Bjerner 1949). A reduction in alpha EEG frequencies is recognised as the cardinal feature of stage 1 sleep (Rechtschaffen and Kales 1968), usually perceived by subjects as a state of drowsiness (Hauri 1982). In a study following 205 hours of sleep deprivation, Naitoh et al (1969) also noted that alpha frequencies progressively disappeared through the increasing duration of sleep loss. Williams et al (1959) scored the percentage of alpha frequencies occurring during the second before and the second after stimuli during a auditory vigilance task, performed before and during the course of total sleep deprivation. EEG signals during errors of omission had lower percentages of alpha
frequency that correct omissions or commissions and errors of commission. Brunner et al (1993), showed increased delta EEG frequency powers during behavioural 'wakefulness' after sleep restriction, also supporting the lapse hypothesis. It may be that functional and neurophysiological sleep states, not necessarily measurable through conventional, averaged, Rechtschaffen and Kales (1968) sleep scoring, can occur during behavioural wakefulness.

The impact of sleep loss on internal psychological state is familiar to most individuals as a result of personal experience. Typically, short-duration compromise of sleep quality or quantity provokes a loss of energy and motivation, while episodes of irritability, aggression and suspiciousness may be produced by extended sleep deprivation (Horne 1988). Experimental sleep fragmentation for 2 nights resulted in significant increases in morning 'unhappiness' (Bonnet 1987) and in both increased 'unhappiness' and decreased 'clear-thinking' on Clyde mood subscale (Bonnet 1985). These behavioural, personality and mood state changes may parallel those documented in case series of SAHS patients (Guilleminault et al 1978).

These studies show that experimental sleep loss results in increased sleepiness, impaired cognitive performance, most noticeably on attention-based tasks, and decreased psychological wellbeing. Thus sleep disruption appears to provoke daytime impairments overlapping closely with those associated with SAHS. These effects are however completely reversible following the recovery of sleep debt (Horne 1988). Following 1 or 2 nights of recovery sleep following sleep disruption, objective and subjective daytime sleepiness are normalised (Carskadon and Dement 1979, Naitoh et al 1969), as are cognitive performance deficits (Williams et al 1959, Horne and Pettitt 1985).

2.7.1.2 Chronic obstructive pulmonary disease (COPD)
COPD is limited as a model for evaluating the isolated effects of hypoxaemia on daytime function, as COPD is associated with significantly disrupted objective (Calverley et al 1982, Fleetham et al 1982) and subjective (McSweeny et al 1982) sleep quality, and with subjective daytime sleepiness (McSweeny et al 1982). Such sleepiness may act as a covariate in the daytime cognitive impairment associated with COPD.

Nevertheless, the continuous hypoxaemia of COPD may provide useful information about the effects hypoxaemia on cognitive function. COPD is associated with
generalised cognitive impairment, including deficits in perceptuomotor skill, motor speed, memory, verbal facility, abstract reasoning, problem-solving and executive functions (Krop et al 1973, Prigitano et al 1983, Grant et al 1982, Huppert et al 1982). The severity of hypoxaemia in COPD is associated with the degree of cognitive impairment in split-group (Krop et al 1973) and correlational (Huppert et al 1982) studies. Because studies find that sleep is less disrupted in more hypoxaemic COPD patients (Douglas et al 1979, Calverley et al 1982), this suggests that hypoxaemia may be more influential in determining cognitive deficit in COPD than sleep disruption.

Krop et al's (1973) split-group study of more and less hypoxaemic COPD patients demonstrated greater impairment on the Bender gestalt, the background interference procedure, finger-tapping and facial recognition task in the more hypoxaemic group, this pattern of neuropsychological dysfunction suggesting diffuse organic damage. Similar, wide-ranging impairments were also shown in large case-control studies (Prigitano et al 1983, Grant et al 1982) employing carefully-matched healthy controls.

Prigitano et al (1983) found that 100 mildly hypoxaemic COPD patients showed impairments in abstract reasoning, perceptuomotor skill, mental set flexibility, memory and language facility compared to well-matched controls. Grant et al (1982) employed the Halstead-Reitan Battery, the Wechsler Memory Scale and pegboard tests to evaluate attention, verbal skills, perceptual-motor performance, sensory function, abstracting facility, motor ability and memory and to provide three summary indices. The COPD patient group were rated as significantly more impaired by all summary indices and in all functional domains examined by the battery. While 14% of the control subjects' scores were clinically judged to indicate moderate or severe cerebral dysfunction, 42% of the COPD patients were rated as moderately or severely impaired.

Cognitive deficits in COPD may be only partially ameliorated by the restoration of normoxia (Krop et al 1973, Heaton et al 1983, Wilson et al 1985). Following continuous oxygen therapy, severely hypoxaemic COPD patients' performance on tests of organicity, motor speed and stamina was no longer worse than that of retested untreated COPD patients with initially less severe hypoxaemia (Krop et al 1973).

The NOTT study group also assessed the effects of oxygen treatment, both continuous and nocturnal, of 6 months and 12 months duration (Heaton et al 1983). On retesting after 6 months of oxygen therapy, COPD patients were found to have made
significantly greater improvements in score than retested controls on the TrailMaking B task, hand dynamometer and the tapping test. When the assessment test scores were grouped into functional areas, such as memory or attention skill, and rated blindly by a clinician, a significantly greater percentage of the patient group showed "slight improvements" in verbal facility, abstraction skill, simple sensory perception and motor speed than in the control group. The authors emphasised that the statistically significant increases in patients' test scores over controls' scores represented only subtle improvements in cognitive function.

A carefully-controlled, crossover-type study by Wilson et al (1985) attempted to examine the effects of shorter administrations of oxygen on COPD patients' mental function. This study compared performance on 20 minutes and 6 hours of room air and enriched oxygen, with the order of treatment type and treatment duration randomised to control for practice effects. The psychophysiological tests used, the repetition test and the critical flicker fusion test, were selected to assess information-processing ability and had the advantage of being less prone to learning-related increases in score than other cognitive tests. No improvements in information-processing ability were found. This may be due to the small sample size of 10 patients, or to the relatively short durations of oxygen treatments used. Patients recruited for this study continued to use nocturnal oxygen therapy on the nights before their assessments and it is possible that nocturnal oxygen treatment already optimises performance. Alternatively, this study could be employed to support the hypothesis that cognitive impairment secondary to hypoxaemia is permanent.

The findings of these studies of cognitive deficits in COPD, like those examining the cognitive impairments of SAHS, showing wide-ranging neuropsychological deficits. The mixed findings from COPD treatment studies do not amount to conclusive proof of improved functioning after the correction of hypoxaemia, but do give some cause for optimism that deficits associated with mild to moderate cerebral hypoxia can be at least attenuated by the restoration of normoxia. Thus if daytime function in SAHS, and most specifically cognitive function, is most closely linked to hypoxaemia, CPAP might be expected to produce minimal or partial reversal of cognitive deficit.

Thus experimental and pathological conditions analogous with the physiological environment of SAHS produce daytime impairments overlapping with those of SAHS. Hypoxaemic processes can cause wide-spectrum cognitive impairments very similar to those documented in SAHS patients. Research on the effects of sleep loss
supports the hypothesis that sleep loss produces measurable deficits in subjective and objective daytime sleepiness and cognitive performance. However, while the restoration of sleep quality following CPAP therapy might be expected to reverse deficits induced by sleep fragmentation, cognitive impairment linked to hypoxaemia might be more resistant to treatment.

2.7.2 Nocturnal predictors of daytime impairment in SAHS
Correlational studies in SAHS patient do not unambiguously select either hypoxaemia-related or sleep fragmentation-related measures as more closely related to daytime dysfunction. A simple comparison of r-values obtained from different studies reflects considerable disagreement. While some find that objective daytime sleepiness is most closely associated with measures of hypoxaemia (Bédard et al 1991a), others document stronger correlations with measures of sleep quality and quantity (Roehrs et al 1989, Poceta et al 1992, Roth et al 1980, Guilleminault et al 1988, Stepanski et al 1984). Cognitive performance has been most closely correlated with hypoxaemic indices by some (Telakivi et al 1988, Findley et al 1986, Berry et al 1986, Bédard et al 1991a) and with measures of sleep quality by others (Cheshire et al 1992).

This ambiguous situation is influenced by problems involving intercorrelations within measures of nocturnal and daytime function, and by variation in the selection and sensitivity of measures in different studies.

Strong intercorrelations between individual polysomnographic variables (r=0.7; Roehrs et al 1989) and between sleepiness and cognitive function (r=0.3-0.6; Carskadon and Dement 1979, Telakivi et al 1988, Cheshire et al 1992) have been documented, reflecting either internal causative relationships or shared antecedents within both nocturnal events and areas of daytime function. Such intercorrelation confounds the use of simple correlational techniques in assessing the contribution of individual nocturnal events to daytime impairments.

All correlational studies of the aetiology of daytime deficits will in addition be limited by the selection, sensitivity and specificity of background nocturnal measures. Hypoxaemia is universally measured using continuous and responsive ear oximetry, providing an abundance of sensitive parameters reflecting duration, severity, frequency and cumulative distributions of hypoxaemia for statistical analysis. But the variability in measures of breathing disorder and sleep fragmentation employed by researchers may have a profound impact on studies' results. The introductory chapter alluded to
shortcomings in the apnoea index as a measure of breathing abnormality during sleep. In addition, the conventional practice within sleep research of using averaged, epoch-based Rechtschaffen and Kales (1968) sleep staging, thus evaluating 30-second blocks of recording for overall sleep quality, underestimates sleep disruption more accurately measured by event-based arousal scoring (Stepanski et al 1984). Reliance in many studies on apnoea index (Roth et al 1980, Greenberg et al 1987, Bédard et al 1991a) and/or averaged sleep staging (Guilleminault et al 1988, Bédard et al 1991a, Mendelson 1992) may result in insensitive variables within correlation matrices. At a more basic level, some studies include no correlations of breathing disturbance separate from oxygenation variables (Findley et al 1986, Telakivi et al 1988) or no evaluation of sleep quality (Yesavage et al 1985, Berry et al 1986, Greenberg et al 1987, Telakivi et al 1988, Johns 1993), thus further limiting these studies’ usefulness in discriminating the aetiology of specific daytime impairments in SAHS.

The problem of intercorrelation of polysomnographic measures, pre-defined by the causative relationships between nocturnal events, may be partially solved through the use of statistical techniques, such as multiple and logistic regression, to disentangle the independent contributions of hypoxaemia-related and sleep disruption-related variables. These can only be compared in studies using measures of both hypoxaemia and sleep disruption.

The studies using such an approach to examine daytime sleepiness (Roehrs et al 1989, Guilleminault et al 1988, Bédard et al 1991a, Mendelson 1992, Cheshire et al 1992) yield mixed results. Neither Guilleminault et al (1988) nor Cheshire et al (1992) were able to build a multiple regression model explaining MSLT scores. Bédard et al (1991a) found no significant contribution from epoch-scored sleep quality to mean sleep onset latency, but found that MSLT score was independently determined by minimum oxygen saturation. The use of relatively insensitive measures of sleep disruption perhaps compromises the robustness of this comparison of the effects of hypoxaemia and sleep fragmentation.

Mendelson (1992) built models showing independent contributions from mean minimum oxygen saturation in REM sleep and AHI to mean sleep onset latency, explaining 67% of variance. Subjective sleepiness, self-rated on a 5 point Likert scale, was explained with a 2-factor equation containing first sleep efficiency and second AHI, together explaining 63% of subjective sleepiness variance. The measures of sleep disruption included only epoch-based scores of nocturnal sleep latency, sleep
efficiency and wakefulness after sleep onset. The insensitivity of measures of sleep disruption in this study might have biased its findings relating hypoxaemia and objective daytime sleepiness, although the independent association between subjective sleepiness and sleep efficiency fits with the hypothesis linking excessive daytime sleepiness most strongly with sleep disruption.

Roehrs et al (1989) used a good-quality array of nocturnal measures to assess arousal from sleep and hypoxaemia, and performed a multiple regression analysis of the effects of polysomnographic variables from nocturnal studies on MSLT scores in 466 SAHS patients. The single best predictor of objective daytime sleepiness was the respiratory arousal index, here defined as an increase in EEG frequencies or EMG activity of 3 seconds’ duration at the termination of an apnoeic or hypopnoeic event. The best two-variable predictor of MSLT score was a combination of the percentage of stage 1 sleep and the total sleep time from the nocturnal study.

Only two studies allow multiple regressions of daytime cognitive performance, through their inclusion of both oxygenation and sleep fragmentation measures (Bédard et al 1991a, Cheshire et al 1992).

Bédard et al (1991a) performed stepwise multiple regression with the correlates of four-choice reaction time, which included epoch-scored sleep quality and oximetry variables. Response time was independently predicted firstly by minimum oxygen saturation and secondly by stage shifts to wakefulness.

Cheshire et al’s (1992) study included a sensitive range of nocturnal background variables measuring sleep disruption and hypoxaemia and proceeded to a construction of individual multiple regression models to explain the determinants of performance on block design, IQ decrement and reaction time, using background variables of arousals, hypoxaemia and AHI. Block design was best explained by a model containing AHI alone, neither minimum saturation nor arousal frequency contributing independently to performance. Reaction time showed equal independent determinants in microarousal index and AHI, with no additional contribution from hypoxaemia. IQ decrement was explained with a model containing first AHI with a minor secondary contribution from minimum saturation. This study, the best available to investigate the aetiology of cognitive impairment in SAHS, thus suggests that sleep disruption and hypoxaemia independently and differentially contribute to specific performance deficits.
The only multiple regression analysis of the contribution of nocturnal variables to daytime mood is that performed on data from 25 patients by Reynolds et al (1984), who constructed a predictive model containing age, use of anti-hypertensive drugs, REM latency and REM density to explain depression self-ratings, selection of these independent factors based on variables shown to influence depression in a median-split analysis. No raw polysomnographic data is presented and while the methods section describes sleep stage scoring it contains no reference to oximetry or to event-scored arousals. It is thus difficult to evaluate whether sensitive measures of hypoxaemia and sleep loss might have been predictors of psychological distress.

Recent studies have attempted further to disentangle the contributions of hypoxaemia and sleep fragmentation to daytime impairments of SAHS through other experimental approaches.

Colt et al (1991) administered two nights of CPAP to 7 SAHS patients under two randomised conditions. In the first condition, CPAP was administered to reduce apnoeas, hypopnoeas, microarousals and desaturations, while in the second, CPAP was administered with the addition of experimental intermittent hypoxia. Mean sleep onset latency was improved by both types of CPAP, and improvements were similar in both conditions, suggesting that the addition of hypoxaemia has lesser influence on objective daytime sleepiness than sleep fragmentation.

Naëgelé et al (1995) investigated the aetiology of cognitive deficit in SAHS by performing logistic regression analyses to examine which cognitive scores discriminated between moderate and severe apnoeic patients, and which between patients with moderate and severe hypoxaemia. Coding efficiency, memory and planning ability appeared to best contrast high and low levels of breathing disruption, while coding ability and abstract reasoning were most different in the contrasted hypoxaemia groups. The study did not include specific measures of sleep quality, and showed overlap in those performance tests related to breathing abnormality and hypoxia, probably as a result of correlation in the two nocturnal measures.

Another recent study has attempted to delineate the respective contribution of hypoxaemia and sleep fragmentation to daytime performance impairment by comparing neuropsychological performance in patients with SAHS and COPD. Roehrs et al (1995) found greater objective and subjective sleepiness in SAHS...
patients, and greater sleep disruption on averaged Rechtschaffen and Kales (1968) sleep scores, supporting a role for sleep fragmentation in inducing excessive daytime sleepiness. COPD patients had greater impairment in motor speed and SAHS patients greater deficit on a visual vigilance task. Within the SAHS patients, the best independent predictor of overall cognitive performance, adjusted for age and education, was objective daytime sleepiness, with a minor contribution from duration of hypoxaemia. This study lacked age-matching in the two patient groups, but its results suggest that sleepiness is more closely related to sleep fragmentation, and that cognitive function may have determinants in both hypoxaemia and sleep disruption.

Thus, only a limited number of clinical studies offer a comparison of the contribution of hypoxaemia and sleep disruption to the domains of daytime impairment associated with SAHS. The balance of evidence may lean towards a role for sleep disruption in determining the excessive daytime sleepiness typical of SAHS. The picture is less clear for the aetiology of cognitive dysfunction in SAHS, although studies containing sensitive nocturnal and daytime variables implicate determining roles for both hypoxaemia and sleep fragmentation.

2.8 Summary
SAHS patients' complaints of excessive daytime sleepiness, cognitive impairment and psychological dysfunction are corroborated by objective case-control studies. Polysomnographically-determined sleep tendency is largely within the pathological range in samples of SAHS patients. Neuropsychological performance drawing on attention, memory and co-ordination is moderately impaired and neurophysiological function may be disturbed. A high incidence of psychological and psychosocial distress is seen in SAHS. Patients with SAHS have an elevated road traffic accident rate, and their sleep-related accidents may claim greater casualties. The severity of nocturnal events in SAHS has been widely associated through correlational and split-sample studies with the patients' degree of sleepiness and cognitive impairment. Psychological distress in SAHS has been associated with the intensity of physical symptoms and role limitations imposed by illness. Evidence both from clinical samples of SAHS patients and from experimental and disease models suggests that excessive daytime sleepiness and attention deficits may be related to sleep fragmentation, while other intellectual deficits may arise as a result both of sleep disruption and intermittent nocturnal hypoxaemia. While daytime symptoms arising from sleep disruption are potentially completely reversible following restoration of sleep quality, the hypothetical reversibility of hypoxia-mediated intellectual deficits
may be more limited. The next chapter reviews the limited number of clinically-based studies examining the efficacy of CPAP treatment in ameliorating daytime impairments in SAHS.
Chapter 3: Daytime function after CPAP

DAYTIME FUNCTION FOLLOWING CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) TREATMENT IN SAHS

Themes developed in the preceding chapter included the hypothetical bases of reversibility of daytime problems associated with SAHS. I now hope to summarise the findings of empirical studies, though limited in number and quality, of daytime neuropsychological function after continuous positive airway pressure (CPAP) therapy in samples of SAHS patients.

The success of CPAP in reversing the nighttime features of SAHS, including apnoeas and hypopnoeas, arterial oxygen desaturations and disruption of sleep architecture, was described in Chapter 1. CPAP can abolish respiratory abnormalities in sleep (Sullivan et al 1981, Sanders 1984) by mechanically maintaining upper airway patency (Issa and Sullivan 1984, Abbey et al 1989). CPAP thus removes the causal agent, airway obstruction, in the triad of nocturnal events characteristic of SAHS, normalising both arterial oxygenation profiles (McEvoy and Thornton 1984) and sleep architecture (Lamphere et al 1989, Guilleminault et al 1992). Because these nocturnal events are the putative aetiological forbears of daytime impairment in SAHS, CPAP may also be effective in reversing patients' daytime deficits.


In many North American centres, research practice involves daytime studies of sleepiness, mood and cognitive performance following a night of polysomnography with CPAP (Lamphere et al 1989, Fry et al 1990, Bédard et al 1993, Kribbs et al 1993b). Such studies have advantages, in that proper CPAP use can be verified during the night before daytime testing, but produce concurrent disadvantages as a result of
the untoward effects of recording procedures on sleep quality, which may have knock-on effects on the subsequent day's function.

Sleep continuity in the laboratory is known to be compromised, partly because of the subject's lack of familiarity with the environment, causing the so-called "first-night effect" (Cooper and Bradbury 1994) of reduced sleep efficiency. Consequently, many research protocols schedule a night's acclimatisation to sleep in the lab before conducting measurements. Naturalistic sleep in a laboratory is also compromised by the presence of equipment such as ear oximeters, oronasal thermistors and EEG wires on the patient's body. This equipment reduces subjects' comfort, easily falls off and becomes tangled during sleep. While an acclimatisation night's sleep may familiarise subjects with the experience of sleeping "wired up", it is likely (although untestable) that the polysomnographic measurement itself reduces sleep continuity. Thus pre-assessment polysomnography, while ensuring CPAP compliance, may skew the results of daytime measures of function.

Despite these reservations applying to almost all of the studies reviewed here, the available evidence suggests that CPAP therapy may be effective in reducing daytime sleepiness, improving cognitive impairment and ameliorating psychological dysfunction.

3.1 Excessive daytime sleepiness after CPAP

As was hinted at in Chapter 2, objective measurements of sleepiness in SAHS represent a 'gold-standard' assessment of excessive daytime sleepiness, as patients' subjective ratings using the Stanford sleepiness scale have been shown to be unreliable in hypersomnolent patients (Dement et al 1978, Roth et al 1980, Browman and Mitter 1988). Objective studies of sleepiness using polysomnographic techniques after CPAP (Wittig et al 1986, Lamphere et al 1989, Walsleben et al 1989, Fry et al 1990, Gaddy and Doghramji 1991, Sangal et al 1992b, Poceta et al 1992, Charbonneau et al 1992, Bédard et al 1993, Kribbs et al 1993b) have shown varying degrees of resolution of daytime sleepiness, perhaps, as explained here, as a function of the precise instructions administered to subjects.

Lamphere et al (1989) showed dramatic improvements in objective daytime sleepiness following CPAP therapy. A single night of CPAP significantly extended daytime sleep latencies during an MSLT from a pre-treatment mean of 3 minutes to 6 minutes (within the 'grey zone' of daytime sleepiness), and following 14 nights of CPAP the
mean sleep latency reached almost 10 minutes. This normalisation in sleep onset latency on the MSLT after CPAP commencement has been corroborated by Wittig et al (1986), who found that daytime mean sleep latencies averaged more than 10 minutes after 6 weeks of CPAP. Thus in these two studies, CPAP precipitated a rise in MSLT score to a level outwith the 'pathological' range and into the normal range of greater than 10 minutes (Carskadon et al 1986).

However, these findings of clinically-significant reversibility in daytime sleepiness have not been replicated by others employing the MSLT to measure changes in sleepiness after CPAP in sleep apnoea. In a preliminary report, Fry et al (1990) reported a change in MSLT scores from 4.1 minutes before the institution of CPAP to 7.8 minutes after at least 2 months of CPAP in 21 patients with SAHS. Similar small improvements, with latencies remaining within the 'grey zone', have also been reported by Gaddy and Doghmjji (1991), Bédard et al (1993) and Kribbs et al (1993b). A pre-treatment mean sleep latency of 6 minutes rose to 9 minutes after CPAP in 63 patients (Gaddy and Doghmjji 1991), and in a small sample of 20 moderate and severe apnoeic patients, 6 months of CPAP resulted in an increase in sleep onset latency from a baseline average of 4.6 minutes to 8.9 minutes (Bédard et al 1993). These findings are paralleled by those of Kribbs et al (1993b) who reported daytime mean sleep latencies before CPAP of around 3 minutes in 15 patients, rising to approximately 6 minutes after at least one month of CPAP.

It remains a possibility that the conflicting evidence for normalisation of MSLT scores after CPAP from these studies reflects differences in CPAP compliance rates or in effectiveness of CPAP in these samples of SAHS patients. However, the studies of Lamphere et al (1989), Bédard et al (1993), Fry et al (1990) and Kribbs et al (1993b) made specific mention that the study subjects attended for polysomnography on the night preceding both the baseline and the post-treatment MSLT, ensuring that CPAP was complied with on at least that one night prior to assessment. In Kribbs et al's (1993b) patient group, a subsample had CPAP compliance rates objectively monitored, but for the majority diaries were the only measure of compliance. If these data are to be trusted, in itself a controversial assumption (Rauscher et al 1993b), CPAP compliance averaged 5.7 hours per night, which compares well to the objective CPAP compliance findings from cross-national studies (Kribbs et al 1993a, Rauscher et al 1993b, Krieger and Kurtz 1988). Thus Kribbs' findings of relatively small improvements in MSLT score cannot be necessarily be attributed to poor CPAP compliance in that sample.
Nor can the relative effectiveness of CPAP in reversing apnoeas and hypopnoeas be blamed for the inter-study variability in patients' MSLT scores after CPAP. Bédard et al (1993) and Lamphere et al (1989) both reported an objectively-demonstrated reduction of respiratory event indices during the CPAP-treated night of polysomnography to around 10 per hour slept. In these two studies then, the effectiveness of CPAP preceding the assessment MSLT were comparable and cannot explain the discrepancies concerning normalisation of objective daytime sleepiness. In the study by Kribbs et al (1993b), respiratory events in sleep on the night preceding the post-CPAP MSLT fell to 3 per hour slept, yet MSLT latencies averaged only 6 minutes.

Some researchers believe that the disappointingly small improvements in MSLT found by some studies after the institution of CPAP may be due to the effect of instruction in the test. The instructions at the commencement of each MSLT nap specifically encourage subjects to "try to fall asleep" (Carskadon et al 1986), relying on an assumption that an increase in alertness (or the ability to remain awake) will provoke a parallel decrease in sleepiness (or the ability to fall asleep). This unidimensional model of a sleepiness/alertness drive has been challenged by recent studies comparing the sleep onset latencies during daytime nap tests when hypersomnolent patients are given paradoxical instructions to remain awake (in the MWT) or to fall asleep (in the MSLT) on succeeding nap opportunities (Sangal et al 1992a, 1992b).

Sangal et al (1992a) performed a factor analysis of the sleep onset latencies obtained from an MSLT and an MWT, performed concurrently, in a heterogeneous sample of 258 hypersomnolent patients. The analysis revealed two major factors corresponding to 'sleepiness' and 'alertness' loaded on MSLT and MWT latencies respectively. One third of a subsample of SAHS patients were shown to have discordant results in the two tests. Sangal et al (1992b) found no significant change in MSLT score, but a significant lengthening of MWT score after treatment in his mixed sample of sleepy patients, suggesting that the ability to stay awake, but not the ability to sleep, was altered with treatment.

The MWT has no established norms, limiting its use in quantifying clinically-significant improvements in excessive daytime sleepiness, but recent studies (Walsleben et al 1989, Poceta et al 1992, Sangal et al 1992b) suggest that it may be
sensitive to treatment-related improvements in excessive daytime sleepiness. Poceta et al (1992) administered the MWT before and after CPAP to a group of 24 SAHS patients with an AHI greater than 5 per hour slept and found significant lengthening of MWT sleep onset latencies from 18 minutes to 32 minutes. Sangal et al (1992b) compared post-CPAP MWT score of 15 SAHS patients to baseline MWT score, showing a significantly increased mean sleep onset latency from 24 minutes to 32 minutes. Walsleben et al (1989) administered the MWT before and then after 2 nights of CPAP, reporting a statistically significant lengthening of sleep onset after CPAP, but included no raw or group data.

Objective studies of daytime sleep tendency using polysomnographic techniques have thus shown improvements in sleepiness in SAHS patients treated with CPAP, as might be predicted from theoretical research linking excessive daytime sleepiness to sleep fragmentation. The only studies reporting no statistically significant improvements in MSLT score after CPAP have been confounded by the inclusion of non-SAHS patients or the inclusion of ineffectively treated SAHS patients. Charbonneau et al (1992) studied a mixed group of 26 snorers and SAHS patients, and found a non-significant drop in MSLT sleep onset latency from 12.3 minutes pre-CPAP to 11.4 minutes after one month of CPAP. The incorporation of non-SAHS patients in this study is reflected in the normal pre-treatment sleep onset latency. Sangal et al (1992b) found no statistical lengthening of MSLT score after treatment in a sample of 26 SAHS patients, but 11 of these subjects were treated with unsuccessfully UPPP, as demonstrated by polysomnography showing a reduction of AHI from 56 to only 45 per hour slept in these 11. Thus the negative findings of these two studies, showing no improvement after CPAP, are potentially unreliable.

A recently developed self-rated scale quantifying daytime sleepiness, the Epworth sleepiness scale (ESS: Johns 1991, 1992 and 1993), may show promise as a more reliable and sensitive measure of daytime sleepiness than the Stanford sleepiness scale (Hoddes et al 1973), whose subjective-perception based items have been shown to be unreliable in hypersomnolent patients (Dement et al 1978, Roth et al 1980, Browman and Mitler 1988). The ESS asks subjects to reflect on their likelihood of experiencing specific sleep-related behaviours under different conditions such as "sitting and reading" or "watching TV", and may thus provide greater reliability in patients who have become inured to the sensations of impending sleep, but can still reliably assess their recent napping behaviour retrospectively.
Chapter 3: Daytime function after CPAP

Factor analysis of the ESS item scores from both healthy and apnoeic samples reveals only one main factor, reflecting internal consistency within the scale (Johns 1992). The total ESS score has been found to discriminate snorers from SAHS patients, to relate to the severity of breathing disruption in sleep (Johns 1991 and 1993) and, unlike the SSS, to correlate significantly with objective measures of sleepiness obtained from the MSLT in hypsomnnolent patients (Johns 1991).

Scores from the ESS were significantly reduced from a pre-CPAP average of 14 to post-CPAP mean of 7 in 54 SAHS patients treated with CPAP for 3 months (Johns 1992). While no measure of compliance was obtained in the SAHS patients to corroborate that ESS score changes were attributable to CPAP, this significant improvement in scores cannot be attributed to an order effect, as in normals test-retest scores are remarkably stable (Johns 1992). Thus a potentially valid subjective sleepiness scale supports objective studies documenting statistical and at least partial clinical improvements in excessive daytime sleepiness following CPAP therapy.

Researchers continue to debate which instrument provides the best measure of sleep tendency and whether the improvement in sleepiness after CPAP is large or small in magnitude, but no researcher has so far found an absence of improvement after CPAP treatment. These empirical findings support the hypothesis that excessive daytime sleepiness in SAHS may arise from reversible nocturnal sleep disruption.

3.2 Cognitive function after CPAP

Both empirical and hypothetical evidence suggested that cognitive impairment in SAHS might result from a combination of hypoxaemia and sleep disruption. Thus the reversibility of cognitive impairment in SAHS, based on models of hypoxic disease, remains ambiguous, and the existing empirical studies in SAHS patients do not conclusively resolve this important question.

Clinical studies of CPAP's effects in SAHS patient samples are limited in both number and quality, at least partially because of the problems of learning curves with repeated testing, which confound the evaluation of true improvements in performance. In fact, research in this important area has been confined to a very few, often preliminary, studies (Bearpark et al 1987, Charbonneau et al 1992, Walsleben et al 1989, Bédard et al 1993, Kribbs et al 1993b, Partlett et al 1994).
### Table 3.1: Changes in cognitive function with CPAP

<table>
<thead>
<tr>
<th>Author</th>
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<tr>
<td>Bearpark et al 1987</td>
<td>12 ‘impaired’ SAHS pts</td>
<td>Uncontrolled, before and after &gt;4 months on CPAP</td>
<td>WMS, BVRT, TM, Stroop, VF, NART</td>
<td>Improvements in WMS, BVRT, VF, Stroop</td>
</tr>
<tr>
<td>Charbonneau et al 1992</td>
<td>26 mixed snorers/SAHS pts</td>
<td>Uncontrolled, before and after 1 month CPAP</td>
<td>DS, memory</td>
<td>Improved memory</td>
</tr>
<tr>
<td>Kribbs et al 1993b</td>
<td>15 SAHS pts</td>
<td>CPAP withdrawal study</td>
<td>RT, DS, DSp, Stroop</td>
<td>RT improved with CPAP but did not fall off after CPAP-withdrawal</td>
</tr>
<tr>
<td>Walsleben et al 1989</td>
<td>7 SAHS pts</td>
<td>AEP controls tested once. Pts assessed before and after 2 nights CPAP</td>
<td>WMS, TM, VF, BD, PB, DS, AEPs</td>
<td>No change in cognitive performance, but improved P3 latency after CPAP.</td>
</tr>
<tr>
<td>Rumbach et al 1992</td>
<td>47 SAHS pts</td>
<td>Partially controlled (controls tested once). Pts assessed before and after 6 weeks CPAP</td>
<td>AEPs</td>
<td>Improved latency and amplitude of N2 and P3, but decrease in amplitude of P2 amplitude with CPAP.</td>
</tr>
<tr>
<td>Bédard et al 1993</td>
<td>10 SAHS pts, 10 controls</td>
<td>Partially controlled (controls tested once). Pts retested after 6 months CPAP</td>
<td>RT, WAIS-R, WMS, LC, PB, TM, VF</td>
<td>Pts improved in RT, Perf IQ, LC, immediate and delayed WMS, PM, PB</td>
</tr>
<tr>
<td>Oveson et al 1992</td>
<td>5 SAHS pts</td>
<td>Withdrawal trial of CPAP</td>
<td>RT</td>
<td>Improvement in RT with CPAP and fall-off on CPAP withdrawal</td>
</tr>
<tr>
<td>Partlett et al 1994</td>
<td>18 SAHS pts</td>
<td>Uncontrolled</td>
<td>RT</td>
<td>No change in median RT</td>
</tr>
</tbody>
</table>

**Key to Table 3.1**

- **WAIS**: Wechsler Adult Intelligence Scale
- **WMS**: Wechsler Memory Scale
- **TM**: TrailMaking
- **LC**: Letter cancellation
- **BVRT**: Benton visual retention test
- **VF**: Verbal fluency
- **PASAT**: Paced auditory serial addition test
- **NART**: National adult reading test
- **AEPs**: Auditory evoked potentials
- **RT**: Reaction time
- **PB**: Pegboard
- **BD**: Block design
- **PM**: Porteus mazes
- **FT**: Finger tapping
- **SR**: Seashore rhythm
- **SP**: Speech perception
- **DS**: Digit symbol substitution
- **DSp**: Digit span
Bearpark et al (1987) was the first to report improvements in cognitive function after CPAP after studying 12 moderate and severe SAHS patients before and at least 4 months after the commencement of CPAP. The authors administered a cognitive battery that included the Wechsler memory scale and the Benton visual retention test as measures of memory, the TrailMaking B task from the Halstead-Reitan battery and the Stroop test as assessors of mental set flexibility, a test of word production and the National Adult Reading Test (NART). The use of the NART allowed Bearpark to identify those 9 patients who were "impaired", by comparing obtained performance IQ measures to the pre-morbid estimates of performance IQ derived by the NART scores. In the 9 impaired patients, Bearpark reported statistically significant improvements in performance scores obtained after CPAP for Wechsler subjective memory, Benton visual memory, verbal fluency and the Stroop test.

Charbonneau et al (1992), in a study already referred to in the review of sleepiness after CPAP, also reported significant improvements in memory on an unspecified test, but no improvement in coding efficiency as assessed by the digit symbol substitution test from the WAIS-R battery, in 26 subjects treated with one month of CPAP.

Both of these studies can be criticised for their lack of control for the effects of learning on measures of performance. Neither a familiarisation session to obtain plateauing of performance, nor a balanced, placebo-controlled crossover design, nor a parallel group design (following untreated as well as treated patients) were employed in these studies, making the assessment of the relative contribution of improved functional ability and learning-related improvement impossible to disentangle. Neither author reported the use of alternative forms of tests, where available, which might mitigate against such learning effects, although since both publications were short reports, pressure of space might have prevented this. In addition, the study by Charbonneau et al (1992) combined snorers with SAHS patients, although even a subsample of 11 severe sleep apnoeics showed no improvement in digit symbol performance after CPAP.

The study by Kribbs et al (1993b) reported the effects of at least one month of CPAP followed by the withdrawal of CPAP for a single night in 15 patients. Performance was evaluated before CPAP, after 2 weeks on CPAP and upon withdrawal of CPAP for one night. The psychometric battery included a Wilkinson-type 4-choice reaction time task, the digit symbol substitution and digit span subtests from the WAIS battery and the Stroop test of mental processing speed under conditions of interference.
Simple reaction time improved significantly from baseline levels after CPAP but did not return to pre-treatment levels after withdrawal of CPAP for a single night. This finding of improvement after CPAP and lack of fall-off after CPAP withdrawal may have been due to practice effects and/or to a carry-over effect of CPAP treatment. Performance on the digit symbol, digit-span and Stroop tests all showed time-course improvement from baseline to on-CPAP to off-CPAP conditions, which the authors attributed to the effects of a learning curve.

Walsleben et al (1989) evaluated cognitive performance before and after 2 nights of CPAP in 7 SAHS patients. Her cognitive assessments included the Wechsler memory scale, a verbal learning test, TrailMaking tasks A and B, a verbal fluency test, the information and block design subtests of the WAIS-R battery, pegboard test of manual dexterity and the symbol digit modalities test. Alternative forms of these tests were reportedly used on the second testing session, although no validated alternative versions of the block design, information or TrailMaking tasks are published. In any case, the results of paired comparisons of pre- and post-CPAP assessments found no significant improvements in any of the tests in this battery. With such a small patient sample, a lack of statistical power may be responsible for the lack of positive finding.

In addition, Walsleben et al (1989) recorded auditory evoked potentials (AEPs) before and after CPAP, finding a post-CPAP trend towards normalisation of P3 latency. The authors conducted a subtrial within the larger study to assess order effects on wave component latencies during repeated testing and found no effect, providing reassurance that the shortened latency of P3 after treatment was not due to a familiarisation effect. These results are supported in a study of 47 SAHS patients, who showed a significant decrease in latency and increase in amplitude of both N2 and P3 wave components after 6 weeks of CPAP (Rumbach et al 1992), although P2, N2 and P3 latencies remained slower than those of a control group, tested once only. P2 amplitude was significantly higher in patients before treatment than in controls, and was significantly decreased after CPAP. This finding is of uncertain significance and was not discussed by the authors. Learning may be less of a problem in these neurophysiological studies than in neuropsychological research, and the shared association between measures of both sleepiness and cognitive processing and AEP waveforms mean that AEPs may prove effective markers for overall treatment response in therapeutic studies.
In Bédard et al's study (1993), a matched control group was tested only once while a patient group of 10 SAHS patients underwent comprehensive neuropsychological testing both before and after 6 months' treatment with CPAP. In this study design no control was provided for the effects of repeated test administration in the patient group. Paired t-tests of pre- and post-CPAP scores in the patient group showed significantly higher scores in the overall performance IQ after CPAP, with individual statistical improvements in performance on the digit symbol, block design, object assembly and picture arrangement subtests. Patients also performed significantly better on repeated testing in the letter cancellation test, four-choice reaction time, immediate and delayed memory from the Wechsler memory scale, WISC mazes and pegboard skills. Some post-CPAP test scores, specifically those for Porteous mazes, TrailMaking B, picture arrangement, verbal fluency and pegboard skills, remained significantly lower than those of the controls. While some post-CPAP increases in test score may have been influenced by learning, the persisting deficits in others on retesting provide support for an argument that SAHS patients are cognitively compromised, even after treatment. Bédard et al (1993) hypothesised that CPAP treatment reverses some cognitive deficits, specifically those affecting attention, memory and constructional abilities, but not others, such as verbal fluency, manual dexterity and planning ability. This conclusion may not be strictly correct, as learning effects might be responsible for some increased scores on second testing. Despite extensive efforts to closely match the 10 cases and controls for background factors, the small number of subjects in this study compromises its reliability. However, the study may support a hypothesis, derived from hypoxic disease models, that some cognitive deficits are irreversible after CPAP, as despite the benefit of extra exposure, the patients' performance remained significantly lower than that of the controls.

A further small-scale study (Oveson et al 1992) examined median reaction time in 5 patients before treatment, after 2 weeks on CPAP and after withdrawal of CPAP for 2 days. Patients’ reaction time shortened with CPAP and extended again after withdrawal, all the magnitude of improvement is difficult to assess against a probable background learning curve.

In contrast to the findings of Oveson et al (1992), Bédard et al (1993) and Kribbs et al (1993b), Partlett et al (1994) found no change in reaction time, this time in a simple unprepared paradigm, in 18 SAHS patients treated with CPAP. Only the second 10 minutes of a 20-minute reaction time task were analysed, when attention deficits provoked by sleep loss are most evident (Donnell 1969, Wilkinson et al 1966).
Although simple unprepared reaction time is relatively free of a learning curve (Wilkinson and Houghton 1975), the use of the latter half of the task provided an extra control for this effect. Compliance with CPAP, assessed by time counters logging time that units were switched on, averaged 4.3 hours, in line with other recent studies of SAHS patient series (Kribbs et al 1993a, Reeves-Hoché et al 1994, Rauscher et al 1993b). All patients reported a subjective improvement in daytime sleepiness, but this was not reflected in improved reaction time. This study, conducted in a larger sample of verifiably compliant patients, raises the possibility that improved subjective sleepiness is not accompanied by improved objective vigilance, or that reaction time tests are not a useful probe for daytime alertness in SAHS.

While the short reports of Bearpark et al (1987) and Charbonneau et al (1992) contain no data on CPAP compliance, polysomnography performed on the night prior to post-CPAP cognitive testing in some studies (Kribbs et al 1993b, Walsleben et al 1989, Bédard et al 1993) provides some assurance that compliance with and pressures of CPAP were acceptable, at least on that single monitored night. Partlett et al (1994) reported average CPAP runtimes.

The empirical evidence on the reversibility of SAHS' cognitive impairment with CPAP remains cloudy, like the hypothetical reversibility based on experimental and disease analogues for SAHS. No large scale, adequately controlled trial has yet been conducted to tip the balance either in favour or against the restoration of cognitive ability after CPAP. This nebulous area thus provides rich research opportunities, to be explored further in the practical work within this thesis.

3.3 Psychological wellbeing after CPAP

Longitudinal measurements of changes in mood, personality and psychological distress pose their own particular methodological problems. The effects of repeated administration of a scale may have an independent effect on responses, as the subject may answer the questions in a comparative rather than absolute manner. Thus controls for repeated administration are desirable. A second methodological problem concerns the anticipation of recovery after clinical intervention, the 'placebo effect'. The expectation of improvement after treatment may confound the measurement of improvement, necessitating in ideal studies the use of a placebo control. In addition, the previously mentioned criticisms of the assumption of acceptable CPAP compliance, common to most CPAP-based studies, apply to psychosocial studies.
The MMPI has been extensively used in studies of personality in SAHS and has been used, perhaps controversially, to show change after successful treatment of the syndrome (Platon and Sierra 1992, Mayleben et al 1990). The MMPI theoretically measures stable and enduring traits, so may not be the most suitable instrument for assessing short-term therapeutic changes in personality. Platon and Sierra (1992) retested a small sample of apnoeic patients after approximately 3, 9 and 12 months of "successful" CPAP treatment, and found that mean MMPI scores that were elevated before therapy were reduced to the normal range after 9 months. Only 4 SAHS patients were re-tested with the MMPI after 12 months of CPAP, but scores for this group were significantly lower than those found at 9 months. The study by Mayleben et al (1990) used paired pre- to post-CPAP treatment comparisons to show that MMPI hysteria, hypochondriasis and depression scores were all significantly reduced following CPAP. Neither author used controls for the effects of repeated administration or for the expectation of improvement after commencement of CPAP. However, both studies suggest that trait evaluations show improved psychological function after CPAP.

Mood state assessment using the POMS adjective checklist featured in a small parallel-group study that controlled for the effects of repeated administration of mood measures by examining the changes in scores in 7 untreated and 7 CPAP-treated patients with SAHS (Derderian et al 1988). ANOVA found that depression-dejection and fatigue-inertia scores were significantly improved by CPAP, as was the total mood disturbance score. Kribbs et al (1993b) examined the change in POMS scores with the withdrawal of CPAP treatment for one night and found a return to pre-CPAP scores in the energetic arousal-loaded subscales of vigour-activity and fatigue-inertia scales. While these results suggested that mood effects may be perceptible after as little as one night off CPAP, the study did not control for the patients' own anticipation of a return of symptoms of SAHS with the withdrawal of CPAP. However, this study was the only one which objectively monitored some patients' compliance with CPAP treatment, via the use of microprocessors concealed within the CPAP units.

Measures of psychiatric morbidity also appear to be sensitive to CPAP-mediated improvements in wellbeing. Millman et al (1989) repeated the administration of the Zung self-rating depression scale in 19 patients after at least 3 weeks of CPAP use and found that the group's mean score, which was above the pathological threshold before treatment, then fell within normal limits. The fall in scores was particularly dramatic in those patients with elevated scores before CPAP, perhaps reflecting a resolution of the
somatic symptoms of SAHS that are embedded within the questionnaire. However, if the limitations of these studies are accepted, they provide evidence for improved psychological well-being after CPAP.

The above studies suggesting, with methodological reservations, improved psychosocial function following CPAP and fit well with Kales et al's (1985) hypothesis that the psychological distress of SAHS is secondary to physical symptoms and limitations. Such studies support CPAP's effectiveness in breaking the mechanistic cycle producing nocturnal events and thereby daytime sequelae.

3.4 Driving performance after CPAP

The observed reductions in excessive daytime sleepiness and the possible improvements in cognitive function implied by the existing studies in clinical SAHS patient samples would be expected to directly effect improvements in road safety for patients. However, objective evidence of such improvement is thin, at least partially because of the relatively recent availability of CPAP. Neither retrospective nor prospective studies examining driving accident rates after CPAP have yet been performed. However, laboratory evaluations of performance on driving simulators suggest that some of the demonstrable deficits driving skills associated with SAHS are reversible (Findley et al 1989a, Haraldsson et al 1991).

Findley et al (1989a) retested 6 SAHS patients after at least 3 months of CPAP on the SteerClear driving-based vigilance task and found that the pre-treatment error score of 29 during the 30-minute task was reduced to 13. This post-CPAP performance was no longer significantly different from that of 7 normals, who were tested only once. The influence of CPAP compliance rates and of repeated testing on this simulation's scores is not known, nor controlled for in the study.

Although the focus of this chapter is the daytime effects of CPAP, a valuable study evaluating post-UPPP driving skills on a realistic driving simulator suggests that treatment with CPAP might provoke significant improvements in road safety in SAHS. Haraldsson et al (1991) matched 10 controls to 15 patients complaining of significant sleepiness whilst driving, and tested both groups twice for 90-minutes in a realistic driving simulator, which measured braking reaction time, swerving and off-road incidents. The patient group's first drive occurred before treatment with UPPP and the second after surgery. Patients' performance, significantly depressed compared to that of controls at baseline, was not significantly different from the controls' second
performance. The study, along with the others above, suggests that driving competence may improve with effective treatment.

3.5 Summary
In keeping with the hypotheses formed in Chapter 2, empirical evidence from limited controlled studies suggest that daytime function may improve, at least partially, after CPAP. Large and small improvements in sleepiness have been shown by objective polysomnographic techniques. Evidence for the reversibility of cognitive deficits after CPAP for SAHS is inconclusive, but studies of psychological health suggest overall improved wellbeing after CPAP. Preliminary laboratory-based studies imply that reductions in sleepiness and, possibly, cognitive deficit indirectly produce improved driving performance. The inconclusiveness of many of the studies reviewed in this chapter, particularly those relating to cognitive performance, preserves the daytime effects of CPAP therapy as an incompletely explored and potentially fruitful research area. Practical studies performed to elucidate the effects of CPAP therapy on daytime neuropsychological function, beginning with a description of the assessment tools used in this project, will now occupy the remainder of this thesis.
Chapter 4:
METHODS OF MEASUREMENT

The aims of this project, to examine changes across a broad range of daytime function in SAHS patients treated with CPAP, required the use of diverse measurement techniques. Polysomnographic methods developed within the field of respiratory sleep research were used to diagnose and characterise patients, and to assess objective daytime sleepiness. Cognitive performance and psychological well-being were assessed using psychometric instruments from the fields of clinical, experimental and health psychology. Mechanical techniques were used to measure objective CPAP compliance.

4.1 Polysomnography

Overnight polysomnographic sleep studies, performed according to the laboratory’s standard procedure (Gould et al 1988), were conducted to diagnose and characterise the severity of SAHS in patients. An example of such polysomnography is shown in Figure 1.1. Physiological measures reflecting patients’ sleep quality, breathing pattern and oxygenation were recorded on a 16 channel chart recorder (SLE, Croydon).

4.1.1 Sleep quality

Electroencephalography (EEG), electo-oculography (EOG) and electromyography (EMG) were recorded from bipolar montages of signals obtained from surface electrodes of chlorided silver placed on the face and scalp. Submental EMG was recorded from two electrodes placed below the ramus of the jaw, the signal from the left chin referred to that from the right chin. EOG was recorded from 4 electrodes, placed at the outer canthus of each eye and on the frontal bone above each eye at sites FP1 and FP2 of the 10/20 electrode placement system. The outer canthus signal from each eye was referred to the frontal bone signal of the contralateral eye to optimise recorded changes in electrical potential created by eye movements. EEG activity was recorded from two scalp electrodes, referred to each other and placed at 10/20 sites Cz and Pz. A ‘mixed’ montage consisting of an EEG-EOG signal was also employed, as this resolves frontally-detected sleep spindles. EEG, EOG and EMG recordings were scored for sleep stage by the conventional criteria of Rechtschaffen and Kales (1968).

In Rechtschaffen and Kales’ (1968) system, information on brain activity from EEG, eye movements from EOG and muscle tone from EMG is synthesised to produce an overall score for sleep stage within a time-window of 20 or 30 seconds. Thus
Rechtschaffen and Kales' (1968) system provides an ‘averaging’ method for examining shifts in sleep stage over the time course of the night.

Awakenings lasting less than half an epoch (10 or 15 seconds) are missed by the macroscopic approach of Rechtschaffen and Kales' (1968), so EEG, EOG and EMG recordings were also scored for microarousals, short awakenings from sleep of 1.5 seconds or more. Microarousals were defined by a return of alpha or theta EEG activity for 1.5 seconds or longer, with a coincident rise in EMG activity of any duration (Cheshire et al 1992). This definition was developed in-house, as no consensus was available at the time of inception of this project. A consensus definition subsequently published by the American Sleep Disorders Association (Atlas Task Force 1992) has yet to be validated. A microarousal index was calculated by dividing the total number of arousals by total time slept.

4.1.2 Breathing pattern
A thermocouple placed on the upper lip sensed both nasal and oral airflow. This signal was scored for apnoeas, which were defined by the cessation of oronasal flow for 10 seconds or more (Guilleminault et al 1978). Abdominal and thoracic breathing movements were recorded using inductance plethysmography (Respitrace) from stretchable bands placed around the trunk. These signals were scored for hypopnoeas, defined by a reduction in thoracoabdominal effort of 50% or more for 10 seconds or longer (Gould et al 1988). Apnoea+hypopnoea index (AHI) was calculated as the frequency of apnoeas+hypopnoeas per hour slept.

4.1.3 Oxygenation
Oxygen saturation was recorded continuously by pulse oximetry (Biox) from a probe placed on the earlobe. This allowed the frequency of desaturation events and the waking and the minimum oxygen saturation during the night to be measured.

4.2 Multiple sleep latency test (MSLT)
Objective daytime sleepiness was measured using the multiple sleep latency test (MSLT), an polysomnographically-based procedure for assessing daytime sleep tendency (Carskadon et al 1986, Thorpy 1992). The test consists of 5 daytime nap opportunities, during which the latency to electrophysiological sleep is measured. The MSLT is considered a gold-standard measure of sleepiness against which subjective scales are measured (Dement et al 1978, Roth et al 1980, Browman and Mitter 1988, Johns 1991, 1992, 1994) and has been widely used for over 10 years in clinical and
experimental sleep research (Dement et al 1978, Carskadon and Dement 1979, Roth et al 1980, Carskadon and Dement 1981, Van den Hoed et al 1981, Richardson et al 1982, Carskadon and Dement 1982, Carskadon et al 1986, Browman and Winslow 1989), allowing norms for the principal outcome measure, mean sleep onset latency, to be established. A mean sleep onset latency of 5 minutes or less is thought to correspond to 'pathological' sleepiness, while a mean latency between 5 and 10 minutes represents moderate sleepiness (Carskadon et al 1986, Thorpy 1992). Mean latencies greater than 10 minutes are considered normal.

The MSLT was conducted according to the research protocol recommended by Carskadon et al (1986), with five daytime nap opportunities during which EEG, EOG and EMG, as described above, were recorded. The nap opportunities were regularly spaced at 2 hour intervals commencing at 10 am and with the last nap at 6 pm, so that circadian variations in sleep tendency were monitored. Each nap opportunity is terminated 15 minutes after the first appearance of sleep or after a maximum 20 minutes (Carskadon et al 1986), thus minimising reductions in sleep drive on subsequent nap opportunities that day. For each nap opportunity, subjects are asked to lie on a bed in a darkened room, and given standardised instructions to 'lie comfortably with your eyes closed and try to sleep'.

Sleep onset latency is usually defined as the time from 'lights out' to the first of three consecutive epochs of stage 1 sleep, or to the first epoch of any other sleep stage (Carskadon et al 1986). However we used a modified criterion for defining sleep onset latency in this study, comprising the latency to the first 20 second epoch of any sleep stage, including stage 1, because in SAHS frequent arousals associated with breathing irregularities interrupt periods of stage 1 sleep and prevent the scoring of three continuous epochs of stage 1 sleep. This criterion was subsequently independently adopted in a consensus paper from the American Sleep Disorders Association (Thorpy 1992). All MSLT traces, including those recorded by Katherine Cheshire, were rescoring using the modified criterion, eliminating inter-rater differences in this outcome measure. The MSLT yielded two measures for subsequent analysis; a mean sleep onset latency (the average of the sleep onset latency for the five nap opportunities), and the minimum sleep onset latency seen on the five nap opportunities.
4.2.1 Reproducibility of MSLT scoring

An intra-rater reliability exercise to assess the reproducibility of MSLT scoring was performed on 21 MSLT records. The values for the first and second scoring of the records, and correlations between the two values, are shown in Table 4.1. Test-retest correlations for individual sleep onset latencies on the 5 nap opportunities and for mean sleep latency were high ($r>0.93$, $p<0.001$), indicating highly acceptable reproducibility (Table 4.1).

Table 4.1: Reproducibility of sleep onset latency scoring

<table>
<thead>
<tr>
<th></th>
<th>First scoring Mean ± SEM</th>
<th>Second scoring Mean ± SEM</th>
<th>r-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 am nap (mins)</td>
<td>9.3 ± 1.5</td>
<td>9.4 ± 1.6</td>
<td>0.99</td>
</tr>
<tr>
<td>12 am nap (mins)</td>
<td>7.2 ± 1.3</td>
<td>6.9 ± 1.2</td>
<td>0.99</td>
</tr>
<tr>
<td>2 pm nap (mins)</td>
<td>6.5 ± 1.2</td>
<td>6.7 ± 1.1</td>
<td>0.93</td>
</tr>
<tr>
<td>4 pm nap (mins)</td>
<td>7.0 ± 1.1</td>
<td>7.1 ± 1.1</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>6 pm nap (mins)</td>
<td>11.0 ± 1.6</td>
<td>10.8 ± 1.6</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Mean sleep onset latency (mins)</td>
<td>8.2 ± 1.1</td>
<td>8.2 ± 1.1</td>
<td>0.99</td>
</tr>
</tbody>
</table>

4.3 Psychometric instruments

A wide variety of neuropsychological tests were used within the project to examine a broad range of daytime function. The chief psychological domains investigated were cognitive performance and well-being.

4.3.1 Cognitive performance tests

Wechsler adult intelligence scale (WAIS; Wechsler 1955) and Wechsler adult intelligence scale-revised (WAIS-R; Wechsler 1981)

General level of intellectual function was assessed using four selected subtests from the Wechsler adult intelligence scale (WAIS; Wechsler 1955) and the revised WAIS (WAIS-R; Wechsler 1981) battery, which consist in their entirety of 11 subtests. The four subtests used in the project, information, arithmetic, block design and digit symbol substitution, have the highest correlations with general intelligence (Lezak 1983) and are the most resistant to learning effects. Performance on WAIS subtests have been found to be impaired in SAHS patients (Bédard et al 1991b) and to correlate with the extent of nocturnal breathing disruption (Greenberg et al 1987). The WAIS and WAIS-R versions of subtests were used in the pilot parallel-group study and the principal crossover study respectively.
Information subtest (British adaptation: Wechsler 1955) comprises a series of general-knowledge questions of progressively increasing difficulty, with points awarded for correct answers. At the easier end of the test, the subject is asked to name four Prime Ministers of Great Britain since 1900; at the most difficult level, the subject is asked to demonstrate more esoteric knowledge such as the name of the writer of Faust. Educational level influences score on this test (Lezak 1983), but the executive function of recall is also called into play in its performance.

Arithmetic subtest (British adaptation: Wechsler 1955) is a task of increasing complexity involving mental arithmetic skills. All questions are presented in practical and concrete, not abstract or mathematical, terms (e.g. if one peach costs 6 pence, how many peaches can you buy for 36 pence?). As the test progresses, the number of arithmetical operations required to produce a correct answer increases, while at the same time a premium in terms of points scored is gained for quick answers. Although this subtest contributes towards the calculation of the Verbal IQ outcome measure, it incorporates non-verbal faculties such as concentration, particularly in the more difficult questions at the end of the test.

Digit symbol substitution subtest (Wechsler 1955, 1981) is a paper-and-pen coding exercise, in which the subject is required to write appropriate abstract symbols underneath one-digit numbers, according to a code key printed at the top of the page. Task duration is limited to 90 seconds and is scored by the total number of correct codings. The task brings into play visuomotor co-ordination, attention and learning.

Block design subtest (Wechsler 1955, 1981) is a construction task in which the subject is requested to replicate 2 dimensional geometric patterns using the top surfaces of coloured 'playing bricks'. The task progresses from simple 4-brick designs to complex and rotated 9-brick designs, with bonus points awarded for quick completion of designs. The test requires attention to detail, gaining zero points in the event of any mistake, however small, and calls into play visuospatial conceptualisation and motor dexterity.

Raw, unscaled scores from the individual WAIS subtests were used in statistical analyses. Scaled scores from block design and digit symbol subtests were used to prorate a performance IQ score and from information and arithmetic subtests to prorate a verbal IQ score (Wechsler 1955, 1981). Full IQ score was estimated from all subtests’ scaled scores.
Chapter 4: Methods of measurement

The additional WAIS-R performance subtests of object assembly, picture completion and picture arrangement, were administered once only, at the familiarisation session of the principal crossover study, and used with block design and digit symbol substitution to rate performance IQ.

**National adult reading test (NART) (Nelson 1982)** is a brief reading task which is used to estimate pre-morbid intellectual ability on the basis that word knowledge is highly correlated with general intelligence, and that the ability to pronounce familiar words is preserved even in organic brain damage (Nelson and McKenna 1975). It has been extensively validated in normal (Crawford et al 1988a, Crawford et al 1989a) and patient samples (Nelson and McKenna 1975, Hart et al 1986, O’Carroll et al 1987, Crawford et al 1988b). The NART comprises a list of fifty English words of increasing obscurity, all of whose pronunciation is irregular with regard to standard phonetic rules (e.g. from the easier level ‘psalm’ to the more difficult ‘demesne’). The subject is asked to read slowly down the list while pronunciation is monitored. The number of correctly pronounced words provides an estimate of pre-morbid IQ.

**IQ decrement score (Langan et al 1991)**

Performance IQ score obtained from the WAIS and WAIS-R performance subtests was subtracted from the NART-estimated pre-morbid performance IQ to calculate an estimated ‘IQ decrement’ score for each patient. While the performance IQ estimate may be the least reliable of the IQ estimates obtained from the NART (Crawford et al 1989a), the performance IQ subtests call on the executive functions disrupted by organic disease (Lezak 1983) and might be expected to prove more sensitive to SAHS-induced deficit.

**TrailMaking tasks A and B (Reitan 1958, Boll 1981)**, paper-and-pen tests from the Halstead-Reitan battery, assess visuomotor tracking using a ‘join-the-dot’ procedure (Figure 4.1). The A task consists of digits 1 to 25 scattered on a page, while the B task uses letters 1 to 13 and letters A to L. The subject is asked to join consecutive numbers in the case of task A, or alternate numbers and letters in task B, as quickly as possible but without making mistakes. The score obtained is the time taken to completion. Any mistakes in connection order are pointed out and the subject is asked to rectify them, thus adding time to the score. These tests are commonly used to assess general cognitive function (Lezak 1983) and TrailMaking B is thought to be particularly sensitive to organic brain damage (Reitan 1958). Performance on the B task has been
Figure 4.1: TrailMaking B task
found to be impaired in SAHS patient samples compared to normals (Bédard et al 1991b) or less hypoxaemic patients (Findley et al 1986).

Paced auditory serial addition test (PASAT) (Gronwall 1977) is an arithmetic-based task requiring sustained concentration. The subject is required to listen to a sequence of 61 one-digit numbers, which are presented at a regular pace on an audio tape, and is instructed to add the first number to the second and give the answer, the second to the third and give the answer, and so on, until 60 sums have been given from the consecutive pairs in the 61-number list. Explanation followed by a practise sequence is administered until the nature of the task is grasped by the subject, who then goes on to attempt the test first at a 4-second per number presentation rate, then at a 2-second per number presentation rate. The PASAT provides information on information-processing speed, attention and concentration ability, and has been shown to reflect cognitive deficit in hypoxaemic SAHS patients (Findley et al 1986).

Inspection time test (IT: Brand and Deary 1982) is a computer-administered task which assesses perceptual intake speed with visual stimuli of short duration. Pairs of vertical bars of markedly different lengths are presented briefly on a computer screen. The subject is required to consider which of the pair was the longer, and indicate, by pressing a computer key their perception. While some presentations will be sufficiently long in duration to allow correct discrimination of the longer bar, short-lasting presentations below a subject's individual information-processing threshold will require a guess on the part of the subject. The task is of variable duration, from 2 to 25 minutes, depending on response consistency assessed by an adaptive staircase psychophysiological procedure. The measures obtained from the task are the stimulus duration for which 80% of responses are correct (the inspection time) and the total number of trial stimuli administered (indicating consistency of response). The reliability of the test is dependant upon reasonable visual acuity in the subject, and test-retest reproducibility requires identical lighting conditions. Thus, the test was administered in a darkened room on a dedicated monochrome monitor whose brightness was controlled.

Rapid visual information processing test (RVIP: Wesnes and Warburton 1983) This 10-minute, computer-administered test based on signal detection theory was included in the cognitive battery as a measure of sustained concentration and information-processing ability and response caution. RVIP performance may be sensitive to cortical arousal mediated by cholinergic activity in the reticular activating
system (Wesnes and Warburton 1983, Petrie and Deary 1989), likely to be altered in SAHS, and correlates well with measures of general intellectual function in patient samples (Deary et al 1992). Single, one-digit numbers are presented at a rate of 100 numbers per minute on a computer screen. The subject is required to press the spacebar when a sequence of 3 consecutive odd or 3 consecutive even numbers occurs: such target sequences are embedded within the digit presentation array at a frequency of 8 per minute. The 'hit score' (number of correct target identifications) estimates subjects' ability to classify, memorise and respond at speed to incoming information, while the 'miss score' (number of incorrect target identifications, i.e. pressing the spacebar when no target triplet has occurred) estimates the subjects' level of response caution.

**Simple unprepared reaction time (RT) tests (Wilkinson and Houghton 1982)**

Reaction time tests, one of the few tasks validated as sensitive to the effects of sleep loss (Williams et al 1959, Wilkinson et al 1966), were administered according to the procedure of Wilkinson and Houghton (1982) using in-house software run on a Commodore computer. Each 4 minute test run comprised 30 visual stimuli, consisting of blocks appearing on a computer screen, to which subjects were requested to react by pressing a button 'as quickly as possible'. The inter-stimulus interval varied pseudorandomly from 1 to 4 seconds, increasing subject unpreparedness. Five reaction time runs were administered during the testing session, yielding a principal outcome measure of average mean reaction time. Mean, rather than the more standard median, RT was selected for analysis because of evidence linking vigilance loss with the appearance of occasional 'lapses' in response (Williams et al 1959, Dinges et al 1987) which skew the mean RT toward slow responses.

**Hick reaction time (Hick 1952, Jensen 1987)**

Reaction time (RT) tests used in the crossover study were based on the Hick paradigm (Hick 1952). This RT testing procedure yields not only mean and median RT values under varying degrees of choice (response uncertainty), but also provides information about the rate of gain of information with increasing complexity of stimulus choice. RT variables, particularly those relating to decision time, give a measure of information-processing ability and are correlated with IQ in healthy (Eysenck 1967, Jensen 1987) and diabetic (Langan et al 1991, Deary 1992, Deary et al 1992) subjects. Decision time variables have proved sensitive to the cognitive effects of organic disease in diabetic patients with repeated severe hypoglycaemia (Langan et al 1991).
Figure 4.2: Jensen-type apparatus for Hick reaction time task
Hick RT tests were conducted on apparatus consisting of a Jensen-type reaction box (Figure 4.2) interfaced with a BBC computer. The reaction box (Electronic Developments Ltd, Hampton, Middlesex) contains 8 yellow stimulus/response buttons in a semi-circular array around a central blue 'home' button. Stimulus/response buttons can be covered by shields, to allow RT testing under different conditions of stimulus choice. Initial depression of the blue 'home' button activates the lighting of a single yellow stimulus/response button after an unpredictable interval. Subjects are instructed to react by pressing the yellow stimulus/response button 'as quickly as possible' after it lights. Software (Mike Holmes, University of Edinburgh) allows a variable number of RT responses to be recorded under varying choice conditions and discriminates decision time (the time from stimulus onset to lifting of the 'home' button) from movement time (the time from lifting of 'home' button to pressing of the stimulus/response button). Decision times are typically longer than movement times.

Subjects were given a total of 80 RT trials, with 20 tests at each of 1-, 2-, 4- and 8-light choice conditions, the session lasting about 20 minutes. RT tests were administered in batches of 10, first in ascending order and then in descending order of choice complexity, in order to prevent within-session learning effects being confounded with response uncertainty. Inter-stimulus interval varied between 150 and 250 ms from re-depression of the 'home' button. The mean, median and standard deviation of decision and movement times were determined for each choice condition, and the slope of the regression of decision time against response uncertainty condition was calculated to estimate the rate of gain of information.

EPIC IV driving simulator (HJ Wildgust) was administered using a BBC computer equipped with a set of pedals and a steering apparatus. The simulator was developed as a divided attention task requiring both steering skills (tracking a randomly moving triangle at the top of the screen) and reaction to stimuli (responding to traffic lights changing colour at a junction). The test was administered as five 3-minute runs after several practises to establish a performance plateau. It could not be said to simulate true driving conditions, as the task was neither as complex nor as boring as real driving, but elements of vigilance skills and mental flexibility were called into play in its performance. The scores obtained from the test were accuracy in steering tracking (with a low score indicating more accurate tracking), average response-time in braking (a low score indicating better performance) and the number of missed reactions to traffic light changes.
SteerClear (Findley et al. 1989a)
SteerClear (Healthdyne, Brussels) is a monotonous, 30-minute, computer-administered vigilance task which assesses attention and reaction speed. Subjects view a schematic representation of a two-lane road with a car travelling up the computer screen. When obstacles in the form of cows appear in the car’s lane, the subject must switch lanes by pressing the spacebar to avoid a collision. Over a thousand cows are presented, but none during three 2-minute periods in the task, when subjects may be lulled into a state of unreadiness for the resumption of cows’ appearances. The score obtained is the number of cows hit, i.e. an error score. Previous research has found that SteerClear performance is impaired in SAHS patients compared to normals, and is improved on retesting after CPAP (Findley et al. 1986).

Borkowski verbal fluency test (Borkowski et al. 1967)
This test of verbal fluency and putatively of frontal lobe function requires subjects to say as many words as possible beginning with a nominated letter within a minute. Subjects were asked to avoid using people’s or place names, to avoid giving words with the same root (such as go and going) and to try not to repeat themselves. Three letters are nominated during the test. The letter triplets FAS, CFL and PRW were administered at the familiarisation session and first and second treatment assessments, respectively, to minimise learning effects in the experimental sessions. These latter two triplets have been validated as alternatives (Lezak 1983). The number of correctly produced words gives a measure of fluency, while perseverative word naming on the task, represented by repetitions and words with the same root, reflects frontal lobe damage (Lezak 1983). In a previous study, verbal fluency was compromised in SAHS patients compared to normals (Bédard et al. 1991b).

Auditory-verbal learning test (AVLT) (Lezak 1983) assesses memory and learning of a list of 15 common words. The subject is asked to repeat as many words as possible after each of five readings of the list by the experimenter. A second word list is then administered as a distracter before the subject is asked to recall the original word list for a sixth time without the benefit of its further repetition. Longer-term memory retention is tested by leaving a 45-minute gap before a final recall, again without the benefit of a further repetition of the list. The sum of words remembered from the first five administrations yields a measure of learning, while the delayed 45-minute recall tests memory retention. Because performance on the AVLT is improved by repeated testing using the same list, even after a 4 week gap, a standardised and validated
alternative word list (Crawford et al 1989b) was used to reduce learning-related improvements in score at the second session.

**Benton visual retention test (revised) (BVRT; Benton 1974)**
The BVRT is a test of immediate memory and putatively of organic brain damage which requires subjects to reproduce designs involving geometric figures using paper and pencil. Each of 10 designs are presented for 10 seconds, then hidden. Immediately after each design presentation, the subject is required to ‘draw what they saw’. Strict scoring rules classify errors of commission and omission in design reproduction. Subjects gain a score for the number of designs correctly reproduced and for their total number of errors. Three alternative versions of the designs are available, two (C and E versions) more similar than the third (Benton 1974). The D version was employed in the familiarisation session, and C and E in the first and second treatment assessments, respectively.

**4.3.2 Well-being scales**
The tests used to assess well-being may be subdivided into those examining psychological distress (HAD scale, GHQ-28), quality-of-life (NHP part 2, SF-36), mood (UMACL), sleepiness (Epworth scale) and symptoms (in-house questionnaire).

**Hospital anxiety and depression (HAD) scale (Zigmond and Snaith 1983)** is a 14 item, multiple choice, self-rated scale assessing the extent of anxiety and depressive symptoms, independent of somatic illness. Thus question items relating to somatic symptoms common to physical and psychiatric illness, such as headache or insomnia, are eliminated. The depression questions focus on symptoms related to the anhedonic state (e.g. ‘I can laugh and see the funny side of things’), while the anxiety questions probe the psychological symptoms of anxiety disorder (e.g. ‘I get a sort of frightened feeling as if something awful is about to happen’). The subject is asked to choose from four answers representing the frequency of the feeling or the intensity of the concordance with the statement, scored form 0 (for no symptom) to 3 (high level of symptom). Its use as a screening instrument for non-psychotic psychiatric illness has been validated in out-patient samples (Zigmond and Snaith 1983, Moorey et al 1991, Janson et al 1994a). A score on either subscale of 11 or more is considered indicative of significant mood disorder (Zigmond and Snaith 1983, Moorey et al 1991), and this threshold was used to identify ‘cases’ of anxiety and depression before and after treatment.
General health questionnaire-28 (GHQ-28: Goldberg and Hillier 1979)
The 28-item GHQ is a widely used multiple-choice, self-rated questionnaire assessing non-psychotic distress. Patients are asked to rate their concordance with statements on health and well-being on a 4-point Likert scale, with responses scored 0-0-1-1. Factor analyses of responses from an out-patient setting indicate that the instrument contains 4 components relating to somatic symptoms, anxiety, social dysfunction and severe depressive symptoms (Goldberg and Hillier 1979). Sample questionnaire items include 'been feeling run down and out of sorts' (somatic symptoms), 'been edgy and bad-tempered' (anxiety), 'been satisfied with the way you have carried out your task' (social dysfunction) and 'felt that life isn’t worth living' (severe depression). The scoring method allows the total GHQ-28 score (the sum of all 28 responses) to be used to screen for minor psychiatric morbidity, with a threshold at 5 or more points used to identify ‘cases’.

Quality of life was measured using the 20-item second part of the NHP, a scale developed to measure the impact of health problems on daily living. Patients are asked to state whether questions concerning the functional areas of paid work, housework, social life, family relationships, sex life and interests and hobbies are true or false. Items include ‘I have difficulty in concentrating at work’, ‘I am talking less at home’ and ‘I find it difficult to get sexually aroused’. The NHP Part 2 has been shown responsive to treatment-induced change in a previous study of surgical hip replacement (Wiklund and Romanus 1991). This scale was selected for its brevity and for its avoidance of items on sleep quality, which might have merely documented symptoms of SAHS. It includes a subscale on sex life, which was considered useful given the high incidence of sexual dysfunction in SAHS (Guilleminault et al 1978, Whyte et al 1989). The total number of positive item responses formed the NHP part 2 score.

UWIST mood adjective checklist (UMACL: Matthews et al 1990)
Transient mood state was rated using the UMACL, consisting of 24 adjectives describing internal states, each with a 4-point scale. Subjects were asked to use the 4-point scale to rate how closely each adjective described their current mood. Factor analyses of mood items reveal a three-factor structure, with dimensions of energetic arousal, tense arousal and hedonic tone reflecting major mood states (Thayer 1989, Matthews et al 1990, Matthews 1992). The 24 adjectives of the UMACL were
selected for their high and specific loadings on the three mood dimensions and including ‘alert’ and ‘sluggish’ (energetic arousal), ‘jittery’ and ‘relaxed’ (tense arousal), and ‘cheerful’ and ‘depressed’ (hedonic tone). The energetic arousal factor is thought to relate to reticular activation, and thus may offer a useful index of physiological activity (Thayer 1989). The energetic arousal subscale score is well-correlated with cognitive performance and is reduced in sleep deprivation (Matthews et al 1990, Matthews 1992), making it particularly relevant to the study of SAHS.

This self-completed subjective sleepiness questionnaire asks subjects to rate their likelihood of dozing on a 4 point scale in each of 8 situations (e.g. sitting and reading, in a car while stopped for a few minutes in traffic, etc.) ‘in the recent past’. Whereas state assessments of sleepiness such as the Stanford sleepiness scale (Hoddes et al 1973) rely on subjects’ recognition of internal feelings associated with impending sleep, the trait-oriented Epworth scale, by assessing remembered behaviours, may represent a more robust measure of sleepiness (Johns 1991). Its internal consistency and test-retest reliability have been investigated in normals, students and sleep disorder patients (Johns 1991, 1992). Epworth scores in small samples of untreated SAHS patients correlate significantly with AHI (Johns 1991, 1993) and with MSLT scores (Johns 1991) and are significantly reduced by CPAP (Johns 1992).

Symptoms were assessed using an in-house questionnaire on which patients rated the presence or absence of symptoms comprising snoring, choking in sleep, morning headaches, morning confusion, wakening during the night, daytime napping, evening napping, and sleepiness whilst driving.

4.4 CPAP compliance

4.4.1 Runtime
The average time in hours per night that CPAP units were switched on over the study period was termed the CPAP ‘runtime’. The method of measurement of this variable differed in the pilot parallel-group and the principal crossover studies.

SleepEasy II and III CPAP units (Respirronics Inc) issued for home use in the pilot parallel-group study were equipped at manufacture with external meters logging the total number of hours that units were switched on. These runtime timeclocks were read at issue and again at the end of the study period. The difference between
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timeclock readings was divided by duration of CPAP treatment to provide an average CPAP runtime in hours per night.

The Sullivan APD-1 CPAP units (Rescare, Abingdon) used in the crossover study were not equipped with timeclocks at purchase, and were modified in-house to facilitate compliance monitoring. The compliance monitoring system was largely hidden within the CPAP unit casing, allowing more discreet assessment of compliance. Runtime measurement in the crossover study was accomplished with a small hour meter (RS part no. RS260-072), glued to the interior of the screwed-down unit casing. This timeclock was connected directly to the on-off power switch of CPAP units so that the switch’s 240V signal triggered logging of time that the unit was switched on (see Figure 4.3). As in the parallel-group study, the runtime timeclock was read at the time the CPAP unit was issued and again on return at the end of the CPAP treatment period, so that average runtime could be calculated for the CPAP treatment duration.

4.4.2 Masktime

Patients’ average effective use of CPAP was termed ‘masktime’. Masktime reflects the time that the CPAP mask is properly applied to the face, rather than the time that the blower unit is switched on and was used in addition to runtime in the crossover study as a measure of CPAP compliance. The mechanical method of detecting effective CPAP delivery was developed by Reeves-Hoché et al (1992, 1994) and adapted for use in the modified APD-1 units issued in the crossover study.

A second hour meter (RS part no. RS260-072) glued inside the APD-1 unit casing monitored masktime. The masktime timeclock was triggered by a pressure-sensitive switch (Europart no 48-BN-02), also hidden inside the unit casing, which detected whether pressure at the mask was within approximately 2 cmH₂O of that prescribed. Mask pressure detection was accomplished with blue narrow-bore tubing which ran inside the CPAP hose from the nasal mask to the pressure switch (see Figure 4.4). The pressure switch operated on the principle of hysteresis, so that the pressure required to activate the switch was greater than that required to switch it off. This meant that the switch was not de-activated during each inspiration, when pressure within the mask falls by around 2 cmH₂O.

The thresholds of the switches could be adjusted so that, if the mask was removed from the face, pressure loss would de-activate the switches. Testing of pressure
Figure 4.3: Interior of modified CPAP unit
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Figure 4.4: CPAP apparatus
thresholds for the monitoring system was conducted in modified CPAP units set across the operating range from 5 to 20 cmH2O. CPAP units were switched on and left to run for at least 3 hours under two conditions: firstly, with the mask lying loose on a counter and secondly, with the mask firmly taped to a counter to simulate the obscuring of the mask by the face. Readings of both runtime and masktime timeclocks were taken before and after the running of CPAP machines under each condition. Separately adjusted pressure switches were found to be required for CPAP units set to deliver 5 cmH2O and those set at higher pressures, as low-set pressure switches in high-pressure CPAP units continued to activate the masktime timeclock when unobscured, because pressure at the mask exceeded 5 cmH2O. Trials were rerun to evaluate the precision of both timecounters in separately modified CPAP units set at 5 cmH2O and higher pressures, and both types were found to log CPAP masktime accurately.

In the crossover study, each unit was unscrewed to be serviced, sterilised and pressure-set before being issued, allowing the runtime and masktime timeclocks to be inspected and shown to be in working order.
Chapter 5:
PARALLEL-GROUP CONTROLLED STUDY OF DAYTIME FUNCTION AFTER CPAP THERAPY: A PILOT STUDY

The literature review presented in Chapter 3 detailed the few, and often preliminary, studies of daytime function after CPAP treatment which were available at the inception of this project. The existing studies using objective daytime sleepiness tests (Wittig et al 1986, Walsleben et al 1989, Lamphere et al 1989, Fry et al 1990, Gaddy and Doghramji 1991) yielded conflicting results on improvements in sleep onset latency after CPAP and lacked objective information on compliance with CPAP on any but those nights preceding the laboratory MSLT or MWT (Lamphere et al 1989, Walsleben et al 1989, Fry et al 1990). The effects of CPAP on cognitive function had been explored only through small-scale, uncontrolled studies (Bearpark et al 1987, Walsleben et al 1989). Finally, the selection of instruments to assess psychological well-being after CPAP were, in some published studies, controversial. Researchers had employed personality inventories, which index relatively stable traits, to assess changes in changeable psychological distress states (Mayleben et al 1990), or had used psychiatric screening instruments which incorporated somatic symptom items thus aggregating symptoms of SAHS and their impact on wellbeing (Millman et al 1989).

The pilot study of daytime function after CPAP in SAHS patients described in this chapter was an attempt to improve on existing studies through two means. Firstly, the study design incorporated a conservatively-treated patient group, acting as a control for the repeated administration of cognitive, psychological wellbeing and objective daytime sleepiness tests. Secondly, the objective measurement of average CPAP compliance rates through the use of CPAP timeclocks allowed the relationship between CPAP usage and benefits in daytime function to be evaluated.

5.1 Subjects and methods
The study was prospective and employed a parallel-group design to compare the change in outcome measures of daytime function following at least 3 months of treatment with either CPAP or conservative therapy only. The conservative treatment regime acted as a control for the effects of learning in this longitudinal study and consisted of advice on weight loss and the avoidance of evening alcohol. Similar advice was given to CPAP-receiving patients.
Patients were recruited from referrals to an out-patient Respiratory Sleep Clinic, who subsequently underwent a clinical sleep study, conducted according to the method described in Chapter 4, to confirm the diagnosis of SAHS (Gould et al 1988). All patients recruited into the study had 15 or more apnoeas+hypopnoeas per hour of sleep and at least two symptoms of SAHS from a list including snoring, excessive daytime sleepiness, nocturnal choking, unrefreshing sleep, ankle oedema and polycythaemia (Whyte et al 1989).

Six of the 43 patients who underwent baseline assessment were lost to post-treatment follow-up. One patient died suddenly soon after starting CPAP therapy, while a further 5 patients were unavailable for follow-up due to residence abroad, or family and work commitments. Twenty-one patients were followed up after CPAP treatment and 16 after conservative treatment.

Allocation to treatment type was not randomised, but was based partially on patient preference. Half of the control group patients chose conservative treatment over CPAP, while the other half were directly assigned to conservative therapy. The clinical features of the patient groups before treatment was commenced are summarised below. The clinical features of the two groups were not significantly different on Student's unpaired t-testing (Table 5.1), but showed more severe mean values for all variables in the CPAP group.

| Table 5.1: Clinical features of treatment groups at baseline assessment |
|-----------------------------------|----------------|----------------|----------------|
|                                   | CPAP patients | Conservative patients |
|                                   | n=21 Mean ± SEM | n=16 Mean ± SEM | p-value |
| Age (years)                       | 53±3 3         | 53±3 3          | 1.00 |
| Body mass index (kg/m²)           | 34±2 2         | 32±2 2          | 0.31 |
| Apnoeas+hypopnoeas/ hr slept      | 57±6 5         | 49±6 6          | 0.38 |
| Microarousals/ hr slept           | 54±5 5         | 45±6 6          | 0.26 |
| MinimumO2 saturation (%)          | 61±5 5         | 69±4 4          | 0.27 |

The CPAP-receiving group underwent a second night of polysomnography in the laboratory with CPAP to titrate the required pressure to minimise both respiratory abnormalities and arousals from sleep. Patients in the CPAP treatment group were educated in the use of CPAP, advised that all-night use was necessary to improve sleep quality and health, and were issued with SleepEasy II or SleepEasy III.
(Respironics Inc) units for home use after the pre-treatment assessment of daytime function.

5.1.1 Assessments
Repeated testing was performed in both treatment groups, first before the commencement of treatment and then on a second occasion at least 3 months after treatment started, in order to allow time for the effects of CPAP or weight loss to become apparent. Although the latency of benefit from CPAP is not well-defined, patients' own reports suggest that subjective improvements in function occur after as little as a single night's CPAP use (Whyte et al 1989), an observation supported by improvements of objective daytime sleepiness after 2 nights of CPAP (Lamphere et al 1989).

At each time of testing, patients underwent a multiple sleep latency test (MSLT) in order to assess objective daytime sleepiness (Carskadon et al 1986) and, on a non-consecutive day, a comprehensive 3-hour psychometric battery, detailed in Table 5.2. The neuropsychological tests used are described in detail in Chapter 4. These tests were administered according to a standardised schedule to control for circadian effects on cognitive performance and well-being. The battery was assembled to test general level of intellectual ability (Wechsler adult intelligence scale [WAIS] subtests, TrailMaking tasks), intellectual deficit (IQ decrement), memory (auditory verbal learning test [AVLT]) and information processing speed (Inspection time [IT] test), and included task-specific tests of concentration ability (paced auditory serial addition test [PASAT]), vigilance (simple reaction time [RT]) and driving-based skills (EPIC IV driving simulator) which might be relevant to sleep-loss induced deficit. The impact of illness on psychological well-being was assessed using the hospital anxiety and depression (HAD) scale.

Because of the considerable time input from patients required by the study, only 20 CPAP-receiving patients and 9 conservatively-treated patients attended for a second multiple sleep latency test, although all had repeated psychometric testing. Breakdown of computer equipment resulted in the loss of full datasets for IT test and simple RT. Paired IT datasets were available for 15 CPAP patients and 14 conservative patients, and for simple RT in 13 conservative patients. The late addition of the EPIC IV driving equipment meant that full data were only available for 12 CPAP patients and 7 controls.
Table 5.2: Parallel-study psychometric battery

<table>
<thead>
<tr>
<th>Psychometric Battery</th>
<th>WAIS subtests-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests of general cognitive function and memory</td>
<td>Information</td>
</tr>
<tr>
<td></td>
<td>Arithmetic</td>
</tr>
<tr>
<td></td>
<td>Block Design</td>
</tr>
<tr>
<td></td>
<td>Digit Symbol Substitution</td>
</tr>
<tr>
<td></td>
<td>Trail Making Tasks A and B</td>
</tr>
<tr>
<td></td>
<td>Auditory-Verbal Learning Test (AVLT)</td>
</tr>
<tr>
<td></td>
<td>Pre-morbid level of cognitive function</td>
</tr>
<tr>
<td></td>
<td>National Adult Reading Test (NART)</td>
</tr>
<tr>
<td></td>
<td>Processing time</td>
</tr>
<tr>
<td></td>
<td>Inspection time (IT) test</td>
</tr>
<tr>
<td></td>
<td>Simple unprepared reaction time (RT)</td>
</tr>
<tr>
<td></td>
<td>Concentration and attention</td>
</tr>
<tr>
<td></td>
<td>Paced Auditory Serial Addition Test (PASAT: 2 and 4 sec presentation rates)</td>
</tr>
<tr>
<td></td>
<td>Epic IV Driving Simulator</td>
</tr>
<tr>
<td></td>
<td>Psychological wellbeing</td>
</tr>
<tr>
<td></td>
<td>Hospital Anxiety and Depression (HAD) Scale</td>
</tr>
</tbody>
</table>
All daytime testing sessions were performed after patients had slept in their own bed, so that poor sleep quality resulting from polysomnography did not independently affect daytime function measures. Patients were asked to avoid caffeine-containing beverages on the days of testing and were offered only non-caffeinated beverages during the day.

Compliance with CPAP therapy was objectively monitored with an external timeclock which logged time that units were switched on (see Chapter 4). These runtime timeclocks were read on issue of CPAP units and at follow-up assessments, in order to calculate an average nightly CPAP runtime for each patient.

The baseline assessments of daytime function of 5 of the CPAP-treated patients and 7 of the conservatively-treated patients were performed by a colleague, as part of a previous study (Cheshire et al 1992). However, standardisation of instruction and scoring on psychometric tests, as well as the inclusion of the colleagues' baseline assessments in both treatment groups, minimised any problems with inter-rater differences in the study.

5.1.2 Statistics
Daytime function outcome variables were analysed using the BMDP package (Dixon 1988). Student's unpaired t-tests were employed to compare differences between the treatment groups at baseline. Two-way analysis of variance (ANOVA) was used to assess the effects of treatment, with treatment as a between subjects factor with two levels (CPAP or conservative therapy) and time as a repeated measure (baseline and follow-up). Mann-Whitney tests were used to assess changes from baseline for non-normally distributed variables (number of inspection time trials, number of missed driving-test responses, and both anxiety and depression scores). Chi-square tests were used to examine the distribution of HAD scale 'cases' between groups.

5.2 Results
5.2.1 Timing of follow-up
The CPAP group underwent their second assessment an average 3.3 months after the start of treatment (range 2.6-4.5 months) while the control group's second assessment occurred on average 9.5 months after treatment commenced (range 2.9-16.8 months). This difference in the timing of the second assessment was significant on unpaired t-testing (p<0.01). The longer treatment duration in the control group was due to the late
recruitment of previously tested, conservatively treated patients from a previous study (Cheshire et al 1992).

5.2.2 Weight changes during treatment
Both treatment groups showed non-significant rises in BMI at follow-up, which were not significantly different between the two groups (CPAP group's mean change +0.4 ± SEM 0.2, conservative group +0.6 ± 0.5 kg/m²; p=0.08). In the CPAP-receiving group, 12 patients at baseline and 13 patients at follow-up were obese (BMI >30 kg/m²: Bray 1979). Of the conservatively-treated patients, 9 at baseline and 10 at follow-up were obese. Only one patient in each group was not overweight (BMI >25 kg/m²: Bray 1979) at follow-up.

5.2.3 Comparison between daytime function tests of treatment groups at baseline
The scores on the cognitive and distress-related tests were not significantly different in the two treatment groups at their first testing (Table 5.3). However the mean sleep latency on the MSLT was significantly longer in the control group (p=0.01), who had a mean sleep onset latency of 5.7 minutes compared to the CPAP group's mean sleep onset latency of 3.4 minutes.
### Table 5.3: Daytime function of treatment groups at baseline

<table>
<thead>
<tr>
<th>Measure</th>
<th>CPAP Group Mean ± SEM</th>
<th>Conservative Group Mean ± SEM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean sleep onset latency (mins)</td>
<td>3.4 ± 0.5</td>
<td>5.7 ± 0.8</td>
<td>0.01**</td>
</tr>
<tr>
<td>Minimum sleep onset latency (mins)</td>
<td>1.3 ± 0.3</td>
<td>2.1 ± 0.5</td>
<td>0.16</td>
</tr>
<tr>
<td>WAIS information</td>
<td>17.5 ± 1.0</td>
<td>18.6 ± 1.1</td>
<td>0.49</td>
</tr>
<tr>
<td>WAIS arithmetic</td>
<td>13.9 ± 0.7</td>
<td>12.8 ± 0.8</td>
<td>0.31</td>
</tr>
<tr>
<td>WAIS block design</td>
<td>33.5 ± 1.5</td>
<td>29.9 ± 1.5</td>
<td>0.11</td>
</tr>
<tr>
<td>WAIS digit symbol</td>
<td>43.9 ± 2.2</td>
<td>46.4 ± 3.7</td>
<td>0.55</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>114.9 ± 3.0</td>
<td>113.4 ± 3.6</td>
<td>0.75</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>108.3 ± 2.6</td>
<td>106.8 ± 3.7</td>
<td>0.74</td>
</tr>
<tr>
<td>Full IQ</td>
<td>113.0 ± 2.5</td>
<td>111.3 ± 3.5</td>
<td>0.68</td>
</tr>
<tr>
<td>Pre-morbid performance IQ</td>
<td>109.5 ± 1.2</td>
<td>108.9 ± 1.2</td>
<td>0.74</td>
</tr>
<tr>
<td>IQ decrement</td>
<td>1.2 ± 2.2</td>
<td>2.1 ± 3.2</td>
<td>0.82</td>
</tr>
<tr>
<td>TrailMaking A (secs)</td>
<td>32.6 ± 2.6</td>
<td>35.6 ± 2.6</td>
<td>0.42</td>
</tr>
<tr>
<td>TrailMaking B (secs)</td>
<td>87.3 ± 8.3</td>
<td>102.5 ± 10.5</td>
<td>0.26</td>
</tr>
<tr>
<td>AVLT short-term recall</td>
<td>45.5 ± 1.7</td>
<td>50.0 ± 2.0</td>
<td>0.12</td>
</tr>
<tr>
<td>AVLT delayed recall</td>
<td>10.0 ± 0.5</td>
<td>10.4 ± 0.7</td>
<td>0.43</td>
</tr>
<tr>
<td>Inspection Time Duration (msecs)</td>
<td>106.3 ± 10.5</td>
<td>81.9 ± 10.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Inspection Time Trials†</td>
<td>150 ± 12</td>
<td>185 ± 26</td>
<td>0.56</td>
</tr>
<tr>
<td>Simple RT (msecs)</td>
<td>310 ± 15</td>
<td>291 ± 20</td>
<td>0.45</td>
</tr>
<tr>
<td>PASAT 4sec presentation</td>
<td>48.4 ± 2.1</td>
<td>51.4 ± 2.2</td>
<td>0.33</td>
</tr>
<tr>
<td>PASAT 2sec presentation</td>
<td>30.0 ± 1.6</td>
<td>33.1 ± 2.7</td>
<td>0.18</td>
</tr>
<tr>
<td>Driving accuracy</td>
<td>40.2 ± 5.0</td>
<td>36.6 ± 5.7</td>
<td>0.65</td>
</tr>
<tr>
<td>Driving response-time</td>
<td>61.0 ± 3.3</td>
<td>52.8 ± 3.2</td>
<td>0.11</td>
</tr>
<tr>
<td>Driving missed responses†</td>
<td>1.4 ± 0.3</td>
<td>1.1 ± 0.4</td>
<td>0.60</td>
</tr>
<tr>
<td>Cognitive Z-score†</td>
<td>-0.8± 1.8</td>
<td>1.5 ± 1.9</td>
<td>0.40</td>
</tr>
<tr>
<td>HAD anxiety score†</td>
<td>7.0 ± 1.1</td>
<td>6.5 ± 0.8</td>
<td>0.83</td>
</tr>
<tr>
<td>HAD depression score†</td>
<td>6.0 ± 1.0</td>
<td>4.5 ± 0.9</td>
<td>0.30</td>
</tr>
<tr>
<td>HAD anxiety ‘cases’‡</td>
<td>n=5</td>
<td>n=2</td>
<td>0.66</td>
</tr>
<tr>
<td>HAD depression ‘cases’‡</td>
<td>n=5</td>
<td>n=0</td>
<td>0.11</td>
</tr>
</tbody>
</table>

† Mann-Whitney test  
‡ Chi-square test  

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5.2.4 Within-group changes in daytime function scores from first to second assessment

The paired data showing baseline and follow-up scores within each of the two treatment groups is shown in Table 5.4.

The CPAP-receiving group showed a significant increase in both mean (p=0.01) and minimum (p=0.02) sleep onset latency measured during the follow-up MSLT, indicating a lessening of daytime sleepiness. This group also showed improvements on second testing in performance on the information (p<0.001) and digit symbol substitution (p<0.001) subtests, and in calculated full-scale IQ (p=0.05). Follow-up scores was also significantly improved for both administered speeds of the PASAT (p≤0.01) and for accuracy in the driving task (p=0.03). All mean values for cognitive performance and well-being were improved on retesting after CPAP, except for the arithmetic subtest and inspection time trials.

The conservatively-treated group had no increase in sleep onset latency following treatment, and in contrast to the CPAP-receiving subjects, showed a non-significant decrease in mean and minimum sleep onset latency. However, this group demonstrated a similar improvement in cognitive performance with retesting to that seen in the CPAP group. The conservatively treated patients demonstrated significant increases in information subtest score (p=0.05) and in calculated scores for verbal (p=0.04), performance (p=0.02) and full-scale IQ (p<0.01). Performance on TrailMaking B (p<0.01) and on the 2-second presentation rate PASAT improved on retesting (p=0.01). All mean cognitive scores, except those for IT duration and simple RT, had improved on second testing. However, in contrast to the CPAP group, the conservatively treated patients had mean HAD scale scores reflecting non-significantly greater distress after the treatment period.
Table 5.4: Within-group and between-group changes in daytime function

<table>
<thead>
<tr>
<th></th>
<th>CPAP GROUP</th>
<th></th>
<th>CONSERVATIVE GROUP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 1</td>
<td>Visit 2</td>
<td>Change</td>
<td>Within group</td>
</tr>
<tr>
<td></td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
<td>p-value</td>
</tr>
<tr>
<td>Mean sleep onset latency</td>
<td>3.5 ± 0.5</td>
<td>5.6 ± 0.7</td>
<td>+2.1 ± 0.8</td>
<td>0.01**</td>
</tr>
<tr>
<td>(mins)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum sleep latency</td>
<td>1.3 ± 0.3</td>
<td>2.6 ± 0.3</td>
<td>+1.3 ± 0.5</td>
<td>0.02*</td>
</tr>
<tr>
<td>(mins)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS information</td>
<td>17.5 ± 1.0</td>
<td>19.0 ± 1.0</td>
<td>+1.4 ± 0.4</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>WAIS arithmetic</td>
<td>13.9 ± 0.7</td>
<td>13.7 ± 0.6</td>
<td>-0.2 ± 0.6</td>
<td>0.76</td>
</tr>
<tr>
<td>WAIS block design</td>
<td>33.5 ± 1.5</td>
<td>33.9 ± 1.3</td>
<td>+0.4 ± 1.0</td>
<td>0.71</td>
</tr>
<tr>
<td>WAIS digit symbol</td>
<td>43.9 ± 2.2</td>
<td>47.5 ± 2.4</td>
<td>+3.6 ± 0.9</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>114.9 ± 3.0</td>
<td>116.6 ± 2.6</td>
<td>+1.8 ± 1.6</td>
<td>0.29</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>108.3 ± 2.0</td>
<td>111.4 ± 2.0</td>
<td>+3.1 ± 1.8</td>
<td>0.11</td>
</tr>
<tr>
<td>Full IQ</td>
<td>113.0 ± 2.5</td>
<td>115.1 ± 2.2</td>
<td>+2.1 ± 1.0</td>
<td>0.05*</td>
</tr>
<tr>
<td>IQ decrement</td>
<td>1.2 ± 2.2</td>
<td>-1.6 ± 1.4</td>
<td>-2.9 ± 2.0</td>
<td>0.17</td>
</tr>
<tr>
<td>TrailMaking A (sec)</td>
<td>32.6 ± 2.6</td>
<td>32.5 ± 2.9</td>
<td>-0.1 ± 2.1</td>
<td>0.96</td>
</tr>
<tr>
<td>TrailMaking B (sec)</td>
<td>87.3 ± 8.3</td>
<td>79.5 ± 6.7</td>
<td>-7.8 ± 5.4</td>
<td>0.17</td>
</tr>
<tr>
<td>AVLT short-term recall</td>
<td>45.5 ± 1.7</td>
<td>49.2 ± 2.1</td>
<td>+3.7 ± 1.9</td>
<td>0.07</td>
</tr>
<tr>
<td>AVLT delayed recall</td>
<td>9.8 ± 0.5</td>
<td>10.4 ± 0.7</td>
<td>+0.6 ± 0.5</td>
<td>0.23</td>
</tr>
<tr>
<td>Inspection Time Duration</td>
<td>110.4 ± 11.8</td>
<td>106.2 ± 12.0</td>
<td>-4.2 ± 9.4</td>
<td>0.66</td>
</tr>
<tr>
<td>(msec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inspection Time Trials†</td>
<td>153 ± 14</td>
<td>161 ± 14</td>
<td>+8 ± 19</td>
<td>0.68</td>
</tr>
<tr>
<td>Simple RT (msecs)</td>
<td>309 ± 15</td>
<td>291 ± 12</td>
<td>-18 ± 15</td>
<td>0.24</td>
</tr>
<tr>
<td>PASAT 4 sec presentation</td>
<td>48.3 ± 2.1</td>
<td>52.7 ± 1.6</td>
<td>+4.3 ± 1.5</td>
<td>0.01**</td>
</tr>
<tr>
<td>PASAT 2 sec presentation</td>
<td>29.0 ± 1.6</td>
<td>34.6 ± 1.6</td>
<td>+5.6 ± 1.7</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Driving accuracy</td>
<td>41.7 ± 6.1</td>
<td>39.8 ± 6.5</td>
<td>-1.9 ± 2.5</td>
<td>0.47</td>
</tr>
<tr>
<td>Driving response-time</td>
<td>60.4 ± 3.3</td>
<td>54.3 ± 1.9</td>
<td>-6.2 ± 2.4</td>
<td>0.03*</td>
</tr>
<tr>
<td>Driving missed responses †</td>
<td>1.4 ± 0.4</td>
<td>1.1 ± 0.3</td>
<td>-0.3 ± 0.4</td>
<td>0.39</td>
</tr>
<tr>
<td>Cognitive Z-score</td>
<td>-0.8 ± 1.8</td>
<td>0.4 ± 2.0</td>
<td>+1.2 ± 1.5</td>
<td>0.42</td>
</tr>
<tr>
<td>HAD anxiety score †</td>
<td>7.0 ± 1.1</td>
<td>7.0 ± 1.2</td>
<td>0.0 ± 0.8</td>
<td>0.95</td>
</tr>
<tr>
<td>HAD depression score †</td>
<td>6.0 ± 1.0</td>
<td>4.8 ± 1.2</td>
<td>-1.2 ± 0.7</td>
<td>0.12</td>
</tr>
<tr>
<td>HAD anxiety 'cases' †</td>
<td>n=5</td>
<td>n=6</td>
<td>+1 case</td>
<td>0.59</td>
</tr>
<tr>
<td>HAD depression 'cases' †</td>
<td>n=5</td>
<td>n=4</td>
<td>-1 case</td>
<td>0.32</td>
</tr>
</tbody>
</table>

†Non-parametric test
5.2.5 Comparison of change in daytime function scores between the two treatment groups
The comparison between the two treatment groups' changes in scores are shown in the last column of Table 5.4.

Mean sleep onset latency from the MSLT was significantly more improved in the CPAP-treated group than in the control group (Figure 5.1). The CPAP group's mean sleep onset latency increased by 2.1 ± 0.8 minutes at the second testing, while the conservative-therapy group showed a decrease in mean sleep onset latency of 1.2 ± 1.0 minutes (F=6.22, p=0.02). The minimum sleep onset latency from the five nap opportunities showed a trend (F=3.96, p=0.06) towards greater improvement after CPAP: the CPAP group's minimum sleep latency increased by 1.3 minutes on follow-up, while the control group's decreased by 0.4 minutes.

![Figure 5.1: Change in mean sleep onset latency in CPAP and conservative patients](image)

No significant differences were found between changes in cognitive performance in the two groups (F<1.39, p>0.2).

The change in raw depression scores between the two groups showed a trend for better improvement in CPAP-receiving subjects than in the conservatively treated group (p=0.07). The frequency of depression 'cases' was better improved in the CPAP-treated group than in the controls (p=0.03), with one depression 'case'
resolving in the CPAP-receiving group while 2 'cases' developed in the conservatively-treated group.

5.2.6 CPAP compliance
The average CPAP usage for the whole group was 5.9 ± SEM 1.4 hours per night, although a wide range of compliance rates was observed (0.3-16.8 hours/night). The individual compliance datapoints are shown in Figure 5.2.

![Figure 5.2: CPAP compliance in the CPAP-treated SAHS patients](image)

**Figure 5.2: CPAP compliance in the CPAP-treated SAHS patients**

**Good CPAP Compliers**
To further investigate the relationship between change in daytime function and CPAP compliance, the CPAP group was divided post-hoc into those who complied well with treatment by using their units for an average 4.5 hours per night or more (n=14), and those who were less assiduous. A further statistical comparison of the change in daytime function in these good CPAP compliers to the change in the control group yielded findings similar to those obtained when comparing all CPAP users to controls.

Objective daytime sleepiness was better improved in good CPAP users than in controls, with mean sleep onset latency rising by 2.1 ± 0.9 minutes in good CPAP compliers, but falling by 1.2 ± 1.0 minutes on retesting of the conservatively-treated control group (F=5.69, p=0.03).
Table 5.5: Within-group and between-group changes in daytime function in good CPAP compliers

<table>
<thead>
<tr>
<th></th>
<th>GOOD CPAP COMPLIERS</th>
<th>CONSERVATIVE GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 1 Mean ± SEM</td>
<td>Visit 2 Mean ± SEM</td>
</tr>
<tr>
<td>Mean sleep onset latency (mins)</td>
<td>3.4 ± 0.6</td>
<td>5.5 ± 0.6</td>
</tr>
<tr>
<td>Minimum sleep onset latency (mins)</td>
<td>1.3 ± 0.3</td>
<td>2.4 ± 0.2</td>
</tr>
<tr>
<td>WAIS information</td>
<td>173.1 ± 11</td>
<td>185.1 ± 12</td>
</tr>
<tr>
<td>WAIS arithmetic</td>
<td>14.4 ± 0.7</td>
<td>14.5 ± 0.5</td>
</tr>
<tr>
<td>WAIS block design</td>
<td>34.6 ± 1.9</td>
<td>35.1 ± 1.6</td>
</tr>
<tr>
<td>WAIS digit symbol</td>
<td>45.1 ± 3.0</td>
<td>49.3 ± 3.2</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>115.4 ± 3.0</td>
<td>117.6 ± 2.8</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>109.3 ± 3.5</td>
<td>112.7 ± 2.5</td>
</tr>
<tr>
<td>Full IQ</td>
<td>113.9 ± 2.5</td>
<td>116.2 ± 2.6</td>
</tr>
<tr>
<td>IQ decrement</td>
<td>0.9 ± 3.2</td>
<td>-2.9 ± 2.0</td>
</tr>
<tr>
<td>TrailMaking A (secs)</td>
<td>33.5 ± 3.1</td>
<td>32.9 ± 4.2</td>
</tr>
<tr>
<td>TrailMaking B (secs)</td>
<td>88.7 ± 11.8</td>
<td>77.9 ± 7.5</td>
</tr>
<tr>
<td>AVLT short-term recall</td>
<td>47.0 ± 2.0</td>
<td>50.1 ± 2.7</td>
</tr>
<tr>
<td>AVLT delayed recall</td>
<td>10.1 ± 0.5</td>
<td>10.9 ± 0.9</td>
</tr>
<tr>
<td>Inspection Time Duration (msec)</td>
<td>97.1 ± 11.8</td>
<td>98.3 ± 14.0</td>
</tr>
<tr>
<td>Inspection Time Trials †</td>
<td>156 ± 20</td>
<td>174 ± 20</td>
</tr>
<tr>
<td>Simple RT (msec)</td>
<td>309 ± 22</td>
<td>289 ± 16</td>
</tr>
<tr>
<td>PASAT 4 sec presentation</td>
<td>50.8 ± 2.2</td>
<td>53.9 ± 2.2</td>
</tr>
<tr>
<td>PASAT 2 sec presentation</td>
<td>30.4 ± 2.2</td>
<td>34.8 ± 2.0</td>
</tr>
<tr>
<td>Driving accuracy</td>
<td>42.4 ± 8.0</td>
<td>40.8 ± 7.6</td>
</tr>
<tr>
<td>Driving response-time</td>
<td>61.3 ± 4.4</td>
<td>54.9 ± 2.5</td>
</tr>
<tr>
<td>Driving missed responses †</td>
<td>1.6 ± 0.5</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td>Cognitive Z-score</td>
<td>0.4 ± 2.0</td>
<td>1.3 ± 2.6</td>
</tr>
<tr>
<td>HAD anxiety score †</td>
<td>5.4 ± 0.8</td>
<td>5.8 ± 1.1</td>
</tr>
<tr>
<td>HAD depression score †</td>
<td>4.9 ± 0.9</td>
<td>3.4 ± 1.0</td>
</tr>
<tr>
<td>HAD anxiety 'cases' †</td>
<td>n=1</td>
<td>n=2</td>
</tr>
<tr>
<td>HAD depression 'cases' †</td>
<td>n=2</td>
<td>n=1</td>
</tr>
</tbody>
</table>

†Non-parametric test
Chapter 5: Parallel-group pilot study

Good CPAP compliers showed a significantly better improvement in raw depression score on the HAD scale than controls (CPAP, -1.5 ± 0.9, conservative +1.2 ± 1.0; p=0.05) (Figure 5.3). The difference in changes in depression 'cases' remained significantly better in the good CPAP users than in the controls (p=0.05).

![Figure 5.3: Change in HAD scale depression score in good CPAP compliers and conservative patients](image)

5.3 Discussion

The results of the parallel-group pilot study supported the proposition that CPAP improves objective daytime sleepiness and psychological wellbeing, but provided no evidence of improved cognitive performance after CPAP.

The positive improvements in objective daytime sleepiness within the CPAP-receiving group and, when the two treatment groups were compared, daytime sleepiness and psychological wellbeing, are evidence to support the effectiveness of CPAP treatment. The lack of weight loss among either treatment group suggested that conservative therapy is an unreliable treatment.

The MSLT results of this study, showing an increase in sleep onset latency following CPAP, corroborated other authors' findings of improved daytime sleepiness after CPAP (Wittig et al 1986, Lamphere et al 1989, Walsleben et al 1989, Fry et al 1990, ...
Chapter 5: Parallel-group pilot study

Gaddy and Doghramji 1991). The scale of improvement in the CPAP-treated sample was less dramatic than that reported by Lamphere et al (1989) and Wittig et al (1986), and bore a closer resemblance to that reported by Fry et al (1990) and Gaddy and Doghramji (1991), who both showed a statistically significant lengthening of sleep onset latency, remaining below the “normal” range, after CPAP. The findings of improved, but not normalised, sleepiness after CPAP may have in part been due to our modification of sleep onset scoring criteria, which has subsequently been independently adopted and recommended by the American Sleep Disorders Association (ASDA: Thorpy 1992). But other recent studies published after this study’s completion have shown similar results, with sleep onset latencies rising following CPAP, but remaining below the normal range (Bédard et al 1993, Kribbs et al 1993b).

The parallel-group pilot study confirmed the results of Derderian et al (1988), which showed significant improvements in self-rated depression after 2 months of CPAP. Derderian’s depression inventory had a high concentration of somatic-symptom items, raising the possibility that subjective improvement in symptoms of SAHS, rather than mood disorder, was being measured. The pilot study avoided this by using a screening instrument specifically designed for use in somatic illness, the HAD scale. The proportion of patients reporting clinically significant depressive symptoms was better improved by CPAP than by conservative treatment, and raw depression score was significantly lessened in the better CPAP compliers compared to ‘controls’.

However, the parallel-group pilot study provided no evidence for improved cognitive performance after CPAP. This null finding on changed cognitive performance after CPAP was compatible with that of the uncontrolled study of Walsleben et al (1989), who also found no change in 7 patients retested after 2 nights on CPAP therapy. However, in this study one or both of the factors of short CPAP treatment and small patient sample (n=7) might have contributed to the lack of apparently improved cognitive performance.

The null findings on cognitive performance after CPAP were contrary to patients’ reports, raising the possibility that it was a Type 2, or ‘false negative’, statistical error (Bryman and Cramer 1990). This might be influenced by features of the study design, which introduced concern of sampling bias. The two treatment groups were not explicitly matched for any background variable. Treatment allocation was not randomised, nor were groups matched for social class or education in this pilot study.
Chapter 5: Parallel-group pilot study

An impression of worse clinical status in the CPAP-treated group at baseline is gained by examining the mean polysomnography values in Table 5.1, although these were not statistically different in the two treatment groups. This perception is supported by the significantly greater objective daytime sleepiness and non-significantly lower mean cognitive z-score of the CPAP group when tested before treatment (Table 5.3). Such observations may imply that the treatment groups were not ideally matched, allowing the potential for sampling differences to obscure treatment effects. These selection factors might influence the magnitude of learning effects in the two treatment groups and contribute to uncertainties in interpretation of results.

A related contributant to a Type 2 error might have been the extensive learning effects on repeated testing. The conservative group showed wide-ranging improvement in cognitive score, despite a lack of weight loss. This observation demonstrates the pervasiveness of learning effects, which occurred even in those tests whose specific detailed format could not feasibly be remembered (for example the PASAT), illustrating the importance of familiarity as well as memory in promoting better performance on repeated testing. The observation of learning effects on repeated testing in the parallel-group trial compromised the reliability of previous and subsequent reports of improved cognitive function after CPAP from uncontrolled, longitudinal studies (Bearpark et al 1987, Bédard et al 1993).

The coexistence of these two potential methodological flaws could together have a deleterious effect on the study's sensitivity to cognitive change. Differences in learning curve in the two non-randomised treatment groups could potentially obscure subtle treatment-related change in cognitive performance.

Another concern presented by the lack of between-group difference in cognitive improvement was that some tests selected for the psychometric battery might be insufficiently sensitive or relevant to the specific deficits of SAHS. In contrast to others' findings in case-control studies (Bédard et al 1993, Greenberg et al 1987), baseline IQ decrement score in the parallel-group pilot study was only marginal in both treatment groups (≤2 IQ points), perhaps indicating a role for monotonous, vigilance-type tasks such as those validated in sleep-deprivation experiments (Wilkinson et al 1966).

Despite potential shortcomings, the parallel-group pilot study provided valuable information which guided the development of the subsequent larger project (Chapter...
Experience with the pilot parallel-group trial aided the refinement, both in structure and of measures of the subsequent full-scale study of daytime function after CPAP treatment for SAHS.

The parallel-group structure, and the lack of randomisation, in the pilot trial allowed inter-individual variability in differing treatment groups to potentially obscure the subtle improvements predicted. Thus the subsequent full-scale study was designed as a randomised-entry, placebo-controlled crossover trial, where each patient acted as their own control, and where the effects of learning could be measured and controlled for by a balanced order of treatments. To attempt to reduce learning-related improvements in cognitive scores, a familiarisation session was built into the protocol.

Experience in the parallel-group pilot study gave some indication of which types of daytime function measures might be useful in the later trial. The utility of objective daytime sleepiness tests and measures of psychological distress were verified in the parallel-group study, as these instruments appeared sensitive to the improvements in daytime function subjectively reported by patients. The test of objective sleepiness, the MSLT was retained in the revised daytime function battery. However, given the small magnitude of observed change in sleep onset latency, the MSLT was supplemented with recently developed subjective scales, in an effort to measure the subjective improvements in daytime sleepiness perceived by patients. The Epworth sleepiness scale asks patients to rate recent napping behaviour, while the energetic arousal subscale of the UWIST mood adjective checklist (UMACL) is thought to index physiological arousal (Thayer 1989). These scales might yield information on CPAP-related changes in trait and state sleepiness, respectively. The HAD scale of psychological distress was supplemented with the similar 28-item General Health Questionnaire (GHQ-28), and well-being measures were extended with the inclusion of the Nottingham Health Profile (NHP), part 2. This questionnaire sought to assess the impact of illness on quality-of-life, through investigating limitations in psychosocial functioning, and additionally contained a subscale on sexual function, which was considered particularly relevant to the study of SAHS. Two subscales from the UMACL, hedonic tone and tense arousal, would also provide information on mood state.

The selection of cognitive tests for the subsequent study was more difficult. Tests which showed no significant within-group improvement in the CPAP group were removed from the battery, on the basis that these could not be sensitive to CPAP-
related improvement in intellectual function. The classical simple, unprepared RT test used in the pilot-study showed no improvement with CPAP, despite others’ findings in uncontrolled studies, emerging over the course of this project, that RT might be improved with CPAP (Oveson et al 1992, Bédard et al 1993, Kribbs et al 1993b). The parallel-group pilot study’s findings of unchanged RT found agreement in another (Partlett et al 1994), which showed no significant improvement after CPAP. Because of the lack of significant improvement in the simple RT task, it was replaced by RT tests administered under the Hick paradigm in the full-scale study, in order to gain extra information on information-processing ability. Information processing was also assessed by the addition of the rapid visual information processing (RVIP) test, based on signal processing theory. The verbally-based AVLT memory task was replaced with a visual memory test, the Benton visual retention test (BVRT), which has been used in other organic syndromes. The EPIC IV driving simulator, which also showed no within-group improvement in the CPAP treated group, was considered stimulating to perform and, being a divided attention task, allowed a 'trade-off' between performance on tracking accuracy and braking response-time, which might reduce sensitivity in either one measure. It was replaced with the long and monotonous SteerClear vigilance task, which yields a single outcome score. Because of evidence linking reduced verbal fluency and hypoxaemia (Nelson 1982), the Borkowski test of verbal fluency was added to the psychometric battery. With these modifications, it was hoped, the effects of CPAP on cognitive function could be better resolved.

The usefulness of objective CPAP timeclock readings in the parallel-group pilot study was corroborated by the fact that better improvement in raw depression score was determined by better CPAP compliance. However, the standard manufacturer-supplied timeclock logged only time that units were switched on, not time that the CPAP mask was worn. The unusually high average use times of three of the subjects (Figure 5.2), exceeding the accepted normal time in bed by some hours, hints that some patients were leaving their CPAP units switched on when not in use. The 'masktime' method for monitoring average CPAP effective use (Chapter 4) was subsequently implemented. With this and the other amendments discussed above, the full-scale crossover study of daytime function was commenced.
Chapter 6: Randomised crossover study

RANDOMISED, PLACEBO-CONTROLLED CROSSOVER STUDY OF DAYTIME FUNCTION ON CPAP THERAPY

Continuous positive airway pressure (CPAP) is the treatment of choice for the sleep apnoea/hypopnoea syndrome (SAHS), and is frequently prescribed to ameliorate the daytime impairments of the syndrome, in which excessive daytime sleepiness (Dement et al 1978, Roth et al 1980), increased road traffic accidents (George et al 1987, Findley et al 1988), deficits in cognitive performance (Greenberg et al 1987, Bédard et al 1993, Cheshire et al 1992) and dysphoric mood (Reynolds et al 1984, Derderian et al 1988) feature prominently. However, few controlled trials exist to show objective improvements in daytime function after CPAP therapy, particularly in the domain of cognitive performance, where learning effects during repeated testing (see previous chapter) produce particular methodological problems. A protocol was adopted which would minimise and control for learning effects, inter-individual variability and expectation of benefit.

6.1 Study protocol

The study was constructed as a prospective placebo-controlled randomised crossover trial of daytime function (Hills and Armitage 1979). Patients spent 4 weeks on CPAP therapy (Sullivan APD-1 units, ResCare, Abingdon, UK), which patients were asked to use all night, and 4 weeks on oral placebo (Ranitidine 300 mg homologue, Glaxo, Greenford, UK) in a dose of two tablets at bedtime, with no intervening washout period between treatments. Study patients were informed of the mechanisms of action of CPAP therapy and were told that the placebo tablets might improve upper airway muscle function in sleep. The study was approved by the local medical ethics subcommittee.

A treatment order schedule consisting of balanced blocks within each of 4 SAHS severity groups was prospectively filled by patient recruits. The severity groups were each formed of 16 patients, with AHI in the ranges 5–14.9 (group 1), 15–24.9 (group 2), 25–39.9 (group 3) and > 49.9 (group 4) per hour slept, respectively. Eight patients commenced treatment with placebo and 8 with CPAP treatment in each group. The randomisation slots of patients withdrawing after treatment commencement were filled by the next available subject with appropriate severity criteria.
6.2 Patients
Subjects were recruited from a consecutive series of outpatients referred for investigation of SAHS, who had at least 2 symptoms of SAHS (Whyte et al 1989). All patients in the consecutive series underwent a clinical sleep study conducted and scored by a standard procedure (Gould et al 1988) with monitoring of EEG, EOG, EMG, thoracic and abdominal respiratory effort, oronasal flow and oximetry to establish a minimum apnoea+hypopnoea index (AHI) of 5 or more per hour slept. Consecutive patients with appropriate AHI, who had no coexisting neurological or sleep disorder causing excessive sleepiness and who lived within 50 miles of the laboratory were approached. Ninety patients were asked to take part in the study, of whom 68 accepted. Of the patients who did not participate, 7 could not afford the required time off work, 7 gave no reason, 2 did not want to use CPAP, 2 did not want to take tablets, 2 were intolerant of a nasal mask due to facial angio-oedema and claustrophobia respectively, and one each had transport or family problems.

Subjects underwent a subsequent night of CPAP titration with polysomnography to establish the therapeutic CPAP pressure at which breathing irregularities and arousals from sleep were minimised. Subjects were instructed to use their CPAP units all night and every night and were specifically asked to use their CPAP units the nights before assessments. All patients were encouraged to report any problems with CPAP use immediately by telephone so that these could be effectively managed and CPAP compliance could be optimised.

Four patients withdrew after treatment was commenced, one each for reasons of work pressure, suspected myocardial infarction, intolerance of CPAP unit noise and relocation. All patients withdrew whilst on the CPAP limb, two having previously completed the placebo limb. The relocating patient continues to use the study CPAP unit (personal communication, M King, Papworth Hospital). The assessment results were excluded from analysis.

The full study group of 64 SAHS patients comprised 57 males and 7 females, who averaged 49 ± SEM 1 years of age, with a mean body mass index of 31 ± 1 kg/m². These patients demonstrated a mean AHI of 35 ± 4 per hour slept on polysomnography, with an average 43 ± 4 microarousals per hour slept (Cheshire et al 1992), mean minimum oxygen saturation of 79 ± 2% and an average 4% desaturation rate of 17 ± 3 per hour slept.
6.3 Assessments

The last day of each treatment limb was spent in the laboratory, when assessments of objective and subjective daytime sleepiness, symptoms, cognitive function and well-being were obtained (see Table 6.1). Each test and questionnaire was administered at the same time of day on each limb in order to avoid the influence of circadian factors on cognitive performance or mood. Questionnaires rating sleepiness, symptoms and well-being were administered in the early part of the day, when endogenous mood symptoms tend to be most severe, while the cognitive tests were administered later in the day. Weight and height were measured at each assessment. At the final assessment, subjects were asked to rate which treatment they preferred.

Objective daytime sleepiness was assessed with the multiple sleep latency test (MSLT: Carskadon et al 1986, Thorpy 1992), consisting of 5 20-minute daytime nap opportunities, during which the latency to the first 20-second period of electroencephalographic sleep is measured. The modified sleep onset criteria of a single 20-second epoch of any sleep stage, subsequently recommended by the American Sleep Disorders Association (ASDA: Thorpy 1992), was employed. Subjective sleepiness was scored using the Epworth sleepiness scale (Johns 1991, 1992, 1993, 1994), a questionnaire asking patients to rate their chance of dozing in each of 8 situations ‘in recent times’, and the energetic arousal subscale of the UMACL, a self-rating of alertness state.

An 8-item symptom questionnaire was formulated in-house, on which patients rated symptoms as present or absent at each assessment. The selected items were common daytime and nocturnal symptoms reported by SAHS patients (Whyte et al 1989), and comprised snoring, choking, morning headaches, morning confusion, frequent wakenings during the night, daytime napping, evening napping and sleepiness whilst driving.

The cognitive tests covered a broad range of function thought to be affected in SAHS (Findley et al 1986, Greenberg et al 1987, Bédard et al 1991a, Cheshire et al 1992), including general intellectual ability (block design and digit symbol subtests from the Wechsler adult intelligence scale-revised [WAIS-R] battery), information processing speed (Hick reaction time [RT], rapid visual information processing [RVIP] test, paced auditory serial addition test [PASAT]), vigilance (SteerClear), visuomotor tracking (TrailMaking), verbal fluency (Borkowski test) and memory (Benton visual retention test [BVRT]). The national adult reading test (NART), administered at the
Table 6.1: Crossover study daytime function assessments

Symptoms
- In-house questionnaire

Sleepiness
- Multiple sleep latency test (MSLT)
- Epworth sleepiness scale

Cognitive function
- WAIS-R block design and digit symbol substitution subtests
- TrailMaking
- National adult reading test (NART)
- Hick reaction time (Hick RT)
- Rapid visual information processing (RVIP) test
- Paced auditory serial addition test (PASAT)
- SteerClear
- Borkowski verbal fluency test
- Benton visual retention test (revised: BVRT)

Well-Being and Mood
- Hospital anxiety and depression (HAD) scale
- General health questionnaire-28 (GHQ-28)
- Nottingham health profile (NHP) part 2
- UWIST mood adjective checklist (UMACL)
familiarisation session only, provided an estimate of pre-morbid level of intellectual function, while the WAIS-R subtests conducted on each treatment were scaled and prorated to provide a current performance IQ score of intellectual function. Performance IQ score on each treatment was subtracted from the NART estimate of pre-morbid IQ to yield an 'IQ decrement score'.

Well-being questionnaires were selected to evaluate the impact of illness in terms of psychological distress (hospital anxiety and depression [HAD] scale and general health questionnaire [GHQ-28]), quality-of-life, excluding perceived sleep function (Nottingham health profile [NHP] part 2), and the mood dimensions of energetic arousal, tense arousal and hedonic tone (UWIST mood adjective checklist [UMACL]).

Only 51 patients were drivers, and thus able to complete the symptom questionnaire item on sleepiness whilst driving. Computer breakdowns reduced the number of complete data pairs for SteerClear to 61, and for the Hick RT task to 59. Two patients suffered from stammering, and thus did not perform the PASAT task requiring rapid verbal answers under conditions of stress. One patient did not have English as his first language, compromising the accuracy of the NART in predicting pre-morbid IQ. This patient also failed to complete TrailMaking B, stating that his native Polish alphabet contained a different letter order. The late addition of the Epworth sleepiness scale into the assessment battery meant that paired ratings both on CPAP and placebo were available for 31 patients only. One patient had no sexual partner and declined to complete the NHP items relating to sexual function. However, full data were obtained for all other measures.

Before the start of the study, subjects attended for a 5-hour session of familiarisation with the psychometric battery, in order to introduce questionnaires and to minimise subsequent test-retest improvements in cognitive test scores. At this session patients were educated in CPAP use and an accurate mask-fitting was performed. Subjects were asked to avoid caffeine-containing beverages before attending for assessments, and were offered decaffeinated beverages only during the assessment day.

Compliance with CPAP therapy was monitored by reading timeclocks hidden within the unit casing which measured total duration that units were switched on ('runtime') and that CPAP was delivered effectively ('masktime': Reeves-Hoché et al 1994).
6.4 Statistical analysis
Effects of treatment were examined by comparing outcome measures from placebo and CPAP assessments. The distributions of non-dichotomous variables were examined and non-normal distributions noted. Floor effects were seen in minimum sleep onset latency and scores for TrailMaking B, misses on the RVIP task, Hick RT movement time, Borkowski verbal fluency perseveration, BVRT errors, UMACL tense arousal, and total scores for HAD anxiety and depression, GHQ-28 and NHP part 2. Ceiling effects were observed in scores for the 4 second presentation rate PASAT, correct BVRT reproductions and UMACL hedonic tone. These non-normal measures, along with those of an interval nature (subscale scores on the GHQ-28 and NHP part 2 questionnaires), were examined using paired Wilcoxon tests. All other dependent variables were continuous and normally distributed, and were analysed using 2-way analysis-of-variance (ANOVA: Hills and Armitage 1979), with treatment order as a between-subjects factor and treatment type as a within-subject factor. McNemar tests were used to examine changes in frequency of individual symptom items and psychiatric ‘cases’ identified by HAD scale and GHQ-28. The binomial test was used to examine the distribution of treatment preference. The influence of illness severity and CPAP compliance on treatment response were investigated by entering these as putative covariates in the ANOVA. All statistical analyses were performed using SPSS-PC+ (Norusis/SPSS Inc. 1988, Bryman and Cramer 1990).

6.5 Results
6.5.1 CPAP compliance
CPAP units were switched on for an average 3.3 ± SEM 0.3 hours/night, and used effectively for 3.0 ± 0.3 hours/night. One-way ANOVA showed no significant variation in effective CPAP compliance across severity groups (F<1.09, p>0.3; Figure 6.1), which averaged 2.8 ± 0.6 (group 1), 2.3 ± 0.6 (group 2), 3.7 ± 0.5 (group 3) and 3.0 ± 0.5 (group 4) hours per night.
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6.5.2 Weight changes
Body mass index (BMI) was slightly but significantly higher on CPAP (30.6 ± 0.9 kg/m²) than on placebo treatment (30.8 ± 0.9; F=4.34, p=0.04).

6.5.3 Daytime function
Mean daytime function scores for assessments at familiarisation and on placebo and CPAP are shown in Tables 6.2 and 6.3. The p-values in both tables are from the comparison of treatment type, i.e. CPAP versus placebo. Outcome measures from the domains of sleepiness, symptoms and cognitive performance are collated in Table 6.2, and those for well-being in Table 6.3.

Better function is indicated by a lower score in Table 6.2 on the Epworth sleepiness scale, symptom total and items, SteerClear, TrailMaking tasks, RVIP misses, movement and decision time variables, Borkowski test perseverations, BVRT errors, and in Table 6.3 by lower score on all GHQ-28, HAD scale, NHP part 2 variables and UMACL tense arousal. Better function is indicated by a higher score in Table 6.2 on MSLT variables, RVIP hits, WAIS-R measures, including IQ decrement, Borkowski test total, PASAT measures and BVRT correct, and in Table 6.3 on hedonic tone.
While of the results of all daytime function outcome analyses are shown in Tables 6.2 and 6.3, significant results are highlighted and illustrated in the preceding sections.

**Table 6.2: Sleepiness, symptoms and cognitive performance at familiarisation and at treatment assessments**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Fam session Mean±SEM</th>
<th>Placebo Mean±SEM</th>
<th>CPAP Mean±SEM</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean sleep onset latency (mins)</td>
<td>—</td>
<td>7.1 ± 0.6</td>
<td>8.4 ± 0.5</td>
<td>12.11 &lt;0.01</td>
</tr>
<tr>
<td>Minimum sleep onset latency (mins) †</td>
<td>—</td>
<td>3.7 ± 0.4</td>
<td>4.5 ± 0.4</td>
<td>— 0.01</td>
</tr>
<tr>
<td>Epworth sleepiness score</td>
<td>12.3 ± 0.7</td>
<td>10.0 ± 0.7</td>
<td>8.1 ± 0.7</td>
<td>10.44 &lt;0.01</td>
</tr>
<tr>
<td>UMACL Energetic arousal</td>
<td>20.5 ± 0.7</td>
<td>20.8 ± 0.7</td>
<td>23.4 ± 0.7</td>
<td>11.83 &lt;0.01</td>
</tr>
<tr>
<td>Symptom total</td>
<td>5.0 ± 0.2</td>
<td>4.0 ± 0.2</td>
<td>2.2 ± 0.2</td>
<td>59.53 &lt;0.001</td>
</tr>
<tr>
<td>Symptom items- Snoring †</td>
<td>n=64</td>
<td>n=60</td>
<td>n=6</td>
<td>— &lt;0.001</td>
</tr>
<tr>
<td>Morning headache †</td>
<td>n=35</td>
<td>n=25</td>
<td>n=14</td>
<td>— 1.00</td>
</tr>
<tr>
<td>Morning confusion †</td>
<td>n=25</td>
<td>n=21</td>
<td>n=16</td>
<td>— 0.33</td>
</tr>
<tr>
<td>Frequent awakening †</td>
<td>n=38</td>
<td>n=41</td>
<td>n=37</td>
<td>— 0.56</td>
</tr>
<tr>
<td>Daytime napping †</td>
<td>n=53</td>
<td>n=46</td>
<td>n=26</td>
<td>— &lt;0.001</td>
</tr>
<tr>
<td>Evening napping †</td>
<td>n=55</td>
<td>n=46</td>
<td>n=36</td>
<td>— 0.06</td>
</tr>
<tr>
<td>Sleepiness while driving †</td>
<td>n=34</td>
<td>n=30</td>
<td>n=6</td>
<td>— 0.07</td>
</tr>
<tr>
<td>SteerClear (obstacles hit)</td>
<td>102.2 ± 5.8</td>
<td>74.0 ± 4.3</td>
<td>69.0 ± 3.4</td>
<td>5.33 0.02</td>
</tr>
<tr>
<td>TrailMaking A (secs)</td>
<td>36.6 ± 1.6</td>
<td>29.5 ± 1.2</td>
<td>30.7 ± 1.2</td>
<td>1.34 0.25</td>
</tr>
<tr>
<td>TrailMaking B (secs) †</td>
<td>79.6 ± 4.2</td>
<td>72.1 ± 3.9</td>
<td>66.3 ± 3.4</td>
<td>— 0.01</td>
</tr>
<tr>
<td>RVIP Hit</td>
<td>27.8 ± 1.5</td>
<td>36.5 ± 1.7</td>
<td>36.4 ± 1.8</td>
<td>0.02 0.90</td>
</tr>
<tr>
<td>RVIP Miss†</td>
<td>11.4 ± 1.9</td>
<td>10.8 ± 2.0</td>
<td>10.3 ± 1.9</td>
<td>— 0.33</td>
</tr>
<tr>
<td>WAIS-R digit symbol</td>
<td>48.5 ± 1.4</td>
<td>52.6 ± 1.5</td>
<td>53.2 ± 1.5</td>
<td>1.11 0.30</td>
</tr>
<tr>
<td>WAIS-R block design</td>
<td>28.5 ± 1.2</td>
<td>31.2 ± 1.1</td>
<td>32.2 ± 1.1</td>
<td>2.21 0.14</td>
</tr>
<tr>
<td>WAIS-R performance IQ</td>
<td>101.2 ± 1.4</td>
<td>106.2 ± 1.7</td>
<td>107.7 ± 1.6</td>
<td>2.74 0.10</td>
</tr>
<tr>
<td>IQ decrement</td>
<td>9.7 ± 1.3</td>
<td>5.0 ± 1.5</td>
<td>3.3 ± 1.4</td>
<td>3.44 0.07</td>
</tr>
<tr>
<td>Median decision time (ms)</td>
<td>359 ± 7</td>
<td>346 ± 6</td>
<td>350 ± 6</td>
<td>1.47 0.23</td>
</tr>
<tr>
<td>Decision time slope (ms/bit)</td>
<td>23.8 ± 2.0</td>
<td>22.1 ± 1.7</td>
<td>22.6 ± 1.9</td>
<td>0.10 0.75</td>
</tr>
<tr>
<td>Median movement time (ms) †</td>
<td>224 ± 10</td>
<td>216 ± 9</td>
<td>214 ± 9</td>
<td>— 0.37</td>
</tr>
<tr>
<td>Borkowski total</td>
<td>37.5 ± 1.5</td>
<td>40.4 ± 1.4</td>
<td>39.7 ± 1.6</td>
<td>0.83 0.30</td>
</tr>
<tr>
<td>Borkowski perseverations †</td>
<td>1.4 ± 0.2</td>
<td>1.6 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>— 0.88</td>
</tr>
<tr>
<td>PASAT 4 sec presentation †</td>
<td>51.6 ± 1.3</td>
<td>53.5 ± 1.3</td>
<td>54.0 ± 1.2</td>
<td>— 0.37</td>
</tr>
<tr>
<td>PASAT 2 sec presentation</td>
<td>32.0 ± 1.1</td>
<td>36.5 ± 1.3</td>
<td>38.9 ± 1.4</td>
<td>13.90 &lt;0.001</td>
</tr>
<tr>
<td>BVRT correct †</td>
<td>7.2 ± 0.3</td>
<td>7.5 ± 0.2</td>
<td>7.6 ± 0.2</td>
<td>— 0.67</td>
</tr>
<tr>
<td>BVRT errors †</td>
<td>3.7 ± 0.4</td>
<td>3.4 ± 0.3</td>
<td>3.1 ± 0.3</td>
<td>— 0.29</td>
</tr>
</tbody>
</table>

† Non-parametric test
Table 6.3: Well-being at familiarisation and at treatment assessments

<table>
<thead>
<tr>
<th></th>
<th>Fam session Mean±SEM</th>
<th>Placebo Mean±SEM</th>
<th>CPAP Mean±SEM</th>
<th>Treatment Effect</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHQ-28 total</td>
<td>6.9 ± 0.8</td>
<td>4.1 ± 0.7</td>
<td>3.0 ± 0.6</td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>GHQ-28 'cases'</td>
<td>n=31</td>
<td>n=17</td>
<td>n=16</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>GHQ-28 subscales</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (somatic symptoms)</td>
<td>1.9 ± 0.3</td>
<td>1.4 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>B (anxiety)</td>
<td>2.0 ± 0.3</td>
<td>1.0 ± 2.0</td>
<td>0.8 ± 0.2</td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>C (social dysfunction)</td>
<td>2.3 ± 0.3</td>
<td>1.4 ± 0.3</td>
<td>0.9 ± 0.2</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>D (severe depression)</td>
<td>0.7 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>HAD anxiety score</td>
<td>7.5 ± 0.5</td>
<td>6.0 ± 0.6</td>
<td>5.6 ± 0.5</td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>HAD depression score</td>
<td>6.1 ± 0.5</td>
<td>4.9 ± 0.5</td>
<td>3.7 ± 0.4</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HAD anxiety ‘cases’</td>
<td>n=14</td>
<td>n=11</td>
<td>n=7</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>HAD depression ‘cases’</td>
<td>n=12</td>
<td>n=6</td>
<td>n=3</td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>NHP Pt 2 total</td>
<td>8.7 ± 0.7</td>
<td>6.8 ± 0.7</td>
<td>5.3 ± 0.6</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>NHP Pt 2 subscales</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work efficiency</td>
<td>1.7 ± 0.2</td>
<td>1.3 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Household jobs</td>
<td>1.5 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Home relationships</td>
<td>1.4 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>Social life</td>
<td>1.5 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Sexual function</td>
<td>1.0 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Hobbies and interests</td>
<td>1.6 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>UMACL Tense arousal</td>
<td>14.9 ± 0.6</td>
<td>13.5 ± 0.7</td>
<td>13.0 ± 0.7</td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>UMACL Hedonic tone</td>
<td>26.3 ± 0.7</td>
<td>27.1 ± 0.6</td>
<td>27.7 ± 0.7</td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>Preferred treatment</td>
<td>—</td>
<td>n=28</td>
<td>n=36</td>
<td></td>
<td>0.38</td>
</tr>
</tbody>
</table>

All non-parametric tests
Sleepiness (Table 6.2):
Both mean and minimum sleep onset latency on the MSLT were significantly lengthened on CPAP compared to placebo (p<0.001: Figure 6.2), reflecting improved objective daytime sleepiness on CPAP. Both measures of subjective sleepiness were also significantly improved on CPAP. Epworth sleepiness scores were significantly lowered on CPAP, reflecting lesser recent sleepiness, (p<0.01). The energetic arousal of the UMACL showed higher scores, reflecting increased state of alertness, at the CPAP assessment (p<0.01).

![Figure 6.2: Mean (± SEM) sleep onset latency on placebo and CPAP](image)

Symptoms (Table 6.2):
Total symptom score was significantly lower on CPAP than placebo (p<0.001), with snoring (p<0.001) and daytime napping (p<0.001) showing significant individual item improvement (Figure 6.3). Trends towards a lowered frequency of patients reporting evening napping (p=0.06), sleepiness while driving (p=0.07) and morning confusion (p=0.09) were seen with CPAP.
Figure 6.3: Individual symptoms on placebo and CPAP
Cognitive function (Table 6.2):
Patients hit significantly fewer obstacles during the SteerClear vigilance task on CPAP than on placebo (p=0.02: Figure 6.4), and completed the TrailMaking B task of mental flexibility significantly more quickly (p=0.01: Figure 6.5). The number of correct mental additions during the 2 second presentation rate PASAT increased significantly on CPAP compared to placebo (p<0.001: Figure 6.5). Trends towards improvements in performance IQ (p=0.10) and IQ decrement score (p=0.07) were observed.

Figure 6.4: SteerClear performance (±SEM) on placebo and CPAP
Figure 6.5: Performance on TrailMaking B (± SEM) on placebo and CPAP

Figure 6.6: PASAT performance (± SEM) on placebo and CPAP
Well-being (Table 6.3):
Psychological distress assessed by the raw depression score on the HAD scale was significantly lessened on CPAP compared to placebo (p<0.01: Figure 6.7). Quality of life score on the NHP part 2 was improved on CPAP compared to placebo (p=0.02: Figure 6.8), with individual score reductions, indicating better function, in the work efficiency and household tasks subscales (p≤0.03). Trends towards improvement in the NHP part 2 sexual function subscale (p=0.06) and in the social dysfunction scale of the GHQ-28 (p=0.08) were observed on CPAP.

Figure 6.7: HAD scale depression rating (± SEM) on placebo and CPAP
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6.5.4 Preferred treatment
Thirty-six of the 64 patients (56%) preferred CPAP when the factors of ease of use and treatment benefit were weighed, but this was not significant (p>0.4). Within each severity subgroup, the frequency of patients preferring CPAP over tablets varied from 7 of 16 patients (44%; group 2) to 10 of 16 (63%; groups 1 and 3).

6.5.5 Order, learning and placebo effects
No significant order effects in variables were found (p>0.06), indicating that the randomised allocation to treatment order was successful. Learning effects during treatment assessments (excluding familiarisation scores) were statistically examined through ANOVA in normally-distributed cognitive and sleepiness scores. Significant treatment x treatment order interactions were observed for SteerClear performance (p<0.001), RVIP hit score (p<0.001), digit symbol substitution (p=0.01), median decision time (p=0.03) and 2 second presentation rate PASAT (p<0.001), all representing better performance on retesting. A significant interaction was also observed for mean sleep onset latency on the MSLT (p=0.03), reflecting lesser sleepiness on first testing. No learning effects were found on subjective symptom, Epworth or energetic arousal variables. The study design, by randomising treatment order, controlled for those learning effects that existed.

Figure 6.8: NHP part 2 score (± SEM) on placebo and CPAP
Visual inspection of the mean scores at familiarisation and at treatment assessments shows the combined impact of learning and expectation of benefit on sleepiness, symptoms, cognitive performance and well-being. All scores, whether subjective or objective, reflected worse function before treatment, and mean values or frequencies representing better status on both CPAP and placebo compared to familiarisation.

6.5.6 Analysis-of-covariance
The investigation of relationships between compliance or polysomnographic severity and changes in daytime function was complicated by the crossover study design, containing two patient groups represented by differing treatment orders. Learning effects in the separate treatment-order groups would act to scatter the differences between CPAP and placebo assessments. Those receiving CPAP first would show smaller improvements in score from CPAP to placebo to those receiving placebo first, in whom the difference with CPAP on second testing would be boosted by learning. Such learning effects, indicated by treatment x treatment order interactions, were demonstrated for cognitive and sleepiness variables (see Section 6.5.5). Because of these, a univariate correlational analysis was not attempted.

Two variables, AHI and CPAP masktime, were selected as putative covariates of the changes of daytime function by treatment type, and were entered into the ANOVA of continuous, normally-distributed variables. AHI showed no significant correlation with treatment changes. Masktime was a significant covariate in the analysis of UMACL energetic arousal (p=0.03) and symptom total (p=0.004), indicating that response to CPAP varied with compliance. In the case of energetic arousal, the addition of masktime as a covariate rendered the analysis of treatment type non-significant (F=0.00, p>0.9), indicating that treatment response in state of alertness was strongly associated with compliance.

6.6 Discussion
The crossover study showed, for the first time in a controlled investigation, objective and subjective improvements in daytime function after CPAP therapy. All of the areas of function examined, including sleepiness, symptoms, cognitive performance and well-being, showed benefits from CPAP.

In contrast to the studies of others (Kribbs et al 1993b, Bédard et al 1993), the use of a familiarisation session, placebo control and balanced treatment order within this study minimised and controlled for the longitudinal learning effects documented in the
previous parallel-group study and observed in the ANOVA analysis in this sample. The observed improvements on CPAP compared to placebo are small in magnitude, but this margin of difference is attenuated by expectation of benefit from placebo, which can have substantial impact on performance and mood (Griffiths 1981). The reductions in all psychological distress scores on placebo compared to familiarisation (Table 6.2) and the high proportion of patients who preferred placebo over CPAP (44%) substantiates the perceived benefit from placebo in this patient sample. Patients were minimally heavier on CPAP over the course of the study, providing assurance that the documented improvements were due to active effects of CPAP, and not to weight loss.

Multiple comparisons of inter-related measures were employed in this study, raising the possibility that the significant improvements shown with CPAP were Type 1, false positive statistical errors, and represented spurious significant findings, occurring at a rate of 1 in 20 comparisons by chance alone (Bryman and Cramer 1990). Thus of the 50 endpoints measured and compared within the study, 2 or 3 might show false positive findings. Although this criticism may be warranted, the use of multiple outcome measures was designed into the study to allow evaluation and comparison of instruments which might prove useful in the discrimination of treatment-sensitive function.

Statistical techniques such as the Bonferroni method have been developed for improving the likelihood of avoiding ‘false positive’ findings (Smith et al 1987, Bland and Altman 1995), although these are more commonly applied to the multiple comparisons of treatment type (Smith et al 1987) than to multiple comparisons of related outcome measures (Bland and Altman 1995), as contained in the crossover study. Bonferroni corrections require the use of more conservative p-value thresholds, which in turn limit statistical power. Thus the application of these more stringent techniques concomitantly reduces the possibility of demonstrating true positive differences, and may result in a requirement for unfeasibly large subject samples in order to produce the very small p-values (which would approximate 0.001 if applied to this study) set as thresholds for significance.

The application of a Bonferroni correction to the crossover study data, with a stringent alpha significance value at p<0.001, would restrict statistical significance to the total symptom score, its individual items of snoring and daytime sleepiness, and the 2-second presentation rate PASAT. This more conservative interpretation still suggests
objective improvement in cognitive function, but would limit CPAP-related improvement to subjective, but not objective, sleepiness, and would exclude improvement in well-being with CPAP.

Although the possibility of Type 1 statistical errors in the more liberal analysis without Bonferroni corrections cannot be discounted, the coherence of the observations of the crossover study support the effectiveness of CPAP therapy for daytime function. It is notable that although 2 or 3 false positives might be expected, 14 significant improvements, all occurring with CPAP and not placebo, were observed.

All measures of sleepiness, whether objective or subjective, were improved on CPAP. Both the Epworth sleepiness score, a measure of recent sleepiness behaviour, and UMACL energetic arousal score, rating state of alertness at assessment, were improved on CPAP. The average Epworth score on placebo lay in the range associated with severe SAHS (Johns 1993), while that on CPAP fell to a level similar to that observed by Johns (1992) in his study of CPAP-treated SAHS patients. The mood dimension of energetic arousal is thought to index excitement in the reticular activating system of the brainstem (Thayer 1989), suggesting that CPAP resulted in a higher level of physiological alertness. The concurrence of all measures of sleepiness in showing improvement on CPAP provides cross-validation and may suggest that these measures share a common biological substrate.

Objective daytime sleepiness was significantly improved, but not normalised, on CPAP, with both placebo and CPAP mean sleep onset latencies falling within the 'grey zone' of 5 to 10 minutes (Van den Hoed et al 1981), which is clinically associated with moderate sleepiness (Thorpy 1992). Mean sleep onset latency rose by only 1.3 minutes, from 7.1 minutes on placebo to 8.4 minutes with CPAP. The small magnitude of improvement is surprising, and may indicate persistent sleepiness following therapy, but may also relate to the choice of the MSLT instrument, to placebo effects dictated by the study design, to patient selection factors with the inclusion of a subsample of patients with mild SAHS, and to the low level of CPAP compliance.

This lack of normalisation in MSLT scores after CPAP is in conflict with the findings of Lamphere et al (1989) and Wittig et al (1986), who showed sleep onset latencies of exceeding the 'normal' threshold of 10 minutes following 14 days or 6 weeks respectively of CPAP treatment. However, the small improvement in objective
daytime sleepiness seen in the crossover study concurs with the findings of others (Fry et al 1990, Gaddy and Doghramji 1991, Bédard et al 1993, Kribbs et al 1993b) showing lengthened, but still moderately 'sleepy' onset latencies below 10 minutes, following CPAP treatment. Thus the majority of studies, like this one, tend to indicate that objective daytime sleepiness as measured by the MSLT may not be normalised by therapy.

It has been argued that the lack of normalisation of MSLT scores in treatment studies demonstrates a lack of sensitivity in the MSLT to treatment-related changes (Mitter et al 1982). The relatively small improvements seen in treated excessively sleepy patients shows a persistence of the ability to fall asleep at will, but may not measure the more clinically relevant ability to stay awake when required. The MSLT and the maintenance of wakefulness test (MWT), a polysomnographic test in which patients are instructed to remain in awake in sleep-conducive environment, appear on factor analyses to measure separate abilities, and the MWT may show greater sensitivity to treatment effects (Sangal et al 1992a, 1992b). Thus the small improvement in sleep latency may in part result from the choice of the MSLT as the measure of objective daytime sleepiness.

The magnitude of change in sleep onset latency is also likely to be attenuated by placebo effects within this study, which would act to prolong sleep onset latencies off CPAP, and reduce the size of effect with CPAP. Mean sleep onset latencies on placebo were in the moderate, and not the severe, range for daytime sleepiness, in contrast to pre-treatment latencies in many other samples of SAHS patients (e.g. Lamphere et al 1989, Kribbs et al 1993b), including those in the pilot parallel-group study. MSLT scores have recently been shown to be alterable with incentive (Page et al 1993), raising the likelihood that placebo effects in this study contributed to these relatively extended sleep onset latencies.

The small magnitude of improvement in MSLT score may also be related to the inclusion of patients with very mild SAHS, who showed normal objective daytime sleepiness on placebo (see Chapter 7). Those studies showing the most dramatic improvements in sleep latency with CPAP (Wittig et al 1986, Lamphere et al 1989) were conducted on patients with severe SAHS (mean AHI 70 per hour slept), in whom treatment benefits might be expected to be greater. The stable MSLT score across treatments in the patients with mild SAHS, described in Chapter 7, would tend to equalise sleep onset latencies within the full patient sample examined in this study.
Chapter 6: Randomised crossover study

Total symptom score was significantly reduced on CPAP, with individual item improvements in the frequency of patients reporting snoring and daytime napping. Since these symptoms are the most frequent reasons for seeking medical intervention (Guilleminault et al 1978, Whyte et al 1989), the study corroborates the usefulness of CPAP in ameliorating major symptoms. The trend towards improvement in sleepiness while driving is particularly relevant given the evidence for increased driving accident rates in SAHS patients (Findley et al 1988). Statistical power was reduced on this item because only a subset of patients were drivers, and the short treatment limbs meant that many patients had not undergone sufficient long drives to assess their sleep propensity under duress. Thus the finding of this trend is notable.

Significant improvements were seen in cognitive tests of vigilance, mental flexibility and concentration ability. Performance of all these tests required rapid and complex responses. Patients with SAHS have previously been shown to have impaired performance on the SteerClear test of vigilance (Findley et al 1989a) on TrailMaking B (Findley et al 1986, Bédard et al 1993), and on the PASAT (Findley et al 1986). Thus improvements in scores on these tests are appropriate and suggest reversibility of at least some of the cognitive deficits induced by SAHS. The tasks improving with CPAP imply that vigilance and psychomotor speed may improve with therapy. The IQ decrement score at familiarisation (before learning effects improved obtained IQ scores) showed, in contrast to the pilot parallel-group study, an average shortfall of 10 IQ points between expected and observed performance in the sample of patients. 39 of 63 patients (62%) demonstrated a positive performance IQ decrement score, suggesting some degree of cognitive deficit. This observation corroborates existing evidence of deficits in executive skills and attention in SAHS (Greenberg et al 1987, Bédard et al 1993), while the statistical trend towards improvement of performance IQ score implies that such skills might benefit from CPAP.

None of the other cognitive scores assessed were significantly different on CPAP and placebo, although most mean scores showed better function on CPAP (Table 6.2). There was no evidence for improvement in information processing speed with CPAP, as neither RVIP test nor Hick RT scores changed with treatment type. This result confirmed the null finding using simple RT in the parallel-group study, despite the use of sophisticated paradigms to examine processing speed. Neither verbal fluency nor the BVRT memory test were influenced by treatment.
The lack of improvement in many cognitive measures may be due to absence of
deficit, persistent impairment after CPAP, or insensitivity of the tests employed, most
of which were developed to detect brain damage. Such tests might prove insensitive to
the subtle and variable deficits induced by sleepiness. The design of the study does not
address this question, and conflict in the literature concerning the specific types of
daytime deficits in SAHS (Greenberg et al 1987, Findley et al 1986, Bédař et al
1993, Naëgelé et al 1995) and their best nocturnal correlates (Berry et al 1986, Bédař
clarify this subsidiary question.

All mean values for well-being scores reflected better function on CPAP, and
significant improvements were found in self-rated depression from the HAD scale
and quality-of-life, assessed by the NHP part 2. The finding of improved depression
rating corroborates previous studies showing lessened depression following treatment
(Derderian et al 1988, Millman et al 1989). The subscales of the NHP part 2 showing
improvement with CPAP, those for work efficiency and household jobs, imply that
CPAP may improve the productivity in the workplace and in the home. The
improvement in quality-of-life (NHP part 2) is supported in the trend towards
improvement in the social dysfunction subscale of the GHQ-28, which investigates
patients' satisfaction with their participation in work and family life. The trend towards
improvement in the sexual function subscale of the NHP may imply that CPAP, far
from discouraging sexual activity, as many patients fear, may facilitate a more
fulfilling sexual life.

Objective CPAP compliance was, on average, much lower than the all-night use
recommended to patients before treatment commencement. However, recent
prospective studies of early CPAP use (Kribbs et al 1993a, Reeves-Hoché et al 1994)
have shown similar, low objective compliance rates. As has been noted (Reeves-
Hoché et al 1995), no standard method for calculating compliance exists, but the stated
CPAP ‘runtimes’ from these two studies (4.9 and 4.7 hours per night respectively)
were skewed towards higher values by their method of calculation. Kribbs et al
(1993a) reported the hours of CPAP use on the nights when CPAP was turned on: a
recalculation including a component from nights when CPAP was not used reduces
this figure to 3.2 hours per night. Reeves-Hoché et al (1994) excluded values from
patients who discontinued CPAP use during the 6 month study: if the CPAP use-rates
for 9 CPAP rejecters are incorporated, average CPAP ‘runtime’ is 3.9 hours per night.
Thus, with adjustments to standardise the CPAP compliance calculation, the average
CPAP 'runtime' in the crossover study of 3.3 hours per night is closely in agreement with that of other studies, all showing that objective CPAP compliance is unexpectedly low.

The minimum therapeutic use-rate for CPAP is as yet unknown, but it seems likely that patients may adjust their CPAP use to a level that produces subjective benefits in daytime function. Our findings of significant improvement in all examined areas of daytime function suggest that full-night CPAP use may not be necessary to reduce daytime deficits.

Effective CPAP compliance was a poor covariate in the analysis of treatment effects, showing strong association only with the treatment effects of UWIST energetic arousal score. The paucity of associations between compliance and other endpoints may relate to inter-individual differences in thresholds for benefit from CPAP, or may result from insufficient sensitivity to fluctuating CPAP use in the objective monitoring system employed. AHI lacked significance as a covariate in the analysis of treatment effect, and thus provided no evidence that patients' response to CPAP varies with their severity of SAHS.

The randomised crossover study demonstrated objective and subjective improvements in daytime function following CPAP therapy. Despite the lack of clear finding from correlations between measures of severity of SAHS and improvement in daytime function, the relationship between SAHS severity and benefit from CPAP remains of great clinical interest. As is described in the introduction to the next chapter, the level of SAHS severity at which CPAP treatment is indicated is not known. However, to attempt to define the lower limit of severity at which daytime benefits from CPAP are produced, a separate analysis of the mildest severity group studied within the crossover protocol was conducted.
Chapter 7: THE EFFECTS OF CPAP ON DAYTIME FUNCTION IN PATIENTS WITH MILD SAHS

Sleepiness and impaired daytime function are major clinical features of the sleep apnoea/hypopnoea syndrome (Whyte et al 1989, Cheshire et al 1992), and the primary indication for CPAP therapy is to try to improve these features. Evidence from previous studies had suggested that CPAP has beneficial effects on daytime sleepiness, cognitive performance and psychological well-being (Bédard et al 1993, Kribbs et al 1993b, Derderian et al 1988), and these were confirmed in the randomised crossover study (Chapter 6). However, the level of severity of the sleep apnoea/hypopnoea syndrome (SAHS) at which treatment is indicated is not well-defined. Patients with mild SAHS (apnoea+hypopnoea index 5 to 15 per hour slept) have, by definition, symptoms of the syndrome, but there is a dearth of data indicating whether their objective daytime sleepiness and performance is abnormal.

Earlier work carried out on a small sample of SAHS patients and controls showed a discontinuity in the symptomatology reported by those with an apnoea+hypopnoea index (AHI) greater than and less than 15 per hour slept (Gould et al 1988). Fewer subjects with the lower level of breathing pauses in this study complained of symptoms of SAHS, leading to the empirical use of this threshold as a cutoff for diagnosis and treatment. However, symptoms and deficits in daytime function have since been observed in patients with low levels of breathing pauses in sleep. Evidence for daytime problems in patients with low AHI is complicated by variation in nocturnal measures used to diagnose SAHS, and thresholds for defining pathology, but it is apparent that patients may experience distressing symptoms at low levels of breathing abnormality in sleep.

Studies in sleep clinic populations have shown considerable congruence in symptomatology of patients above and below AHI thresholds of 5 (Hillerdal et al 1991) or 10 (Hoffstein and Szalai 1993). This lack of specificity in the symptoms of SAHS has also been demonstrated by a large community-based study, in which excessive daytime sleepiness was reported by 41% of subjects with an AHI greater than 15, but by 37% of subjects with AHI less than 15 (Olson et al 1995). Patients with the upper airway resistance syndrome (UARS) have, by definition, low AHIs (mean values < 5) and daytime symptoms in the form of excessive daytime sleepiness (Guilleminault et al 1992, 1993, Downey et al 1993), which are thought to result from
elevated frequencies of EEG arousals during sleep. Thus symptoms, a prerequisite in diagnosing SAHS (Gould et al. 1988), do not appear to be necessarily linked to a ‘diagnostic’ AHI.

Few studies have attempted to tie the chief measure of breathing disruption in sleep, AHI, to daytime deficits at the lower SAHS severity range, although nocturnal correlates of daytime deficits have previously been found in more severe samples of SAHS patients (Roehrs et al. 1989, Bédard et al. 1991a, Poceta et al. 1992, Cheshire et al. 1992). One report showed that symptomatic patients with AHIs < 20 have impaired quality-of-life, specifically in the areas of social and emotional function and vitality, compared to others with no daytime symptoms (Gall et al. 1993). This finding suggests that daytime deficits may occur even at the lower severity range in SAHS.

Symptoms of SAHS, such as snoring, may help identify a patient group without ‘significant’ polysomnography according to local conventions, but suffering daytime impairment. Evidence in the literature links snoring with significant daytime deficits (Telakivi et al. 1988, Jønnum and Sjøl 1994, Janson et al. 1994b). Snorers with 4% desaturation rates < 5 per hour slept show high incidences of daytime fatigue and sleepiness, including while driving (Janson et al. 1994b). Epidemiological (Jønnum and Sjøl 1994) and case-control (Telakivi et al. 1988) studies have shown associations between snoring, daytime sleepiness and cognitive and memory problems. Snorers without diagnostic AHIs show a significant correlation between snoring frequency and epoch-scored awakenings from sleep (Hoffstein et al. 1991), and in a mixed group of snorers both with and without diagnostic AHIs, microarousal frequency correlated with clinical assessment of excessive daytime sleepiness (Zucconi et al. 1995). These data suggest that snoring without ‘significant’ levels of breathing disruption may fragment sleep and produce daytime impairment.

CPAP has been recommended as a treatment both for ‘heavy snorers disease’ (Lugaresi et al. 1989) and UARS (Guilleminault et al. 1993, Strollo and Sanders 1993). CPAP treatment in UARS patients results in decreased microarousal frequency in sleep and improvement in objective daytime sleepiness (Guilleminault et al. 1993). However, the effects of CPAP treatment in mild SAHS have yet to be assessed. The inclusion within the crossover protocol of a randomised subgroup of patients with mild SAHS (AHI 5-15) allowed the individual daytime functions induced by CPAP in such patients to be assessed.
7.1 Study protocol
A subgroup of mild subjects, participating in the larger crossover study (Chapter 6), were analysed separately. The protocol and methods were thus the same as the larger crossover study.

7.2 Patients
Subjects were prospectively recruited from consecutive sleep clinic outpatients referred for investigation of SAHS. Entry criteria required two or more symptoms of SAHS (Whyte et al 1989) and an AHI in the range 5.0 to 14.9 per hour slept during clinical polysomnography, conducted and scored according to our usual method (Gould et al 1988). Patients with coexisting neurological or sleep disorder, or residence outwith a 50 mile radius of the laboratory, were excluded.

Twenty-eight subjects were invited to participate in the study, of whom 18 accepted. Of the 10 non-acceptors, 4 declined to participate because work pressure meant they could not spend the required 3 full days in the sleep laboratory. Four non-acceptors gave no reason and 2 were intolerant of nasal CPAP during the pre-treatment CPAP titration trial. Two patients withdrew after study treatment was commenced, both during the CPAP limb, and were excluded from analysis. One of these moved away unexpectedly, and remains on CPAP therapy, while the other was intolerant of noise from his CPAP unit and declined to complete the treatment limb. The treatment order slots of patients withdrawing after treatment commencement were filled with the next available subject.

The 16 studied patients, 12 of whom were male, averaged 52 ± SEM 2 years of age, with a mean body mass index of 29.8 ± 1.8 kg/m². The subjects demonstrated a mean AHI of 11 ± 1 per hour slept, with an average 24 ± 3 microarousals per hour slept (Cheshire et al 1992), mean minimum oxygen saturation of 86 ± 1 % and average 4% desaturation rate of 4 ± 1 per hour slept.

7.3 Statistical analysis
Outcome measures of daytime function from placebo and CPAP assessments were compared. Continuous, normally-distributed data were examined with 2-way ANOVA, with treatment order as a between-subjects factor and treatment type as a within-subject factor. Paired Wilcoxon tests were conducted in interval and non-normal data. The binomial test was used to examine the distribution of treatment preference, and McNemar tests to assess changes in frequency of individual
symptoms. Patients were split into better and poorer compliers, using median effective CPAP use as a cutpoint. A subanalysis comparing CPAP and placebo outcome measures was conducted within the better-complying group. Mann-Whitney tests were conducted to compare background variables in better and poorer CPAP compliers. All statistical analyses were performed using SPSS-PC+ (Norusis/SPSS Inc. 1988).

7.4 Results
7.4.1 Full group
CPAP units were run for an average $3.2 \pm 0.7$ hours per night, and used effectively for a mean $2.8 \pm 0.6$ hours per night (Figure 7.1).

![Figure 7.1: CPAP compliance in patients with mild SAHS](image)

Mean values and treatment effects for daytime function scores are shown in their entirety in Table 7.1, with selected results highlighted in Figures 7.2 to 7.5.
Table 7.1: Daytime function at familiarisation and at treatment assessments

<table>
<thead>
<tr>
<th></th>
<th>Fam session Mean±SEM</th>
<th>Placebo Mean±SEM</th>
<th>CPAP Mean±SEM</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.8 ± 1.8</td>
<td>30.0 ± 1.9</td>
<td>30.1 ± 1.9</td>
<td>2.06 0.17</td>
</tr>
<tr>
<td>Mean sleep onset latency (mins)</td>
<td>---</td>
<td>9.9 ± 1.5</td>
<td>10.0 ± 1.2</td>
<td>0.05 0.83</td>
</tr>
<tr>
<td>Minimum sleep onset latency (mins) †</td>
<td>---</td>
<td>5.4 ± 1.3</td>
<td>5.6 ± 1.0</td>
<td>--- 0.73</td>
</tr>
<tr>
<td>Epworth sleepiness score</td>
<td>14.2 ± 0.9</td>
<td>10.0 ± 1.2</td>
<td>10.1 ± 1.4</td>
<td>0.00 1.00</td>
</tr>
<tr>
<td>Symptom total</td>
<td>4.9 ± 0.4</td>
<td>3.7 ± 0.4</td>
<td>2.0 ± 0.3</td>
<td>10.65 &lt;0.01</td>
</tr>
<tr>
<td>SteerClear (obstacles hit)</td>
<td>119.9 ± 9.3</td>
<td>75.3 ± 8.9</td>
<td>74.8 ± 7.3</td>
<td>0.59 0.45</td>
</tr>
<tr>
<td>TrailMaking A (secs)</td>
<td>35.6 ± 3.0</td>
<td>30.2 ± 2.9</td>
<td>30.8 ± 2.7</td>
<td>0.05 0.83</td>
</tr>
<tr>
<td>TrailMaking B (secs) †</td>
<td>81.3 ± 7.0</td>
<td>77.7 ± 9.2</td>
<td>64.1 ± 5.5</td>
<td>--- 0.02</td>
</tr>
<tr>
<td>RVIP Hit</td>
<td>23.7 ± 3.2</td>
<td>34.8 ± 3.2</td>
<td>36.9 ± 3.2</td>
<td>0.58 0.46</td>
</tr>
<tr>
<td>RVIP Miss †</td>
<td>16.5 ± 2.5</td>
<td>18.0 ± 6.0</td>
<td>20.0 ± 5.3</td>
<td>--- 0.98</td>
</tr>
<tr>
<td>WAIS -R digit symbol</td>
<td>50.4 ± 2.9</td>
<td>56.0 ± 3.2</td>
<td>55.1 ± 3.3</td>
<td>0.86 0.37</td>
</tr>
<tr>
<td>WAIS-R block design</td>
<td>25.7 ± 2.3</td>
<td>29.3 ± 2.5</td>
<td>28.6 ± 2.1</td>
<td>0.43 0.52</td>
</tr>
<tr>
<td>WAIS-R performance IQ</td>
<td>102.8 ± 2.9</td>
<td>108.5 ± 3.9</td>
<td>106.2 ± 3.5</td>
<td>2.53 0.13</td>
</tr>
<tr>
<td>IQ decrement</td>
<td>9.3 ± 2.5</td>
<td>5.3 ± 3.5</td>
<td>7.0 ± 3.1</td>
<td>1.62 0.23</td>
</tr>
<tr>
<td>Median decision time (ms)</td>
<td>372 ± 19</td>
<td>356 ± 14</td>
<td>365 ± 16</td>
<td>1.52 0.24</td>
</tr>
<tr>
<td>Decision time slope (ms/bit) †</td>
<td>30.7 ± 5.1</td>
<td>25.2 ± 4.3</td>
<td>27.9 ± 4.7</td>
<td>--- 0.71</td>
</tr>
<tr>
<td>Median movement time (ms) †</td>
<td>220 ± 25</td>
<td>209 ± 20</td>
<td>212 ± 19</td>
<td>--- 0.88</td>
</tr>
<tr>
<td>Borkowski total words</td>
<td>34.5 ± 3.1</td>
<td>39.2 ± 3.1</td>
<td>38.5 ± 3.5</td>
<td>0.44 0.52</td>
</tr>
<tr>
<td>Borkowski perseverations †</td>
<td>1.5 ± 0.5</td>
<td>1.6 ± 0.4</td>
<td>1.2 ± 0.3</td>
<td>--- 0.38</td>
</tr>
<tr>
<td>PASAT 4sec presentation †</td>
<td>47.8 ± 3.4</td>
<td>49.8 ± 3.3</td>
<td>51.1 ± 3.1</td>
<td>--- 0.29</td>
</tr>
<tr>
<td>PASAT 2sec presentation †</td>
<td>29.9 ± 2.4</td>
<td>35.3 ± 2.8</td>
<td>37.8 ± 3.3</td>
<td>2.59 0.13</td>
</tr>
<tr>
<td>BVRT correct †</td>
<td>7.2 ± 0.5</td>
<td>7.3 ± 0.6</td>
<td>7.3 ± 0.6</td>
<td>--- 0.96</td>
</tr>
<tr>
<td>BVRT errors †</td>
<td>3.6 ± 0.8</td>
<td>3.8 ± 0.8</td>
<td>3.6 ± 0.8</td>
<td>--- 0.76</td>
</tr>
<tr>
<td>GHQ-28 total †</td>
<td>5.7 ± 1.7</td>
<td>3.2 ± 1.3</td>
<td>1.4 ± 0.6</td>
<td>--- 0.22</td>
</tr>
<tr>
<td>GHQ-28 ‘cases’ †</td>
<td>n=6</td>
<td>n=3</td>
<td>n=3</td>
<td>--- 1.00</td>
</tr>
<tr>
<td>HAD anxiety score †</td>
<td>6.4 ± 1.2</td>
<td>5.1 ± 1.1</td>
<td>4.5 ± 1.2</td>
<td>--- 0.48</td>
</tr>
<tr>
<td>HAD depression score †</td>
<td>5.6 ± 0.9</td>
<td>5.0 ± 1.0</td>
<td>3.4 ± 0.9</td>
<td>--- 0.03</td>
</tr>
<tr>
<td>HAD anxiety ‘cases’ †</td>
<td>n=3</td>
<td>n=3</td>
<td>n=2</td>
<td>--- 1.00</td>
</tr>
<tr>
<td>HAD depression ‘cases’ †</td>
<td>n=1</td>
<td>n=2</td>
<td>n=1</td>
<td>--- 1.00</td>
</tr>
<tr>
<td>NHP Pt 2 total †</td>
<td>6.9 ± 1.4</td>
<td>5.8 ± 1.4</td>
<td>3.8 ± 1.1</td>
<td>--- 0.17</td>
</tr>
<tr>
<td>UMACL Energetic arousal</td>
<td>21.9 ± 1.6</td>
<td>22.7 ± 1.7</td>
<td>25.4 ± 1.4</td>
<td>3.14 0.10</td>
</tr>
<tr>
<td>UMACL Tense arousal †</td>
<td>13.9 ± 1.2</td>
<td>13.3 ± 1.5</td>
<td>12.1 ± 1.1</td>
<td>--- 0.55</td>
</tr>
<tr>
<td>UMACL Hedonic tone †</td>
<td>27.0 ± 1.3</td>
<td>28.3 ± 1.1</td>
<td>28.4 ± 1.1</td>
<td>--- 0.95</td>
</tr>
</tbody>
</table>

† Non-parametric test
Average objective daytime sleepiness measured by the MSLT approached the normal range on placebo and was not significantly improved by CPAP (p>0.8; Figure 7.2). The subjective Epworth sleepiness score remained in the severe range on both treatments (p>0.9), but energetic arousal score from the UMACL showed a trend towards increase in state of alertness on CPAP (p=0.10). Total symptom score (Figure 7.3) was significantly lower on CPAP than placebo (p<0.001), reflecting an improvement in status. Performance on the TrailMaking B task of mental flexibility was significantly improved on CPAP (p=0.02; Figure 7.4), but no other treatment effects on cognitive performance were found. Self-rated depression score on the HAD scale was significantly reduced by CPAP (p=0.03, see Figure 7.5), corresponding to lower distress. Ten of 16 patients (p>0.4) preferred CPAP when the factors of ease of use and treatment benefit were weighed.

Treatment order effects in variables examined in the above analysis were non-significant (p>0.12), with the exception of mean sleep onset latency, which was significantly longer in patients treated first with CPAP than in those commencing treatment with placebo (p=0.05). Since mean sleep onset latency showed no significant effect for treatment, this was not considered crucial. The lack of treatment order effects provided assurance that the balancing of treatment order could control for learning effects. Such learning effects, represented by a significant treatment x treatment order interaction, were demonstrated for SteerClear performance (p<0.001), WAIS-R performance IQ score (p=0.05), RVIP hit score (p<0.01) and verbal fluency total score (p<0.01).
Figure 7.2: Mean sleep onset latency on placebo and CPAP

Figure 7.3: Symptom total score on placebo and CPAP
Figure 7.4: TrailMaking B performance on placebo and CPAP

Figure 7.5: HAD depression rating on placebo and CPAP
7.4.2 Better CPAP compliers

The patient group was split by median effective CPAP use into better and poorer compliers (n=8 in each group). Mean effective CPAP compliance averaged 5.0 ± 0.6 hours per night in the better users, and 1.1 ± 0.2 in the poorer users. Four patients commenced treatment with tablets in each group.

As in the full group, the better compliers (Table 7.2) showed significant CPAP-related improvement in symptom total score (p<0.02), TrailMaking B performance (p=0.04) and HAD scale depression rating (p=0.04). In addition, NHP part 2 score was significantly reduced on CPAP (p=0.03; Figure 7.6), indicating improved quality-of-life. The only individual subscale of the NHP showing improvement within the group was that for social life (p=0.04). The somatic symptom subscale of the GHQ-28 showed an individual reduction in score (p=0.04), reflecting lesser distress from physical symptoms, but total GHQ-28 score was not significantly reduced on CPAP (p>0.1). Six of the eight better compliers preferred CPAP treatment (p>0.2).

![Figure 7.6: Quality-of-life on placebo and CPAP in better CPAP compliers](image-url)
### Table 7.2: Good compliers’ daytime function at familiarisation and at treatment assessments

<table>
<thead>
<tr>
<th></th>
<th>Fam session Mean±SEM</th>
<th>Placebo Mean±SEM</th>
<th>CPAP Mean±SEM</th>
<th>Treatment Effect</th>
<th>F-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>31.3 ± 3.1</td>
<td>30.7 ± 2.5</td>
<td>30.8 ± 2.6</td>
<td>0.64</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td><strong>Mean sleep onset latency (mins)</strong></td>
<td>10.8 ± 2.3</td>
<td>11.0 ± 2.1</td>
<td></td>
<td>0.74</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td><strong>Minimum sleep onset latency (mins)</strong></td>
<td>6.4 ± 2.3</td>
<td>6.0 ± 1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Epworth sleepiness score †</strong></td>
<td>17.0 ± 0.0</td>
<td>6.7 ± 1.5</td>
<td>7.3 ± 3.5</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Symptom total</strong></td>
<td>4.9 ± 0.9</td>
<td>3.6 ± 0.8</td>
<td>1.5 ± 0.3</td>
<td>9.53</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td><strong>SteerClear (obstacles hit)</strong></td>
<td>122.1 ± 16.6</td>
<td>83.7 ± 11.8</td>
<td>81.7 ± 12.1</td>
<td>2.16</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td><strong>TrailMaking A (secs)</strong></td>
<td>39.9 ± 5.6</td>
<td>30.4 ± 4.2</td>
<td>29.5 ± 3.6</td>
<td>0.10</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td><strong>TrailMaking B (secs) †</strong></td>
<td>82.1 ± 14.2</td>
<td>76.1 ± 14.1</td>
<td>61.9 ± 9.1</td>
<td></td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td><strong>RVIP Hit</strong></td>
<td>20.4 ± 5.0</td>
<td>36.6 ± 4.0</td>
<td>34.4 ± 3.5</td>
<td>0.63</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td><strong>RVIP Miss †</strong></td>
<td>17.4 ± 6.3</td>
<td>20.6 ± 9.6</td>
<td>14.6 ± 6.3</td>
<td></td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td><strong>WAIS -R digit symbol</strong></td>
<td>46.1 ± 5.2</td>
<td>53.6 ± 5.6</td>
<td>52.6 ± 5.6</td>
<td>0.78</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td><strong>WAIS-R block design</strong></td>
<td>23.9 ± 3.2</td>
<td>27.4 ± 2.8</td>
<td>26.3 ± 2.6</td>
<td>0.25</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td><strong>WAIS-R performance IQ</strong></td>
<td>100.4 ± 3.5</td>
<td>106.6 ± 5.6</td>
<td>103.6 ± 5.4</td>
<td>0.74</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td><strong>IQ decrement</strong></td>
<td>9.2 ± 3.8</td>
<td>5.9 ± 5.4</td>
<td>7.0 ± 4.4</td>
<td>0.19</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td><strong>Median decision time (ms)</strong></td>
<td>368 ± 24</td>
<td>365 ± 18</td>
<td>386 ± 25</td>
<td>0.51</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td><strong>Decision time slope (ms/bit) †</strong></td>
<td>37.5 ± 10.3</td>
<td>27.9 ± 7.2</td>
<td>27.5 ± 6.0</td>
<td>0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median movement time (ms) †</strong></td>
<td>221 ± 30</td>
<td>198 ± 21</td>
<td>204 ± 25</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Borkowski total words</strong></td>
<td>32.7 ± 6.3</td>
<td>36.7 ± 5.4</td>
<td>35.0 ± 5.8</td>
<td>3.53</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td><strong>Borkowski perseverations †</strong></td>
<td>2.1 ± 1.0</td>
<td>1.4 ± 0.6</td>
<td>1.1 ± 0.4</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PASAT 4sec presentation †</strong></td>
<td>43.0 ± 7.0</td>
<td>48.4 ± 5.4</td>
<td>48.3 ± 5.3</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PASAT 2sec presentation</strong></td>
<td>28.4 ± 4.8</td>
<td>33.3 ± 4.1</td>
<td>37.4 ± 5.7</td>
<td>2.49</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td><strong>BVRT correct †</strong></td>
<td>6.9 ± 1.0</td>
<td>7.1 ± 0.7</td>
<td>7.1 ± 0.9</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BVRT errors †</strong></td>
<td>3.7 ± 1.3</td>
<td>3.8 ± 1.0</td>
<td>3.5 ± 1.0</td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GHQ-28 total †</strong></td>
<td>7.0 ± 3.0</td>
<td>3.3 ± 1.9</td>
<td>0.3 ± 0.3</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GHQ-28 ‘cases’ †</strong></td>
<td>n=3</td>
<td>n=1</td>
<td>n=0</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HAD anxiety score †</strong></td>
<td>5.6 ± 2.1</td>
<td>4.5 ± 1.7</td>
<td>3.9 ± 1.8</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HAD depression score †</strong></td>
<td>5.7 ± 1.5</td>
<td>4.8 ± 1.5</td>
<td>2.5 ± 1.0</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HAD anxiety ‘cases’ †</strong></td>
<td>n=1</td>
<td>n=1</td>
<td>n=1</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HAD depression ‘cases’ †</strong></td>
<td>n=1</td>
<td>n=1</td>
<td>n=0</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NHP Pt 2 total †</strong></td>
<td>8.0 ± 2.3</td>
<td>6.8 ± 2.5</td>
<td>2.4 ± 1.5</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UMACL Energetic arousal</strong></td>
<td>20.0 ± 2.2</td>
<td>23.0 ± 2.8</td>
<td>27.8 ± 1.6</td>
<td>3.48</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td><strong>UMACL Tense arousal †</strong></td>
<td>14.0 ± 1.8</td>
<td>12.9 ± 1.9</td>
<td>13.3 ± 1.9</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UMACL Hedonic tone †</strong></td>
<td>26.0 ± 2.3</td>
<td>29.6 ± 1.1</td>
<td>30.4 ± 1.0</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Non-parametric test
Background features of better and poorer CPAP compliers were compared to identify predictors of greater CPAP use. The variables that were compared included polysomnographic measures, symptoms and sleepiness reported at familiarisation and sleep onset latency off CPAP (Table 7.3). Both microarousal index (p<0.01) and AHI (p=0.02) were significantly higher in better compliers. However, ranges for microarousal index (Figure 7.7) and AHI (Figure 7.8) overlapped in good and poor compliers. There was no difference between pre-treatment symptom score in poor and good compliers, and no difference in sleepiness measures off CPAP between the two groups.

Table 7.3: Differences in background features of poor and better CPAP compliers

<table>
<thead>
<tr>
<th></th>
<th>Poor compliers Mean ± SEM</th>
<th>Better compliers Mean ± SEM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI (per hour slept)</td>
<td>9.6 ± 0.7</td>
<td>12.5 ± 0.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Microarousal index (per hour slept)</td>
<td>16.6 ± 3.4</td>
<td>32.2 ± 3.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Minimum O2 saturation (%)</td>
<td>87 ± 1</td>
<td>85 ± 2</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>4% desaturations (per hour slept)</td>
<td>2.3 ± 1.1</td>
<td>5.3 ± 1.7</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Symptom score</td>
<td>5.1 ± 0.2</td>
<td>4.8 ± 0.8</td>
<td>&gt;0.4</td>
</tr>
<tr>
<td>Epworth sleepiness score</td>
<td>13.8 ± 1.1</td>
<td>15.0 ± 2.0</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>UMAACL energetic arousal score</td>
<td>22.6 ± 2.4</td>
<td>21.1 ± 2.2</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Placebo mean sleep onset latency (mins)</td>
<td>9.0 ± 2.0</td>
<td>10.8 ± 2.3</td>
<td>&gt;0.5</td>
</tr>
</tbody>
</table>

Figure 7.7: Microarousal index in poorer and better CPAP compliers
7.5 Discussion

This study suggests that patients with mild SAHS may improve symptoms, cognitive performance and psychological distress on CPAP, as was documented in the wider-severity sample examined in Chapter 6. Thus, the study extends the previous findings of the therapeutic value of CPAP to apply to symptomatic patients with 5 to 15 apnoeas+hypopnoeas per hour of sleep, and indicates that such patients should be given a trial of CPAP therapy.

Those daytime function tests showing improvement in patients with mild SAHS-symptoms, cognitive performance and depression ratings- were also improved by CPAP in the wider-severity study of daytime function in SAHS, corroborating the sensitivity of these measures to CPAP effects. In patients with mild SAHS and higher levels of CPAP compliance, additional benefits for quality-of-life, which was also improved in the wider-severity study, were found with CPAP.

The inclusion of multiple measures of outcome in daytime function, as in the crossover study of the full group of SAHS patients (Chapter 6), increases the
possibility that the improvements seen are Type 1, 'false positive' statistical errors (Smith et al 1987, Bland and Altman 1995). A comparatively large number of endpoints was measured in order to identify CPAP-sensitive instruments for future studies. Although the criticism of multiple comparisons cannot be discounted, it is mitigated by the observation that all improvements related to CPAP administration and none to placebo treatment.

Neither objective (MSLT) nor subjective (Epworth scale) sleepiness was improved by CPAP in mild SAHS patients. Mean sleep onset latency approached the normal range on both placebo and CPAP (Thorpy 1992), while subjective sleepiness was elevated on both placebo and MSLT (Johns 1993). The study's findings using the MSLT contrast with those from studies of 'upper airway resistance syndrome' (UARS) patients (Guilleminault et al 1992, 1993), whose short sleep onset latencies, indicative of moderate or severe sleepiness before treatment, were extended into the normal range (Thorpy 1992) by CPAP. Recent CPAP-treatment studies in more severe samples of SAHS patients have shown statistical improvement, but a lack of normalisation in objective daytime sleepiness with CPAP (Bédard et al 1993, Kribbs et al 1993b). Thus the utility of the MSLT in treatment-related studies may be questioned.

The cognitive task showing improvement with CPAP (TrailMaking B) required rapid and complex responses. Performance on this particular test is impaired in patients with severe SAHS (Findley et al 1986, Bédard et al 1993). However, only a small proportion of the cognitive tests administered showed improvement on CPAP. This may reflect marginal cognitive impairment in mild SAHS, may relate to the difficulties in detecting sleepiness-induced deficit with cognitive tests (Wilkinson 1964), or may show insensitivity in the tests employed.

The HAD scale depression self-rating has previously been shown to be responsive to CPAP's effects on well-being, both in the pilot parallel-group study (Chapter 5) and the full-scale crossover study (Chapter 6). Quality-of-life, most notably in social function, was also improved in better CPAP compliers. Impaired social function is associated with greater sleepiness (Briones et al 1995) and has been identified as impaired in mild SAHS subjects (Gall et al 1993). Thus this finding suggests that CPAP may reverse some of the functional and behavioural limitations seen in mild SAHS.
The study was carried out in patients with mild SAHS who had 5 to 15 apnoeas/hypopnoeas per hour slept, using standard definitions for apnoeas (Guilleminault et al 1978) and hypopnoeas (Gould et al 1988). These data cannot be directly extrapolated to the UARS (Guilleminault et al 1993), although it is likely that an overlap between patients diagnosed with mild SAHS in this study would be classified as having UARS elsewhere.

An earlier study of CPAP administration in 15 snorers with AHI less than 5 found that no subjects opted for long-term therapy (Guilleminault et al 1991). In this study, 10 of the 16 patients (and 6 of 8 better CPAP compliers) preferred CPAP and opted for home CPAP therapy. The discrepancy between CPAP treatment acceptance in these two studies is likely to relate to the symptomatology of the patient samples. All subjects in the current study complained of two or more symptoms of SAHS, while the level of daytime problems in the previous study were low.

The low objectively monitored CPAP compliance rates might be considered disappointing, but are similar to those observed in other prospective studies of early CPAP compliance rates in new users (Kribbs et al 1993a, Reeves-Hoché et al 1994) and in both parallel-group (Chapter 5) and crossover studies (Chapter 6) of this thesis. Although clinicians recommend all-night CPAP use, there is little research defining the relationship between use-rate and benefit. Patients with mild SAHS are likely, like patients with the UARS (Downey et al 1993) or snorers with AHI < 10 (Zucconi et al 1995), to show proportionately less disturbed sleep than those with more severe SAHS. It is possible that such patients may thus require shorter CPAP administration each night to acquire the 'core sleep' required for normal daytime function (Horne 1988).

It is suspected that many of the poorer CPAP users heeded requests to use CPAP on the nights immediately preceding assessments, despite low averaged effective compliance rates in this group. Providing that the latency to benefit from CPAP is as short as one or two nights, as has previously been suggested (Lamphere et al 1989), pre-assessment CPAP use would tend to equalise performance on state assessments of sleepiness and cognition in better and poorer compliers.

The examination of background differences between good and poorer CPAP compliers found evidence of greater microarousal frequency and higher AHI in better compliers. This empirical finding may support the role of sleep fragmentation in
inducing daytime deficits (Cheshire et al 1992, Guilleminault et al 1993, Zuconi et al 1995), particularly in patients at the milder end of the spectrum. However, no predictors of future CPAP compliance rate were found in patients' symptoms or sleepiness.

It is concluded that CPAP therapy improves symptoms and daytime function in patients with mild SAHS. Thus a therapeutic trial of CPAP therapy may be clinically-indicated for symptomatic patients with 5 to 15 apnoeas+hypopnoeas per hour of sleep. However, further controlled studies in this patient group are required to help identify whether the improvements in daytime function are sustained, to identify whether other features of SAHS are improved by CPAP, and to help predict patients' CPAP use.
Chapter 8:
AUDITORY EVOKED POTENTIALS AFTER CPAP IN PATIENTS WITH SAHS

Auditory evoked potentials (AEPs) are electroencephalographic waveform complexes elicited during the cerebral processing of auditory information (see Section 2.3 for explanation, and Figure 2.1 for illustration). While the shorter latency N1 and P2 peaks are thought to index cerebral sensation of information, the later N2 and P3 components appear to reflect higher cognitive information processing (Blackwood et al 1987). All wave components may show smaller amplitudes and delayed latency with cognitive deficit (Blackwood et al 1987) and with sleepiness (Weitzman and Kremen 1965), both of which are common complaints amongst patients with SAHS (Cheshire et al 1992). Because of the convergence of symptoms of SAHS and correlates of AEP conformation, AEP testing may offer a useful probe for clinical evaluation of SAHS patients and for assessment of treatment response.

Case-control studies have suggested that AEP conformation is altered in SAHS, showing extended latency and diminished amplitude of N2 and P3 components (Walsleben et al 1989) or slowed latency of P2, N2 and P3 and smaller amplitude of P3 peak (Rumbach et al 1991). These same studies assessed the effects of 2 nights (Walsleben et al 1989) or 6 weeks (Rumbach et al 1991) of CPAP therapy on AEP variables. The 14 patients studied by Walsleben showed improved, but not normalised, P3 latency after therapy, while the 47 subjects in Rumbach’s trial showed improvements in latency and amplitude of N2 and P3 components, and normalisation of P3 amplitude. These data are compatible with studies of daytime function, which suggest improvements in cognitive function and daytime sleepiness with CPAP, but a lack of normalisation in objective daytime sleepiness after CPAP (Bédarid et al 1993). However, like many of studies of daytime function after CPAP, neither AEP study conducted in SAHS patients offered a control for repeated testing or for expectation of benefit. The use of a crossover design in the study below allowed these factors to be controlled by the study procedures.

8.1 Methods
8.1.1 Study protocol
SAHS patients were prospectively recruited for a placebo-controlled crossover study of AEPs after CPAP. Most of the patients undergoing AEP testing were participating simultaneously in the crossover study of daytime function (Chapter 6), with the AEP
testing session inserted into the larger protocol. Patients spent 4 to 5 weeks on CPAP and on an oral placebo, with assessments of weight and AEPs conducted after a minimum of 21 and maximum 35 days on each treatment, with no washout period between the two treatment limbs. Fifteen patients underwent the daytime function tests of the crossover study (Chapter 6) in addition to AEP assessment, and in these treatment order was randomised by the daytime function study schedule. Three patients underwent assessments of AEPs and ambulatory blood pressure (Chapter 9) only, and with these an attempt to balance treatment order was made. All patients underwent education in the mechanisms of CPAP before treatment commencement, and attended for a night of CPAP titration. For the CPAP treatment limb, patients were issued APD-1 CPAP units equipped with hidden timeclocks (see Chapter 4) logging total time that units were switched on and that CPAP was effectively delivered.

8.1.2 Patients

Eighteen patients (14 male) complaining of least two symptoms of SAHS (Whyte et al 1989) were prospectively recruited from a sleep clinic series. All demonstrated an apnea-hypopnea index (AHI) of 5 or more per hour slept during clinical polysomnography, conducted and scored according to our usual method (Gould. et al 1988). Microarousals were scored according to the method of Cheshire et al (1992), consisting of a return of faster EEG frequencies lasting 1.5 seconds or more, and coinciding with any duration of elevated EMG activity. The background features of participants are shown in Table 8.1. Seven patients commenced treatment with placebo and 11 with CPAP.

Table 8.1: Background features of AEP study subjects

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SEM</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48 ± 2</td>
<td>32-66</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>35.4 ± 2.3</td>
<td>22.5-49.8</td>
</tr>
<tr>
<td>AHI (per hour slept)</td>
<td>38 ± 6</td>
<td>7-88</td>
</tr>
<tr>
<td>Microarousal index (per hour slept)</td>
<td>45 ± 6</td>
<td>12-115</td>
</tr>
<tr>
<td>Minimum O₂ saturation (%)</td>
<td>77 ± 4</td>
<td>22-94</td>
</tr>
</tbody>
</table>
8.1.3 Auditory evoked potentials (AEPs) assessment

AEPs were recorded with the subject seated comfortably in an armchair. The AEP paradigm consisted of an 'oddball' task, in which patients were asked to listen to tones through headphones, and were required to ignore frequent low-pitched tones, but to count rare high-pitched tones. Rare tones occurred at pseudo-random intervals, at a frequency of 1 in 10 tones. Four hundred tones of 100 ms duration were played at a stimulus rate of 1 tone per 1.25 seconds, frequent tones at a frequency of 1 kHz and rare tones at 1.5 kHz. The AEP response at Cz (vertex) was recorded for 750 ms at each tone on Nicolet equipment with a low frequency pass at 30 Hz. AEP responses to rare and frequent tones were separated and averaged on-line. Latency and baseline-to-peak amplitude of 'sensory' N1 and P2 components were measured on the averaged response to ignored frequent tones, while those of 'cognitive' N2 and P3 components were assessed in the averaged response to counted infrequent tones.

8.1.4 Data analysis

Outcome measures obtained on placebo and CPAP were examined using 2-way repeated measures ANOVA, with treatment order as a between-subjects factor and treatment type as a within-subject factor. This analysis assessed the effects of treatment type (CPAP versus placebo), treatment order (placebo first or CPAP first) and their interaction, representing learning. A separate subanalysis was conducted in better CPAP compliers using their units effectively for 3 hours or more per night.
8.2 Results

CPAP units were switched on for an average 4.4 ± SEM 0.7 hours per night, with mean effective CPAP use of 4.2 ± 0.6 hours per night. The comparison of AEP wave component variables obtained on placebo and CPAP is shown in Table 8.2 and Figure 8.1. There were no significant treatment effects found, although a trend for improved N2 amplitude on CPAP emerged (p=0.08). Patients’ BMI was significantly increased on CPAP (34.9 ± 2.3 kg/m²) compared to placebo (34.5 ± 2.2 kg/m²; p=0.03).

![Figure 8.1: AEPs on placebo and CPAP in full group](image)

**Table 8.2: AEPs on placebo and CPAP**

<table>
<thead>
<tr>
<th></th>
<th>Placebo Mean ± SEM</th>
<th>CPAP Mean ± SEM</th>
<th>Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N1 latency (msecs)</strong></td>
<td>97 ± 2</td>
<td>98 ± 2</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>N1 amplitude (µV)</strong></td>
<td>5.1 ± 0.7</td>
<td>4.9 ± 0.6</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>P2 latency (msecs)</strong></td>
<td>179 ± 6</td>
<td>180 ± 6</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>P2 amplitude (µV)</strong></td>
<td>5.8 ± 1.0</td>
<td>5.6 ± 0.8</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>N2 latency (msecs)</strong></td>
<td>238 ± 7</td>
<td>227 ± 7</td>
<td>1.16</td>
</tr>
<tr>
<td><strong>N2 amplitude (µV)</strong></td>
<td>3.0 ± 0.7</td>
<td>3.8 ± 0.7</td>
<td>3.50</td>
</tr>
<tr>
<td><strong>P3 latency (msecs)</strong></td>
<td>345 ± 9</td>
<td>333 ± 9</td>
<td>2.37</td>
</tr>
<tr>
<td><strong>P3 amplitude (µV)</strong></td>
<td>7.3 ± 0.9</td>
<td>7.7 ± 2</td>
<td>0.36</td>
</tr>
</tbody>
</table>
8.2.1 Good CPAP compliers

Ten patients used CPAP effectively for 3 hours per night or more. Four of these commenced treatment with placebo and 6 with CPAP. A second ANOVA was performed on the data for these 10 subjects (Table 8.3 and Figure 8.2). Again, no significant differences were found between AEP variables on CPAP and placebo, although a different trend, this time for improved P3 latency on CPAP ($p=0.06$) was seen.

![AEPs on placebo and CPAP in the good compliers](image)

**Figure 8.2: AEPs on placebo and CPAP in the good compliers**

**Table 8.3: AEPs on placebo and CPAP in good compliers**

<table>
<thead>
<tr>
<th></th>
<th>Placebo Mean ± SEM</th>
<th>CPAP Mean ± SEM</th>
<th>Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F-value</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>N1 latency (msecs)</td>
<td>99 ± 3</td>
<td>99 ± 3</td>
<td>0.12 0.73</td>
</tr>
<tr>
<td>N1 amplitude (µV)</td>
<td>4.9 ± 0.6</td>
<td>4.4 ± 0.5</td>
<td>0.97 0.35</td>
</tr>
<tr>
<td>P2 latency (msecs)</td>
<td>180 ± 9</td>
<td>183 ± 10</td>
<td>0.72 0.42</td>
</tr>
<tr>
<td>P2 amplitude (µV)</td>
<td>4.5 ± 0.6</td>
<td>4.8 ± 0.8</td>
<td>3.35 0.11</td>
</tr>
<tr>
<td>N2 latency (msecs)</td>
<td>237 ± 10</td>
<td>222 ± 9</td>
<td>0.84 0.39</td>
</tr>
<tr>
<td>N2 amplitude (µV)</td>
<td>3.7 ± 1.2</td>
<td>4.7 ± 1.0</td>
<td>1.81 0.22</td>
</tr>
<tr>
<td>P3 latency (msecs)</td>
<td>347 ± 13</td>
<td>318 ± 9</td>
<td>4.90 0.06</td>
</tr>
<tr>
<td>P3 amplitude (µV)</td>
<td>7.1 ± 0.8</td>
<td>7.7 ± 2.5</td>
<td>0.24 0.64</td>
</tr>
</tbody>
</table>
8.2.2 Learning effects

A significant treatment x treatment order interaction was seen for P2 amplitude in the full group (p<0.01), representing a learning effect of improved amplitude on second testing, irrespective of treatment type (Table 8.4).

Table 8.4: Learning effects in full group

<table>
<thead>
<tr>
<th></th>
<th>Visit 1 Mean ± SEM</th>
<th>Visit 2 Mean ± SEM</th>
<th>Treatment order x treatment interaction F-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 latency (msecs)</td>
<td>98 ± 2</td>
<td>97 ± 2</td>
<td>0.62</td>
<td>0.44</td>
</tr>
<tr>
<td>N1 amplitude (µV)</td>
<td>5.0 ± 0.6</td>
<td>4.9 ± 0.7</td>
<td>0.11</td>
<td>0.75</td>
</tr>
<tr>
<td>P2 latency (msecs)</td>
<td>176 ± 5</td>
<td>183 ± 5</td>
<td>2.75</td>
<td>0.12</td>
</tr>
<tr>
<td>P2 amplitude (µV)</td>
<td>5.2 ± 0.8</td>
<td>6.1 ± 0.9</td>
<td>10.70</td>
<td>0.005</td>
</tr>
<tr>
<td>N2 latency (msecs)</td>
<td>230 ± 7</td>
<td>235 ± 7</td>
<td>1.16</td>
<td>0.30</td>
</tr>
<tr>
<td>N2 amplitude (µV)</td>
<td>3.2 ± 0.6</td>
<td>3.5 ± 0.6</td>
<td>0.90</td>
<td>0.36</td>
</tr>
<tr>
<td>P3 latency (msecs)</td>
<td>339 ± 9</td>
<td>338 ± 13</td>
<td>0.20</td>
<td>0.66</td>
</tr>
<tr>
<td>P3 amplitude (µV)</td>
<td>6.9 ± 0.9</td>
<td>8.0 ± 1.3</td>
<td>1.09</td>
<td>0.31</td>
</tr>
</tbody>
</table>

8.3 Discussion

This randomised study does not provide conclusive evidence of improvements in AEP conformation after CPAP therapy for SAHS, in contrast to previous uncontrolled studies (Walsieben et al 1987, Rumbach et al 1991). Improvements in N2 amplitude with CPAP remained statistically non-significant in the full group, as did the shortening of P3 latency in better CPAP compliers. Thus, although N2 and P3 components appeared on average to be improved by CPAP (see Figures 8.1 and 8.2), inter-subject variability in AEP treatment response resulted in trends only towards shortened latency or increased amplitude of 'cognitive' N2 and P3 components with CPAP. Although a statistically significant increase in BMI on CPAP compared to placebo was observed, the trivial magnitude of the increase would not be thought likely to have a substantial impact on response to CPAP.

The lack of statistical improvement in AEPs with CPAP may reflect insensitivity of AEPs as a measure of higher cortical function in SAHS, particularly in the light of the observed improvement in cognitive and sleepiness measures from the daytime crossover study (Chapter 6). Alternatively this negative finding may relate to persistent deficit after treatment for SAHS, which has been previously suggested in a small-scale study of cognitive function (Bédard et al 1993) and in studies showing lack of normalisation of objective daytime sleepiness (e.g. Kribbs et al 1993b, Bédard et al 1993). The limited sample size may also contribute to a Type 2 statistical error, a
significant possibility in such a small-scale study as this, which indicated substantial, hypothesised trends towards improvement after CPAP. The presence of a learning effect representing improved P2 amplitude with repeated testing is a cause for methodological concern which may have contributed to the positive findings of previous, uncontrolled and longitudinal studies (Walsleben et al 1989, Rumbach et al 1991).

AEPs have been considered potentially useful tools to assess impairment at diagnosis, and to assess treatment response. The data from this study gave encouragement to the idea that AEPs might improve with treatment, a finding that might well emerge with a larger patient sample. Significant improvements in AEP markers would be cross-validated by the demonstrated improvements in cognitive performance and alertness following CPAP (Chapter 6). But this study may also have added methodological complexity to the usefulness of this technique in a clinical setting, due to the learning effects demonstrated. However, it may be that further validation will establish consistent age-based norms for cognitive potentials, which may supplement other investigations in judging overall daytime impairment in SAHS patients.
Chapter 9:
AMBULATORY BLOOD PRESSURE ON AND OFF CPAP THERAPY IN PATIENTS WITH SAHS


This association may relate to systemic hypertension and SAHS having in common the epidemiological risk factors of obesity and age. This view is supported by studies showing that the best, and often sole, correlate of casual daytime (Stradling and Crosby 1990, Rauscher et al 1992, Millman et al 1991) and nocturnal BP (Wilcox et al 1992, Wilcox et al 1994) in the community (Stradling and Crosby 1990) and in SAHS patient populations (Rauscher et al 1992, Rauscher et al 1993a, Wilcox et al 1992, Wilcox et al 1994) is body mass index (BMI), and not breathing disruption in sleep.

However, other recent evidence from large samples in the community (Hla et al 1994) and in sleep patient series (Carlson et al 1994) suggests that disrupted breathing in sleep, obesity and age are independent and additive risk factors for both daytime (Carlson et al 1994, Hla et al 1994) and nocturnal (Hla et al 1994) BP elevation. Nocturnal BP elevation may represent an added risk to sleep apnoea patients, as inadequate overnight dropping of BP ('non-dipping') is associated with cardiovascular events (Verdecchia et al 1990). The high prevalence of hypertension in SAHS populations, of whatever cause, is likely to contribute to the excess mortality (Partinen et al 1988, He et al 1988) and morbidity (Hung et al 1990) from cardiovascular disease reported in SAHS.

CPAP, by blocking nocturnal events in SAHS (Sullivan and Issa 1980), may reduce one sequela in the form of nocturnal and/or daytime hypertension (Working Group on OSA and Hypertension 1993). Previous studies of the effects of CPAP (see Table 9.1) on nocturnal, casual daytime or ambulatory BP (ABP) have yielded mixed results. Some researchers have documented improvements in nocturnal, but not daytime BP with CPAP (Davies et al 1994a), or have found no changes in sleeping (Ali et al 1992) or casual daytime (Rauscher et al 1993a) BP after therapy. Others have
### Table 9.1: Studies of blood pressure with CPAP in SAHS

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Methods</th>
<th>Outcome measures</th>
<th>Effect of CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jennum et al</td>
<td>14 SAHS pts, some hypertensives off Rx</td>
<td>Continuous nocturnal BP</td>
<td>Nocturnal BP</td>
<td>Decrease in nocturnal BP</td>
</tr>
<tr>
<td>1989</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayer et al</td>
<td>12 SAHS, all hypertensives off Rx, after 6 months on CPAP</td>
<td>Continuous nocturnal BP, casual daytime BP</td>
<td>Nocturnal and daytime BP</td>
<td>Decrease in both nocturnal and daytime systolic and diastolic BP</td>
</tr>
<tr>
<td>1991</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ali et al</td>
<td>8 SAHS pts on and off CPAP within the same night</td>
<td>Beat-to-beat nocturnal BP</td>
<td>Waking and sleeping BP</td>
<td>Decrease in variability only of sleeping systolic and diastolic BP</td>
</tr>
<tr>
<td>1992</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsnop et al</td>
<td>18 SAHS pts, 7 hypertensives on Rx, after 10 nights on CPAP</td>
<td>Casual BP</td>
<td>Daytime BP</td>
<td>In hypertensives only, a decrease in systolic and diastolic BP</td>
</tr>
<tr>
<td>1993</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rauscher et al</td>
<td>33h SAHS pts, all hypertensives on Rx, after 2 years on CPAP</td>
<td>Casual BP</td>
<td>Daytime BP and hypertensive status</td>
<td>No effect on BP independent of weight loss</td>
</tr>
<tr>
<td>1993a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suzuki et al</td>
<td>9 SAHS pts, 5 hypertensives on Rx, after 5 weeks CPAP</td>
<td>ABP</td>
<td>Daytime and nocturnal BP</td>
<td>In hypertensives only, a decrease in daytime heart rate and nocturnal systolic BP and heartrate</td>
</tr>
<tr>
<td>1993</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilcox et al</td>
<td>14 SAHS pts, some hypertensives off Rx, after 8 weeks CPAP</td>
<td>ABP</td>
<td>Nocturnal and daytime BP</td>
<td>Decrease in 24-hour and daytime systolic and diastolic BP, and nocturnal systolic</td>
</tr>
<tr>
<td>1993</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davies et al</td>
<td>11 SAHS pts, some hypertensives on Rx</td>
<td>ABP</td>
<td>Nocturnal and daytime BP</td>
<td>Decrease in nocturnal systolic BP</td>
</tr>
<tr>
<td>1994a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hedner et al</td>
<td>12 SAHS pts, some hypertensives off Rx, after 1-2 years on CPAP</td>
<td>ABP</td>
<td>Nocturnal and daytime BP</td>
<td>No change in mean 24-hour BP</td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ABP - ambulatory blood pressure


Blood pressure might be expected to show a 'white coat effect' of higher BP on first recording, which would predispose to findings of lower BP after treatment in longitudinal intervention studies. However, only one of the studies of BP after CPAP in SAHS (Table 9.1) employed a control for repeated BP measurement (Davies et al 1994a). Aside from those studies conducted during CPAP administration (Jennum et al 1989, Mayer et al 1991, Ali et al 1992), there is little objective corroboration of patients' self-reports of acceptable CPAP compliance (Wilcox et al, Suzuki et al 1993, Worsnop et al 1993, Davies et al 1994a, Hedner et al 1995). The only study objectively monitoring average CPAP use times (Rauscher et al 1993a) attributed BP reductions to weight loss.

The study reported here investigated the influence of CPAP therapy on nocturnal and daytime BP during normal activities within a controlled crossover trial.

9.1 Study protocol
Thirteen SAHS patients were prospectively recruited for the placebo-controlled crossover study of ABP on CPAP. Most of the patients undergoing ABP testing were participating simultaneously in the crossover study of daytime function (Chapter 6), with the ABP testing session inserted into the larger protocol. Patients spent 4 to 5 weeks on CPAP and on oral placebo, as previously described (Chapter 6), with assessments of weight and ABP conducted after a minimum of 21 and maximum 35 days on each treatment.
A CPAP titration study, performed before the commencement of treatment, established the therapeutic pressure at which hypopnoeas and electroencephalographic arousals from sleep were minimised. CPAP units (ResCare, Abingdon, UK) issued for home use contained hidden timeclocks (Reeves-Hoché et al 1994; see Chapter 4), read at the beginning and end of the treatment limb, which logged hours of effective CPAP use over the treatment limb. Patients were contacted during the second week of treatment to check progress with treatment and encouraged to report any problems with CPAP use.

9.2 Subjects
A total of 16 patients were recruited from a sleep clinic series complaining of least two symptoms of SAHS and demonstrating an AHI of 5 or more/hour slept during clinical polysomnography conducted according to our usual method (Gould et al 1988). Complete assessment datasets were obtained in 13 subjects, one case each being lost due to equipment unavailability, poor ABP quality and patient non-attendance.

Ten of the 13 patients participating in the BP trial were also taking part in the crossover trial of daytime function, so that treatment order in these patients was effectively randomised by the schedule of that trial. An attempt to balance treatment order was made with the last 3 patients recruited for ABP and auditory evoked potential assessments only. Seven patients commenced treatments with CPAP and 6 with placebo tablets.

These 13 patients (11 male) averaged 51 ± SEM 3 years of age with a mean BMI of 36.0 (± 2.6) kg/m². Clinical sleep study yielded an average AHI (Gould et al 1988) of 48.7 (± 8.6) per hour slept, ranging from 13.5 to 118.2 per hour slept, an average microarousal index (Cheshire et al 1992) of 49 ± 11 per hour slept and average minimum oxygen saturation of 71 ± 6 percent. Four were taking hypertensive medication, which remained stable throughout the study period.

9.3 Ambulatory blood pressure assessment
ABP was recorded using an oscillometric method (SpaceLabs 90207), the equipment consisting of an inflatable brachial cuff connecting via a hose to a pump/solid-state memory unit, the size of a Walkman, worn belted to the waist. The cuff was automatically inflated and measurement of systolic, diastolic and mean arterial BP made at half-hourly intervals throughout the day and night of a 24-hour period.
Patients were encouraged to conduct their normal day-to-day activities during the recording periods. Subjects underwent three cuff inflations before leaving the lab, to familiarise them with the measurement procedure and to reduce any ‘white coat effect’. Systolic, diastolic and mean arterial BP was calculated for 24-hour, daytime (08.00-00.00) BP and nocturnal (00.00-08.00) period and percentage nocturnal dip (nocturnal BP dip/daytime BP: Verdecchia et al 1990) in systolic, diastolic and mean arterial BP determined.

9.4 Data analysis
Ambulatory BP data obtained on CPAP and placebo were compared using 2-way analysis-of-variance, with treatment order as a between-subjects factor and treatment type as a within-subject factor. The change in frequency of ‘non-dipping’ and hypertensive ‘cases’ was examined with McNemar tests. Because of the large number of outcome variables, an alpha value at \( p \leq 0.01 \) was adopted to denote significance. Subgroups of patients classed as ‘non-dippers’ (placebo-limb nocturnal BP dip/daytime BP < 10%: Verdecchia et al 1990), hypertension ‘cases’ (placebo-limb 24-hour systolic BP > 134 mmHg and diastolic BP > 84 mmHg: Consensus document 1990) and good CPAP compliers (effective average CPAP use \( \geq 3 \) hours/night) were selected for further exploratory analysis. Comparisons between ‘dippers’ and ‘non-dippers’ were made using unpaired t-tests and chi-square tests.

9.5 Results
9.5.1 Full group
Effective CPAP use averaged 4.3 \( \pm 0.6 \) hours/night over the treatment limb, although all patients reported using their CPAP on the night of their assessment. The patient group showed a non-significantly higher BMI on CPAP (35.8 \( \pm 2.5 \) kg/m\(^2\)) compared to placebo (see Table 9.2).

No significant differences between BP variables on placebo and on CPAP were found (\( p > 0.05 \); see Table 9.2), and mean values for ABP variables showed similar profiles on the two treatments. No significant changes in the frequency of hypertensive ‘cases’ (placebo 5 versus CPAP 5; \( p = 1.00 \)) or ‘non-dippers’ (placebo 5 versus CPAP 6; \( p = 1.00 \)) were found. No significant order effects on ABP were found (\( p > 0.12 \)).
### Table 9.2: CPAP and placebo BP assessment in all patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo (Mean ± SEM)</th>
<th>CPAP (Mean ± SEM)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour SBP (mmHg)</td>
<td>135 ± 4</td>
<td>134 ± 5</td>
<td>0.63</td>
</tr>
<tr>
<td>24-hour DBP (mmHg)</td>
<td>83 ± 3</td>
<td>81 ± 3</td>
<td>0.33</td>
</tr>
<tr>
<td>24-hour MAP (mmHg)</td>
<td>100 ± 3</td>
<td>99 ± 3</td>
<td>0.46</td>
</tr>
<tr>
<td>Daytime SBP (mmHg)</td>
<td>139 ± 3</td>
<td>138 ± 4</td>
<td>0.68</td>
</tr>
<tr>
<td>Daytime DBP (mmHg)</td>
<td>86 ± 3</td>
<td>84 ± 3</td>
<td>0.13</td>
</tr>
<tr>
<td>Daytime MAP (mmHg)</td>
<td>103 ± 3</td>
<td>102 ± 3</td>
<td>0.26</td>
</tr>
<tr>
<td>Nighttime SBP (mmHg)</td>
<td>129 ± 7</td>
<td>124 ± 5</td>
<td>0.28</td>
</tr>
<tr>
<td>Nighttime DBP (mmHg)</td>
<td>76 ± 4</td>
<td>74 ± 4</td>
<td>0.40</td>
</tr>
<tr>
<td>Nighttime MAP (mmHg)</td>
<td>94 ± 5</td>
<td>91 ± 4</td>
<td>0.31</td>
</tr>
<tr>
<td>Nocturnal SBP dip (%)</td>
<td>7.3 ± 3.2</td>
<td>10.2 ± 2.2</td>
<td>0.36</td>
</tr>
<tr>
<td>Nocturnal DBP dip (%)</td>
<td>11.7 ± 3.7</td>
<td>12.6 ± 2.9</td>
<td>0.83</td>
</tr>
<tr>
<td>Nocturnal MAP dip (%)</td>
<td>9.0 ± 3.5</td>
<td>11.1 ± 2.5</td>
<td>0.55</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>35.8 ± 2.5</td>
<td>36.3 ± 2.6</td>
<td>0.08</td>
</tr>
</tbody>
</table>

ABP- ambulatory BP  
SBP- systolic BP  
DBP- diastolic BP  
MAP- mean arterial pressure  
bpmm- beats/minute
9.5.2 'Non-dippers'

Five 'non-dippers' were identified, 3 commencing treatment with placebo. Examination of background features showed that these patients were not significantly older or more overweight than 'dippers' (p>0.22). Frequency of apnoeas+hypopnoeas, microarousals and 4% desaturations, documented during nocturnal polysomnography, were not significantly different in 'dippers' and 'non-dippers' (p>0.05).

The comparison of BP variables obtained on placebo and on CPAP in 'non-dippers' is shown in Table 9.3. Daytime mean arterial pressure fell significantly from 102 ± 4 mmHg on placebo to 98 ± 4 mmHg with CPAP (p=0.01; see Figure 9.1). Two of the 5 'non-dippers' became 'dippers' with CPAP, increasing their nocturnal dipping percentage from 1% and 7% on placebo to 27% and 13% on CPAP, respectively, but the change in frequency of dipping within the subgroup was not significant (p=0.50).

![Figure 9.1: Mean arterial blood pressure in 'non-dippers' and 'dippers' on placebo and CPAP](image-url)
### Table 9.3: CPAP and placebo ABP assessment in 'non-dippers'

<table>
<thead>
<tr>
<th></th>
<th>Placebo (Mean ± SEM)</th>
<th>CPAP (Mean ± SEM)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour SBP (mmHg)</td>
<td>139 ± 7</td>
<td>133 ± 7</td>
<td>0.03</td>
</tr>
<tr>
<td>24-hour DBP (mmHg)</td>
<td>83 ± 4</td>
<td>79 ± 4</td>
<td>0.05</td>
</tr>
<tr>
<td>24-hour MAP (mmHg)</td>
<td>102 ± 5</td>
<td>97 ± 5</td>
<td>0.06</td>
</tr>
<tr>
<td>Daytime SBP (mmHg)</td>
<td>140 ± 6</td>
<td>136 ± 7</td>
<td>0.14</td>
</tr>
<tr>
<td>Daytime DBP (mmHg)</td>
<td>84 ± 4</td>
<td>81 ± 4</td>
<td>0.06</td>
</tr>
<tr>
<td>Daytime MAP (mmHg)</td>
<td>102 ± 4</td>
<td>98 ± 3</td>
<td>0.01</td>
</tr>
<tr>
<td>Nighttime SBP (mmHg)</td>
<td>144 ± 15</td>
<td>125 ± 11</td>
<td>0.09</td>
</tr>
<tr>
<td>Nighttime DBP (mmHg)</td>
<td>85 ± 7</td>
<td>74 ± 7</td>
<td>0.17</td>
</tr>
<tr>
<td>Nighttime MAP (mmHg)</td>
<td>105 ± 10</td>
<td>91 ± 8</td>
<td>0.11</td>
</tr>
<tr>
<td>Nocturnal SBP dip (%)</td>
<td>2 ± 6</td>
<td>9 ± 5</td>
<td>0.17</td>
</tr>
<tr>
<td>Nocturnal DBP dip (%)</td>
<td>0 ± 5</td>
<td>10 ± 6</td>
<td>0.33</td>
</tr>
<tr>
<td>Nocturnal MAP dip (%)</td>
<td>2 ± 5</td>
<td>9 ± 6</td>
<td>0.22</td>
</tr>
</tbody>
</table>

ABP- ambulatory BP  
SBP- systolic BP  
DBP- diastolic BP  
MAP- mean arterial pressure  
bpm- beats/minute
9.5.3 Hypertensive ‘cases’ and good CPAP compliers

Five patients were classified as hypertensive (24-hour systolic BP > 134 and diastolic BP > 84 mmHg) and 9 patients used CPAP effectively for more than an average 3 hours/night. CPAP did not alter BP significantly in either the hypertensive ‘cases’ or the good CPAP compliers.

9.6 Discussion

Although based on a limited patient sample, as are all other studies examining ABP with CPAP (Davies et al 1994a, Wilcox et al 1993, Suzuki et al 1993, Hedner et al 1995), the study shows no generalised improvement in BP profile with CPAP. These findings are compatible with those of Suzuki et al (1993) and Hedner et al (1995). The study protocol contained the additional control of treatment randomisation to remove order effects during repeated testing, the only investigation to provide this. Body mass index remained stable both in the full group and in ‘non-dippers’, providing assurance that weight changes were not interacting in outcomes.

Because of the limited sample size, a post-hoc power analysis was conducted to assess the ability of the study to show differences in BP. Assuming a 5 mmHg change in BP as the effect size, the power of the study to show differences at the 0.01 significance level in diastolic BP and mean arterial pressure is 95% and 75% respectively. Because of the larger standard deviation in changes in systolic BP with treatment, the power to detect a 5 mmHg difference in BP at the 0.05 level was reduced to 65%.

The findings within the subgroup of ‘non-dippers’ suggest that some patients with SAHS may benefit from reduction in daytime mean arterial BP with the use of CPAP therapy. These findings within a subgroup are compatible with those of others showing improved daytime BP with CPAP, measured either casually (Mayer et al 1991) or with ABP (Wilcox et al 1994).

In some studies, improvements in daytime (Mayer et al 1991, Worsnop et al 1993) and nocturnal (Jennum et al 1989, Mayer et al 1991, Suzuki et al 1993) BP were found in hypertensive patients only. Such results were not replicated within the subgroup of hypertensive SAHS patients, who showed no changes in BP with CPAP. However, selective improvement in daytime BP with CPAP therapy was observed within a subgroup of ‘non-dippers’.
The only other study which attempted to examine the role of 'dipping' status in BP response to CPAP was thwarted by the low frequency of 'non-dippers' (1 of 9 subjects) in the patient group (Suzuki et al 1993). The incidence of 'non-dipping' in the studied sample (5 of 13 patients) was similar to that in a larger but non-interventional study of ABP in SAHS patients, 29% of whom were 'non-dippers' when withdrawn from hypertensive medication (Wilcox et al 1992). 'Dipping' effects were found to be independently determined only by BMI in Wilcox et al's study (1992), although no significant differences were found between BMI in 'dippers' compared to the CPAP-responsive group of 'non-dippers'. However, the study's findings suggest that patients most at risk for cardiovascular disease (Verdecchia et al 1990) may obtain the greatest benefit from CPAP.

The study's attempt to relate changes in BP profiles to objectively monitored CPAP compliance was unsuccessful. A differential response to CPAP could not be identified in good CPAP compliers, but this lack of finding may be due to the limited specificity of compliance averaged over a month's treatment, as well as other potential confounders, such as 'dipping' status.

The lack of improvement in nocturnal BP and in extent of nocturnal dipping with CPAP may conflict with the demonstrated improvement in daytime BP in 'non-dippers', as any improvement in daytime BP status is hypothesised to arise as a consequence of attenuation of nocturnal cardiac load (Working Group on OSA and Hypertension 1993). However, the lack of finding may result from methodological limitations in using ABP, which provokes both autonomic and electroencephalographic arousal from sleep (Davies et al 1993, Davies et al 1994b). Nevertheless, use of a cuff-inflating device is the only method available to record 24-hour BP in mobile patients, and may well have a lesser effect on sleep quality than the invasive methods used by others (Jennum et al 1989, Mayer et al 1991). Individuals may differ in their degree of autonomic response during arousals, whether caused by breathing pauses or by cuff inflation, thus explaining the selective daytime benefits of CPAP for BP in 'non-dippers' with SAHS.
Chapter 10: Nocturnal correlates of daytime function in patients with SAHS

The cause of the daytime problems of SAHS is not well understood, although putative determinants in either the sleep fragmentation or hypoxaemia experienced by SAHS patients during sleep, or a combination of the two factors, are thought to be involved. The literature is equivocal on the best nocturnal correlates of both objective daytime sleepiness and cognitive dysfunction.

As described in Section 2.7.2, evidence can be found to support hypotheses that any one of the nocturnal physiological events of SAHS is most closely related to each aspect of daytime impairment. In previous correlative studies, there is little agreement on the strongest nocturnal correlate of the daytime impairments of SAHS. Objective daytime sleepiness has been correlated most highly, or independently in multiple regression models, with AHI in some studies (Yesavage et al 1985, Poceta et al 1992, Johns 1993), but with minimal oxygen saturation (Mendelson 1992, Bédard et al 1991a) or arousal frequency (Roehrs et al 1989, Stepanski et al 1984) in others. Cognitive performance has been significantly correlated with AHI (Yesavage et al 1985, Naégelé et al 1995), measures of hypoxaemia (Findley et al 1986, Bédard et al 1991a, Naégelé et al 1995) and nocturnal indices of sleep fragmentation (Cheshire et al 1992).

This conflict in the literature is likely to relate to differences in both the sensitivity and selection of nocturnal measurements, as well as to the intercorrelation within the nocturnal and daytime measures being assessed. Some studies did not include a representative sample of measures of individual nocturnal events, while in those that did, the contrasts in the strongest correlates of daytime impairments might suggest that nocturnal events are so tightly bound as to be inconsistently separable.

Even studies designed to elucidate this question (Colt et al 1991, Naégelé et al 1995) have not provided clear-cut descriptions of the specific daytime impairments attributable to oxygen desaturation or to sleep disruption. Nevertheless, the question of the nocturnal determinants of daytime impairment in SAHS has considerable clinical salience. As outlined in Chapter 2, the reversibility of daytime consequences of hypoxaemia may be different from that of deficits related to sleep fragmentation. Thus
the focus of this thesis, the reversibility of daytime impairments in SAHS patients by
CPAP, may be conditional to the source of these deficits.

Although the crossover study (Chapter 6) was designed as a treatment-intervention
study, the protocol design yielded data that could be used to examine the relationships
between nocturnal events and daytime function. Patients participating in the crossover
study of daytime function underwent full polysomnography and also attended for a
psychometric familiarisation session before proceeding to treatment. These
assessments provide a baseline dataset of nocturnal and daytime function, free from
learning, placebo or active treatment effects, allowing an correlative analysis of
putative determinant variables and dependent daytime function variables to be
undertaken.

A large number of variables were obtained from the assessments of
polysomnography, cognitive performance and well-being. To reduce their number, but
still retain the information underlying the variables, principal components analysis was
conducted. This exploratory factor analysis simplifies the complex structure of
intercorrelations between variables by 'pulling out' underlying patterns common to
variables, which can then be expressed as variables in themselves. Principal
components analysis is also useful in describing the tightness of the relationships
between variables, by providing a quantitative measure of the proportion of total
variance in variable scores explained by individual components.

Thus principal components analyses of measures within nocturnal
(polysomnography) and daytime (cognitive performance and well-being) domains
were conducted, in order to investigate the underlying structure among these measures
and to provide a rational basis for reducing the number of these variables. Such
'simplified' factor scores, along with an objective measure of sleepiness, were then
inserted in a correlation matrix, to examine relationships between putative determinant
nocturnal variables and dependent daytime variables.

10.1 Patients
Sixty-six patients, including two who withdrew during the subsequent treatment
protocol, had baseline polysomnography, psychometric familiarisation and objective
daytime sleepiness tests off active (CPAP) treatment. These formed the sample for the
exploratory factor and correlative analyses. The patient sample comprised 59 men and
7 women, with an average of age of 49 ± SEM 1 years and mean body mass index of
31.2 ± 1.0 kg/m². Polysomnography (see below) showed that patients had an average AHI of 35 ± 4, microarousal index of 43 ± 4 and 17 ± 3 4% desaturations per hour slept. Mean minimum oxygen saturation was 79 ± 2%. Mean sleep onset latency on the placebo limb, reflecting objective daytime sleepiness off active treatment, averaged 7.0 ± 0.6 minutes.

10.2 Assessments

10.2.1 Polysomnography

Full polysomnography was conducted in all patients and included monitoring of EEG, EOG, EMG, respiratory movement by inductance plethysmography, oronasal airflow by thermistor and oxygen saturation by pulse oximetry. Summary indices of frequency of apnoeas and hypopnoeas (Gould et al 1988), microarousals from sleep (Cheshire et al 1992) and 4% oxygen desaturations were calculated. Minimum oxygenation level was noted. These variables were considered putative predictors of daytime function.

10.2.2 Daytime function tests

Assessments at the familiarisation battery included tests of symptoms, subjective sleepiness, cognitive performance and well-being. Scores from these tests formed the dependent variables. Symptoms were assessed using the in-house symptom questionnaire and sleepiness with the subjective Epworth sleepiness scale. The mean sleep onset latency from the placebo assessment MSLT was used as a measure of objective daytime sleepiness off active treatment. Performance tests administered at the familiarisation session comprised the National Adult Reading Test (NART), the object assembly, picture completion, picture arrangement, block design and digit symbol substitution performance subtests from the WAIS-R battery, TrailMaking tasks A and B, Hick reaction time (RT) test, rapid visual information processing (RVIP) test, SteerClear, PASAT at 4 and 2 second presentation rates, the Borkowski verbal fluency test and the Benton visual retention test (BVRT). Psychological distress was assessed with the hospital anxiety and depression (HAD) and general health questionnaire-28 (GHQ-28) scales. Quality-of-life was rated using the Nottingham health profile (NHP) part 2 and mood state with the UWIST mood adjective checklist (UMACL).
10.3 Data analysis

10.3.1 Principal components analysis of measures

Principal components analysis can be used to examine the framework of association between measures. Using algebra or geometry, principal components analysis can construct mathematical representations of the relationships between the multiple measures of large datasets. In a geometric representation, vectors representing the size and direction of correlations between 3 or more variables can be plotted in multidimensional space. Reference vectors, set orthogonally (at 90 degrees) to each other, can then be applied to a grouping of plotted variable vectors, to quantify the associations between the variable correlations and the reference vectors. The reference vectors represent putative 'factors', patterns of common structure, to which some variable vectors may have a significant relationship. The relative position of a variable vector to a reference vector can be mathematically transformed into a test statistic known as a 'loading', a quantitation of the degree of association between the variable and the factor. The variable loadings on the first reference vector, or factor, applied to the plot will subsume the largest proportion of variance within variable scores, subsequently extracted factors accounting for smaller and smaller proportions of total variance. The strength of a principal component factor in explaining total variance is expressed in a test statistic known as an eigenvalue, comprising the sum of the squares of the loadings on a factor, divided by the number of variables. In principal components analyses which extract more than one significant factor, the contrasts between the individual factor loadings of a single variable are not always maximised, with many variables showing significant but low loadings on multiple factors. The differences between factor loadings of different variables can be enhanced subsequently by spatially rotating the reference vectors. This has the effect of providing greater interpretability to the matrices of variables' factor loadings, by maximising disparities between the loadings on different factors of different variables.

Variables within each of the domains of polysomnography, cognitive function and well-being were subjected to exploratory factor analysis (Child 1990) in order to simplify the structure, and rationally reduce the number of variables for subsequent correlation.

The principal components analysis of the domain of polysomnography was conducted on the variables AHI, microarousal index, minimum oxygen saturation and 4% desaturation rate.
Within the cognitive domain, variables that were transformations of other raw scores (performance IQ, IQ decrement), or inverses of other raw scores (BVRT errors) and those which were excessively truncated (Borkowski perseverations) were excluded, as recommended (Child 1990). Cognitive scores considered to be primarily for task practice (4 second presentation rate PASAT, TrailMaking A) were also excluded, to reduce the number of variables so that an acceptable ratio between sample size and variable number was achieved (Child 1990). Remaining variables for the exploratory factor analysis of cognitive function comprised the scores for NART pre-morbid performance IQ estimate, all WAIS-R performance subtests, TrailMaking B, RVIP hits and misses, BVRT correct, 2 second presentation rate PASAT, SteerClear, verbal fluency word naming total, and median decision and movement times and decision time slope from the Hick RT.

The factor structure of the domain of well-being was examined using principal components analysis of the total scores of the GHQ-28 and NHP part 2, and subscale scores for anxiety and depression (HAD scale) and energetic arousal, hedonic tone and tense arousal (UMACL).

In each of these separate principal components analyses, factors with eigenvalues greater than 1.00 were extracted, and, when multiple factors were identified, subjected to oblique rotation. Oblique rotation was selected in preference to orthogonal rotation due to the intercorrelation of the extracted factors (r approximating 0.30). Variable factor loadings greater than 0.30 were considered significant. Following oblique rotation, the structure factor matrix was selected in preference to the pattern matrix because of the exploratory nature of the analysis (Child 1990).

Factor regression scores, derived from equations modelling the loadings of test scores on factors, were calculated to reflect each subjects' scores for principal components and rotated factors. These factor regression scores were saved and used in the subsequent correlational analysis.

10.3.2 Correlation analysis
Putative determinant variables in the form of polysomnographic measures were entered into a correlation matrix with the factor scores created as a result of the factor analyses above. Daytime sleepiness and mood were considered potential predictors of cognitive function, so mean sleep onset latency and the 'well-being' factor score were tested both as putative determinants of daytime function and as dependent variables.
Non-normal data, comprising all the polysomnographic variables, were normalised with log transformation. Partial Pearson correlations, controlling for age, were conducted between the dependent daytime variables and putative determinants. Dependent variables showing multiple significant correlations with individual polysomnographic variables were subjected to multiple regression to seek independent correlates of daytime function. Multiple regression was conducted by a mixed direct and stepwise method, first entering age directly, then proceeding to stepwise addition of significant correlates. In this technique, successive predictive variables which explain a significant proportion of variance in test scores are entered into an equation. This technique takes account of the intercorrelations between putative determinant variables, as the first entered of two nearly-identical determinants will subsume nearly all the variance explained by the second. Because the determinants are entered in a stepwise fashion, i.e. starting with the best correlate of the dependent variable, the strongest correlates of dependent variables will gain a larger role in the equation, at the expense of weaker but related correlates.

10.4 Results
10.4.1 Principal components analysis of polysomnography
Principal components analysis of AHI, microarousal index, minimum oxygen saturation and 4% desaturation rate extracted a single component with eigenvalue 3.30, explaining 83% of the total variance in polysomnographic measures (Table 10.1). This component was called 'SAHS severity'.

Table 10.1: Polysomnographic principal components matrix

<table>
<thead>
<tr>
<th></th>
<th>First principal component</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>0.94</td>
</tr>
<tr>
<td>4% desaturation rate</td>
<td>0.93</td>
</tr>
<tr>
<td>Microarousal index</td>
<td>0.89</td>
</tr>
<tr>
<td>Minimum O2</td>
<td>-0.86</td>
</tr>
</tbody>
</table>

10.4.2 Principal components analysis of cognitive performance
Principal components analysis extracted four factors. The first unrotated principal component and the four rotated factors are shown in Table 10.2, with significant loadings highlighted with bold typeface.

The first unrotated principal component had an eigenvalue of 6.44, accounting for 40% of the total variance in scores. This principal component corresponded with
Spearman's 'g', or general ability factor, which determines the largest proportion of individuals' variance in cognitive skill (Spearman 1927). This first principal component showed significant loadings on all variables except decision time slope and RVIP hit score, the highest of these on tests of general performance ability, including the digit symbol and block design subtests from the WAIS-R battery, and TrailMaking B. This component was called 'general ability' for the subsequent correlational analysis.

Table 10.2: Cognitive domain: first unrotated principal component and rotated factor structure matrix

<table>
<thead>
<tr>
<th></th>
<th>First PC 'General ability'</th>
<th>Factor 1 'Fluid ability'</th>
<th>Factor 2 'Crystallised ability'</th>
<th>Factor 3 'Perceptual speed'</th>
<th>Factor 4 'Response speed'</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS-R Block design</td>
<td>0.77</td>
<td>0.81</td>
<td>0.50</td>
<td>0.28</td>
<td>-0.33</td>
</tr>
<tr>
<td>RVIP misses</td>
<td>-0.45</td>
<td>-0.77</td>
<td>-0.12</td>
<td>0.14</td>
<td>0.20</td>
</tr>
<tr>
<td>BVRT correct</td>
<td>0.67</td>
<td>0.76</td>
<td>0.19</td>
<td>0.38</td>
<td>-0.37</td>
</tr>
<tr>
<td>TrailMaking B</td>
<td>-0.83</td>
<td>-0.74</td>
<td>-0.47</td>
<td>-0.41</td>
<td>-0.38</td>
</tr>
<tr>
<td>WAIS-R Digit symbol</td>
<td>0.80</td>
<td>0.73</td>
<td>0.37</td>
<td>0.43</td>
<td>0.55</td>
</tr>
<tr>
<td>WAIS-R Picture arrangement</td>
<td>0.74</td>
<td>0.55</td>
<td>0.78</td>
<td>0.29</td>
<td>-0.28</td>
</tr>
<tr>
<td>WAIS-R Picture completion</td>
<td>0.59</td>
<td>0.34</td>
<td>0.74</td>
<td>0.04</td>
<td>-0.37</td>
</tr>
<tr>
<td>NART estimated IQ</td>
<td>0.64</td>
<td>0.30</td>
<td>0.72</td>
<td>0.54</td>
<td>-0.21</td>
</tr>
<tr>
<td>WAIS-R Object assembly</td>
<td>0.57</td>
<td>0.47</td>
<td>0.59</td>
<td>0.20</td>
<td>-0.17</td>
</tr>
<tr>
<td>Decision time slope</td>
<td>-0.22</td>
<td>-0.30</td>
<td>0.41</td>
<td>-0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>RVIP Hit</td>
<td>-0.30</td>
<td>0.07</td>
<td>0.02</td>
<td>0.81</td>
<td>-0.13</td>
</tr>
<tr>
<td>SteerClear</td>
<td>-0.74</td>
<td>-0.55</td>
<td>-0.39</td>
<td>-0.59</td>
<td>0.51</td>
</tr>
<tr>
<td>PASAT 2 second rate</td>
<td>0.70</td>
<td>0.51</td>
<td>0.37</td>
<td>0.54</td>
<td>-0.50</td>
</tr>
<tr>
<td>Median decision time</td>
<td>-0.50</td>
<td>-0.28</td>
<td>-0.01</td>
<td>-0.27</td>
<td>0.88</td>
</tr>
<tr>
<td>Median movement time</td>
<td>-0.50</td>
<td>-0.31</td>
<td>-0.16</td>
<td>-0.09</td>
<td>0.78</td>
</tr>
<tr>
<td>Verbal fluency total</td>
<td>0.73</td>
<td>0.38</td>
<td>0.58</td>
<td>0.49</td>
<td>-0.59</td>
</tr>
</tbody>
</table>

The extracted components were then rotated, and factor loadings examined to interpret the loadings' mapping of areas of cognitive skill (Table 10.2). The first oblique rotated factor had significant loadings on many of the scores in the performance battery, but the highest of these were on block design, Benton visual retention and RVIP miss scores. The WAIS-R subtests showing high loadings on this factor, block design and digit symbol, are those relying most on abstract skills and least on culturally and educationally derived knowledge. This pattern of loading, in contrast to that of the second oblique rotated factor described below, appeared to be biased towards tests of reasoning and conceptual ability. In examinations of the higher-order factors extracted during analyses of intellectual performance, these types of skills have been linked to
the factor called ‘fluid ability’ (Horn and Cattell 1966). This factor is thought to relate to inherited, or otherwise biologically-determined, intellectual ability. Because of this speculative resemblance between the first oblique rotated factor and Horn and Cattell’s (1966) fluid intelligence, this factor was called ‘fluid ability’.

The second oblique rotated factor showed highest loadings on the picture arrangement, object assembly and picture completion subtests of the WAIS-R battery, the most culture-dependent subtests of the WAIS-R performance battery. Performance on these subtests requires culturally-obtained knowledge, such as familiarity with stylised graphic images (object assembly), the existence of a rowlock on a rowing boat (picture completion), or the humorous sequence of events in cartoons (picture arrangement). This factor also had a high loading for the NART score, dependent on educationally-obtained knowledge of esoteric vocabulary. The suggestion from this segregation was that the second factor might reflect ‘crystallised ability’ in intellectual function (Horn and Cattell 1966), another higher-order factor indexing the accretion of cultural and educational influences. Thus this factor was named ‘crystallised ability’.

The third oblique rotated factor showed high loadings on RVIP hit score, SteerClear and 2 second presentation rate PASAT. All of these are challenging tasks in which subjects are under pressure to process information rapidly. The SteerClear task resembles a prolonged reaction time test with frequent stimuli, while the PASAT requires shorter periods of intense information processing. The RVIP hit score is a measure of ‘signal detection’ ability and is both extended and cognitively challenging. These three tests are rapid, complex and require the maintenance of concentration; all might be thought likely to index physiological activation. This third factor appeared to load most heavily on tests requiring vigilance and attention, and bore similarities to, and was thus named after, the primary-order factor described as ‘perceptual speed’ by Horn and Cattell (1966).

The fourth oblique rotated factor showed its largest loadings on reaction times (both movement and decision) and on verbal fluency total. It also showed significant loadings on digit symbol, PASAT and SteerClear. All of these test scores are strongly determined by cognitive and motor speed. The fourth oblique rotated factor had high loadings for decision and movement times from the Hick RT task and verbal fluency total, all dependent on subject pacing, and was thus named ‘response speed’.
10.4.3 Principal components analysis of well-being

Principal components analysis of scores for HAD scale anxiety and depression, GHQ-28, NHP part 2 and the UMACL scores for energetic arousal, tense arousal and hedonic tone extracted a single component, with eigenvalue 4.68 (Table 10.3). This component accounted for 67% of total variance in well-being scores.

Table 10.3: Well-being principal components matrix

<table>
<thead>
<tr>
<th>First principal component</th>
<th>HAD Depression</th>
<th>NHP part 2 total</th>
<th>HAD Anxiety</th>
<th>GHQ-28 total</th>
<th>UMACL tense arousal</th>
<th>UMACL hedonic tone</th>
<th>UMACL energetic arousal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.89</td>
<td>0.87</td>
<td>0.80</td>
<td>0.80</td>
<td>0.80</td>
<td>-0.78</td>
<td>-0.76</td>
</tr>
</tbody>
</table>

The principal components analyses described above provided a rational structure for reducing the number of variables in each of the examined domains of function. Only one significant factor could be resolved within the respective domains of polysomnography and well-being, suggesting that the variables within each of these domains were largely determined by single underlying attributes. The analysis of cognitive function suggested that four significant factors could be identified to explain the patterns of scores.

The factor regression scores derived from factors resolved by the above principal components analyses were used pragmatically as variables in themselves, and entered into a subsequent correlational analysis.
10.4.4 Correlations between nocturnal variables and domains of daytime function

The constructed correlation matrix (Table 10.4), controlled for age, was used to examine associations between putative determinants ('SAHS severity' component score, individual polysomnographic scores, placebo mean sleep onset latency, 'well-being' factor score) and dependent daytime function variables ('general ability', 'fluid ability', 'crystallised ability', 'perceptual speed' 'response speed' and 'well-being' factor scores, placebo mean sleep onset latency and symptom total).

Better status in the correlation matrix was reflected by lower scores for the 'SAHS severity' factor, AHI, microarousal index, 4% desaturation rate, 'well-being' and 'response speed' factors, and for symptom total. Better status was reflected by higher score for minimum oxygen saturation, mean sleep onset latency, and for 'general ability', 'fluid ability', 'crystallised ability' and 'perceptual speed' factors.

Six significant correlations were observed in the correlation matrix, all of these weak in magnitude. 'SAHS severity' score correlated significantly with the 'general ability' and 'crystallised ability' cognitive factors, linking greater illness severity with poorer cognitive performance. 'SAHS severity' score, AHI and minimum oxygen saturation each correlated significantly, and in the expected direction, with mean sleep onset latency. These correlations associated greater SAHS illness severity with greater objective daytime sleepiness. Minimum oxygen saturation showed a significant, positive relationship with symptom total, linking worse illness status with lesser symptom complaints.

Mean sleep onset latency showed plural suggestive relationships with putative determinants, by correlating significantly with the individual polysomnographic variables of AHI and minimum oxygen saturation. A multiple regression analysis was thus conducted, to investigate which of these individual polysomnographic variables independently showed the closest relationship with the daytime function variables. After the variance attributable to age had been subtracted, by forcing age into the regression model, the only independent correlate of placebo sleep onset latency was AHI (multiple r=0.36, p=0.01).
Table 10.4: Partial correlation, controlling for age, between polysomnographic, sleepiness and mood-related determinants and daytime function scores

<table>
<thead>
<tr>
<th></th>
<th>'SAHS Severity' component</th>
<th>AHI</th>
<th>Micro-arousal index</th>
<th>Minimum O₂ saturation</th>
<th>4% desat rate</th>
<th>Mean sleep onset latency</th>
<th>'Well-being' component</th>
</tr>
</thead>
<tbody>
<tr>
<td>'General ability' component</td>
<td>-0.27*</td>
<td>-0.23</td>
<td>-0.10</td>
<td>0.23</td>
<td>-0.04</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>'Fluid ability' factor</td>
<td>-0.07</td>
<td>0.00</td>
<td>0.07</td>
<td>0.09</td>
<td>-0.09</td>
<td>0.07</td>
<td>-0.05</td>
</tr>
<tr>
<td>'Crystallised ability' factor</td>
<td>-0.27*</td>
<td>-0.25</td>
<td>-0.15</td>
<td>0.24</td>
<td>-0.03</td>
<td>0.00</td>
<td>0.11</td>
</tr>
<tr>
<td>'Perceptual speed' factor</td>
<td>0.06</td>
<td>0.07</td>
<td>-0.01</td>
<td>-0.06</td>
<td>0.01</td>
<td>0.04</td>
<td>-0.13</td>
</tr>
<tr>
<td>'Response speed' factor</td>
<td>-0.14</td>
<td>-0.09</td>
<td>-0.21</td>
<td>0.17</td>
<td>-0.07</td>
<td>0.04</td>
<td>0.22</td>
</tr>
<tr>
<td>MSLT</td>
<td>-0.31*</td>
<td>-0.30*</td>
<td>-0.16</td>
<td>0.26*</td>
<td>-0.24</td>
<td>----</td>
<td>0.19</td>
</tr>
<tr>
<td>'Well-being' component</td>
<td>-0.19</td>
<td>-0.10</td>
<td>-0.10</td>
<td>0.10</td>
<td>-0.01</td>
<td>0.19</td>
<td>----</td>
</tr>
<tr>
<td>Symptom total</td>
<td>-0.19</td>
<td>-0.16</td>
<td>-0.14</td>
<td>0.27*</td>
<td>-0.13</td>
<td>-0.02</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*0.01 ≤ p ≤ 0.05
10.5 Discussion

This exploratory analysis of baseline data used principal components analysis to rationally reduce the large number of nocturnal and daytime function variables obtained in the SAHS patient sample. The reduced variables were then examined using univariate and multiple correlation techniques, to investigate possible determinant relationships. The age-controlled correlation analysis showed significant but modest relationships between AHI and sleepiness and between the overall severity of SAHS and cognitive impairment. These findings indicate that overall severity of SAHS contributes to the scale of daytime impairments. One of the aims of this study, to examine the relative strength of hypoxaemic and sleep-disruptive processes in determining daytime impairments, was thwarted by the paucity of significant relationships between individual nocturnal events, biased towards measuring sleep fragmentation or hypoxaemia, and daytime function. Nevertheless, the principal components analysis of the domains of polysomnography, cognitive performance and well-being provided useful information on the structure underpinning the scores in the domains.

The principal components analyses of daytime function variables in the domains of polysomnography, cognitive function and well-being produced coherent factor explanations. Tight linkage between the variables within the respective domains of polysomnography and well-being was observed. Within each of these domains, only a single factor was demonstrated, explaining in each case a substantial majority of the total variance in scores. These principal component analyses suggested that a high degree of intercorrelation existed within the psychological distress variables and the polysomnographic variables respectively. Thus high scorers for quality-of-life, for example, were also likely to score highly for depression, and patients with a minimal AHI also demonstrated few microarousals.

The principal components analysis of the cognitive domain extracted a first, unrotated principal component and four oblique rotated factors. These rotated factors showed segregation in item loadings consistent with some of the first and second order factors in intellectual ability identified by Horn and Cattell (1966), towards which the cognitive battery was biased. The cognitive factor scores thus appeared to demonstrate internal coherence.

In the univariate correlational analysis (Table 10.4), three significant nocturnal correlates of objective daytime sleepiness were found, comprising the ‘SAHS
Chapters 10: Nocturnal correlates of daytime function

severity' component, AHI and minimum oxygen saturation. The multiple regression of objective daytime sleepiness showed AHI as the only independent correlate amongst the individual polysomnographic measures. This finding corroborated others' reports of AHI as the best nocturnal predictor of sleep onset latency (Yesavage et al 1985, Poceta et al 1992, Johns 1993), and may help cross-validate AHI as the best currently available measure of severity of SAHS, as suggested in other studies of polysomnographic techniques in diagnosing SAHS (Gould et al 1988). Nevertheless, the correlation between AHI and mean sleep onset latency was moderate in size (multiple r=0.36), explaining only 13% of the variance in scores.

'SAHS severity' score related significantly, and in the hypothesised direction, with the 'general ability' and 'crystallised ability' cognitive factor scores. The correlation with 'general ability' is coherent, suggesting that overall cognitive performance is related to overall severity of SAHS. It was perhaps surprising that 'SAHS severity' score was also significantly related to the 'crystallised ability', but not the 'fluid ability', cognitive factor. These cognitive factor names are speculative and tentative, but may nevertheless suggest the 'flavour' of the factors. It is 'fluid intellect' (Horn and Cattell 1966) which is considered most related to biological determinants of CNS function, such as inheritance or organic insults, while 'crystallised intellect' may index the cognitive performance attributes relating to acquired knowledge and environmental influence. It may be that the severity of SAHS causes selective impairment to educationally-obtained knowledge and learned skills, rather than to biological information-processing ability, but wide-ranging conclusions should not be drawn from this result. Although the correlation with 'crystallised ability' (r=-0.27) is larger in magnitude than that demonstrated for the 'fluid ability' score (r=-0.07), these correlation coefficients are unlikely to be significantly different.

In the correlation analysis, minimum oxygen level was positively related to larger symptom score. This finding indicates that more severe hypoxaemia was associated with a fewer number of symptom complaints. This may reflect the loss of awareness of impairment with greater hypoxaemia, or possible over-rating of symptom severity in the milder patients of this study, but may also reflect the poor value of symptoms in predicting severity of SAHS. The lack of specificity of symptom complaints for predicting illness severity has previously been reported by others (Hillerdal et al 1991, Hoffstein and Szalai 1993, Olson et al 1995).
The correlation between minimum oxygen saturation and symptom complaints may also represent a Type 1 statistical error, two or three of which might be expected by chance alone in a correlation matrix containing 56 cells. However, the potential for spurious findings in the correlational analysis was reduced by the use of two-tailed probabilities and principal components analysis, which consolidated factors underpinning test scores and minimised the number of correlations conducted.

The well-being factor score showed no significant correlations with either nocturnal determinants or daytime impairments, suggesting that simple, positive and linear relationships between severity of SAHS and distress were not observed. However, a preliminary report has previously documented a counter-intuitive negative correlation between depression ratings and AHI (Watson et al 1985), linking greater distress with milder SAHS. This report is also consistent with the finding associating greater symptom complaints with milder hypoxaemia, discussed above.

The findings from the crossover study of CPAP (Chapter 6) indicated that the daytime impairment of SAHS were to some degree reversible, although the scale of these CPAP-mediated improvements was not clarified due to the study design. Nevertheless, the breadth of the improvements across the range of daytime function might support the hypothesis that sleep fragmentation was the more potent determinant of impairment. This suggestion is supported by similarities in type and scale of impairment in sleep-fragmented normals (Martin et al 1995c) and improvements with CPAP in the crossover study (Chapter 6). However, in the current study, hypoxaemic-weighted and sleep disruption-weighted variables did not show selective or independent associations with specific daytime impairments. This may relate to the peculiarities of the patient sample, biased towards milder patients, but may also be due to the tight intercorrelations between nocturnal events.

This latter view is supported by the findings of the principal components analysis of the polysomnographic variables, which showed only one factor underlying the variance in these measures, and determining the substantial majority of total variance. This study’s lack of success in extracting individual polysomnographic determinants of most daytime deficits, has been encountered by others (Guilleminault et al 1988, Cheshire et al 1992) using multiple regression. Their lack of success in building multiple regression models, and ours in demonstrating individual polysomnographic predictors of sleepiness and cognitive impairment, may be related to the tightly-bound structure of the nocturnal measures, which are so closely linked as to defy
disentanglement. The demonstration of this strong principal component may help explain the disparity in previous studies regarding the best correlates of daytime function, as findings will be heavily influenced by the loading of particular measurement sensors or scoring techniques on this primary severity factor.

In this study, objective daytime sleepiness was found to be independently determined only by AHI, with no additional significant contribution from microarousal index, minimum oxygen saturation or 4% desaturation rate. None of the cognitive performance factor scores correlated significantly with individual polysomnographic variables that were hypoxaemia-weighted or sleep disruption-weighted.

These findings conflict with the work of others, showing significant relationships between cognitive performance and both hypoxaemia (Findley et al 1986, Cheshire et al 1992, Bédard et al 1991a, Naëgelé et al 1995) and microarousal frequency (Cheshire et al 1992), and between daytime sleepiness and hypoxaemia (Mendelson 1992, Bédard et al 1991a) or microarousal frequency (Roehrs et al 1989, Martin et al 1995b). This may result in part from a bias towards milder patients in this current sample. Alternatively, it may reflect that, with the exception of Cheshire et al (1992) and Martin et al (1995b), no adjustment for age, in the form of a partial correlation, was made. Greater age might be expected to be associated with both worse SAHS severity and lesser cognitive performance, and might thus contribute to the correlations between nocturnal events and daytime deficits.

In contrast to the studies of others, performed in the same laboratory (Cheshire et al 1992, Martin et al 1995b) and elsewhere (Roehrs et al 1989), this study showed no significant correlations between microarousal index and daytime function. In other Scottish National Sleep Lab (SNSL) studies, microarousals formed coherent and significant (if weak) associations with cognitive function (Cheshire et al 1992) and objective daytime sleepiness (Martin et al 1995b). In these, worse sleep fragmentation was associated with greater daytime impairment. Part of this discrepancy may arise from the bias towards patients with mild illness in the present study. A further potential explanation for the surprising lack of microarousal correlates in this study is the fact that it alone of the SNSL microarousal studies used several scorers of microarousals. It may be that inter-rater variability compromised the reliability of the microarousal variable.
Recent interest has been generated in 'sub-cortical' arousals, changes in autonomic markers such as blood pressure, that precede full-blown 'cortical' arousals measured by scalp EEG techniques (Davies et al 1993, 1994b, Rees et al 1993, Rees and Calverley 1995, Calverley and Rees 1995, Rees et al 1995, Sahloul et al 1995). Part of this interest has been generated by the observations of relatively weak associations between EEG measures of sleep fragmentation and daytime function. It may be that future research may validate novel, autonomic markers of sleep disturbance as more sensitive to daytime deficits.

In summary, significant but modest relationships were observed between polysomnographic illness severity and both cognitive performance and objective daytime sleepiness. The factor score for 'SAHS severity' correlated significantly with cognitive impairment, while AHI was identified as the only independent correlate of daytime sleepiness. Principal components analysis identified tight linkage between the polysomnographic variables examined. This close association between polysomnographic measures may explain our own inability to describe hypoxaemic- or sleep fragmentation-related determinants of daytime impairment, and others' difficulties in building multiple regression models of daytime function by hypoxaemia-weighted versus sleep fragmentation-weighted variables. Greater hypoxaemia was linked to lesser symptom complaints by patients. Impairments in well-being were not associated with the severity of SAHS. The relative paucity of significant correlations, and their small magnitude, may be due in part to peculiarities of the patient sample, or to possible technical deficiencies in scoring reproducibility. However, these findings may demonstrate that few simple dose-response relationships between nocturnal events and daytime function exist, and that the impact of illness is not mechanistically linked to individual nocturnal events.
Chapter 11: Questionnaire study

SELF-REPORTED USE OF CPAP AND BENEFITS OF CPAP THERAPY: A PATIENT SURVEY

CPAP is effective in reducing nocturnal events of SAHS (Sullivan and Issa 1980), and it has been suggested both in the crossover study (Engleman et al 1994b; Chapter 6) and by others to improve objective daytime sleepiness, cognitive function and wellbeing (Kribbs et al 1993b, Bédard et al 1993, Derderian et al 1988). Yet CPAP is frequently rejected by patients (Waldhorn et al 1990, Rauscher et al 1991), at least partly because of the unwieldy and inconvenient nature of the treatment. Patients’ use of CPAP is likely to be determined by perceived benefits and drawbacks of treatment, but the determinants of these factors are not well understood.


CPAP use rate varies between 3.2 to 6.7 hours/night, depending on whether new CPAP users (Kribbs et al 1993a, Reeves-Hoché et al 1994, Engleman et al 1993, Engleman et al 1994a, Engleman et al 1994b), cross-sectional CPAP clinic populations (Krieger 1992, Rauscher et al 1993b, Pépin et al 1995) or selected long-term acceptors of CPAP (Fleury et al 1994, Meurice et al 1994, Fletcher and Luckett 1991) are studied. The literature on the determinants of CPAP compliance and acceptance is contradictory, with CPAP use predicted by polysomnographic severity in some (Rauscher et al 1991, Rauscher et al 1993b, Meurice et al 1994) and not other

A particular area of interest is the effect of CPAP on driving competence. The road traffic accident rate in SAHS is increased by a factor of 2 to 7 times that of the normal population (Findley et al 1988, George et al 1987), either as a result of sleep intrusion (Horne 1992) or generalised performance deficits (Cheshire et al 1992). Sleep-related accidents cause more fatalities than other accidents (Parsons 1986, Zomer and Lavie 1990, Horne and Reyner 1995). A short report has suggested a relationship between driving accident rate and sleep apnoea severity (Findley et al 1989b). Lab-based studies, whether using monotonous driving-based vigilance tasks (Findley 1989a) or more realistic simulators (Haraldsson et al 1991), suggest improved driving performance after CPAP (Findley et al 1989a) and uvulopalatopharyngoplasty (Haraldsson et al 1991), but actual driving competence after CPAP has not been evaluated.

This questionnaire-based study therefore assessed reported use of CPAP and perceived benefits and drawbacks of CPAP therapy in a clinic population, so that these factors could be described and relationships between them could be examined.

11.1 Methods
11.1.1 Study design
A questionnaire (Appendix A) was sent in June 1994 to all patients issued with CPAP units by the Scottish National Sleep Laboratory (SNSL) for 2 weeks or longer. Questionnaire data were supplemented with information, obtained from SNSL records, on age, sex, polysomnographic SAHS severity, objective CPAP use from runtime clock readings and objective daytime sleepiness on the multiple sleep latency test (MSLT) (Carskadon et al 1986, Thorpy 1992). Information from the questionnaire and SNSL sources were grouped into domains of illness severity, CPAP compliance, road traffic incidents and sleepiness before and after CPAP, perceived change in function and symptoms, problems with CPAP use and weight change.
11.1.2 Questionnaire

All 253 patients issued with CPAP unit by the SNSL, and their partners, were sent a four-page questionnaire (Appendix A) enquiring about use of CPAP, sleepiness and road traffic incidents before and after CPAP, changes in nocturnal and daytime function, problems with CPAP therapy and weight change.

Self-reported CPAP use

Patients were asked how many nights per week and for how long each night CPAP was used. This data allowed an average self-reported use-rate to be calculated.

Epworth Sleepiness Score

Patients’ subjective sleepiness after and, retrospectively, before CPAP was rated by patients and their partners using the Epworth sleepiness scale (Johns 1991, 1992, 1993, 1995), a self-rating of sleepiness behaviour in the recent past.

Road traffic incidents

Drivers were asked their yearly mileage and the frequency of road traffic incidents in the 5 years before starting CPAP and in the time since CPAP was commenced. Self-reported incidents were divided into near-misses, casualty-free collisions ('minor' collisions) and accidents causing injury ('major' collisions) and further subdivided for those felt to be sleep-related or not. The rates of road traffic incidents per 10,000 miles were calculated for each class of event.

Function and symptoms

Patients were asked to rate changes in function and symptoms on a bipolar 5-point scale with options of much worse, worse, no change, better and much better, coded -2,-1,0,+1,+2 respectively. Items rated by patients were snoring, breathing pauses, daytime sleepiness, sleep quality, tiredness, concentration ability, ability to drive long distances safely, work efficiency, time taken off work, sex drive and general health. Partners were asked to rate change in patients’ snoring, breathing pauses, daytime sleepiness and temper.

Problems with CPAP use

Patients were presented with a 12-item list of frequently reported side-effects and problems with CPAP use, and asked to indicate on a 4 point-scale whether each problem was absent, a minor problem, a significant problem but not interfering with
CPAP use or a significant problem interfering with CPAP use. The items comprised nasal stuffiness, dry throat, red/sore eyes, leaking mask, cold airstream, nosebleeds, mask rubbing, difficulty exhaling, more frequent awakenings, excessive noise from CPAP unit, stomach bloating/flatulence and chest wheeze.

Change in weight
Patients were asked to report any weight gain or loss since the commencement of CPAP treatment.

Items not completed by or inapplicable to individuals were excluded from relevant item analyses.

11.1.3 Statistics
The significance of reported changes with CPAP were assessed using Wilcoxon tests.

Principal components analysis (Child 1990) was conducted within the two domains of change in function and symptoms and CPAP-related problems, to reduce the number of variables for subsequent rank correlation (see Section 10.3.1 for explanation). Variables with excessively skewed distributions (nosebleeds, wheezing, sore eyes, difficulty exhaling) or with reduced sample sizes (sex drive, bloating, work efficiency, days taken off work, ability to drive long distances safely) were excluded. Components with eigenvalues greater than 1 were extracted and rotated using the varimax method. Significance for variable factor loadings was set at 0.30. Rank correlation of putative determinant and dependent variables was performed, to examine relationships between pre-treatment status, CPAP compliance, benefits and problems with CPAP. All analyses were performed using SPSS-PC+ (Norusis/SPSS 1988).

11.2 Results
11.2.1 Questionnaire response
Of 253 patients issued with CPAP units, 215 (85%) returned questionnaires. Non-responders were significantly younger (mean age 46 ± SEM 1 years) than responders (53 ± 1 years; p<0.0001), but were otherwise no different from the responders, who had a mean apnoea+hypopnoea index of 47 ± 3 per hour slept, 47 ± 3 microarousals per hour slept, average minimum oxygen saturation of 74 ± 1 percent and mean duration of CPAP treatment of 632 ± 43 days.
Eleven patients (5% of responders) stated that they no longer used CPAP. Three patients cited mask discomfort as a factor, three lack of benefit and one each frequent awakenings, excessive CPAP pressure and throat dryness. One patient’s nasal stuffiness, following nasal surgery, precluded CPAP use. Three patients gave no reason for discontinuing treatment. Of CPAP users, 21 patients (10%) had an AHI <15. The responses of the 204 patients who indicated that they were continuing with CPAP therapy were analysed.

11.2.2 Self-reported and objective CPAP use
Self-reported compliance in 204 CPAP users averaged 5.8 ± 0.1 hours per night, ranging from 0.1 to 9.5 hours per night. Synchronous CPAP runtime clock readings, available in 62 patients, yielded an average objective CPAP use of 5.1 ± 0.3 hours per night, significantly lower than that reported by the same patients (6.0 ± 0.2 hours per night; p=0.0003). Subjective and objective compliance data were significantly correlated (r=0.68, p<0.0001: Figure 11.1).

![Figure 11.1: Scattergram of objective and subjective CPAP use](image-url)

*Figure 11.1: Scattergram of objective and subjective CPAP use*
11.2.3 Change in subjective and objective sleepiness with CPAP

Patients’ sleepiness, whether subjectively rated by patient or partner, was significantly improved with CPAP, as was objective daytime sleepiness assessed by MSLT (Table 11.1). Pre-CPAP MSLT data were available in 52 patients and post-MSLT data in 41 patients. Pre-CPAP scores on Epworth scale and MSLT correlated significantly ($r=-0.38$, $p=0.01$), but post-CPAP scores for the two measures of sleepiness did not ($r=0.06$, $p>0.36$).

<table>
<thead>
<tr>
<th>Table 11.1: Sleepiness before and after CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Epworth sleepiness score (patient)</td>
</tr>
<tr>
<td>Epworth sleepiness score (partner)</td>
</tr>
<tr>
<td>Mean sleep latency (MSLT; mins)</td>
</tr>
</tbody>
</table>
11.2.4 Changes in road traffic incidents with CPAP

Information on road traffic incidents were obtained from 147 driving patients. The prevalence of road traffic incidents, divided into sleep-related and non-sleep-related incidents, is shown in Figure 11.2. and detailed in Table 11.2. These data were unadjusted for time on CPAP therapy. Sleep-related driving impairment in the form of near-misses were reported by 39% of patients, and sleep-related collisions admitted by 8%. These frequencies were reduced to 5% and 2% respectively following CPAP therapy. No sleep-related major collisions were reported after CPAP commencement.

![Figure 11.2: Prevalence of road-traffic incidents before and after CPAP](image)

<table>
<thead>
<tr>
<th></th>
<th>Before CPAP</th>
<th>After CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All incidents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Near-Misses</td>
<td>67 (46%)</td>
<td>22 (15%)</td>
</tr>
<tr>
<td>Minor</td>
<td>29 (20%)</td>
<td>11 (7%)</td>
</tr>
<tr>
<td>Major</td>
<td>5 (3%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td><strong>Sleep-related incidents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Near-Misses</td>
<td>57 (39%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Minor</td>
<td>12 (8%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Major</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Mileage- and time-adjusted road traffic incident rates showed a significant reduction in the rate of near-miss incidents after CPAP therapy (Table 11.3), which fell to a third of the pre-CPAP rate. No significant difference in major or minor accidents rates were
seen following CPAP, although the mileage-adjusted major collision rate fell to a fifth of its former level after therapy. However, the number of patients reporting actual collisions was low both before and after CPAP (Table 11.2), limiting statistical power to detect change.

**Table 11.3: Mileage-adjusted road traffic incident rates before and after CPAP**

<table>
<thead>
<tr>
<th>Incident rate (per 10,000 miles)</th>
<th>Pre-CPAP Mean ± SEM</th>
<th>Post-CPAP Mean ± SEM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near-Miss</td>
<td>0.92 ± 0.25</td>
<td>0.32 ± 0.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Minor</td>
<td>0.09 ± 0.04</td>
<td>0.09 ± 0.04</td>
<td>&gt;0.3</td>
</tr>
<tr>
<td>Major</td>
<td>0.005 ± 0.002</td>
<td>0.001 ± 0.001</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Total incidents</td>
<td>1.02 ± 0.26</td>
<td>0.41 ± 0.13</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep-Related incident rate (per 10,000 miles)</th>
<th>Pre-CPAP Mean ± SEM</th>
<th>Post-CPAP Mean ± SEM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near-Miss</td>
<td>0.86 ± 0.24</td>
<td>0.11 ± 0.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Minor</td>
<td>0.07 ± 0.04</td>
<td>0.03 ± 0.02</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Major</td>
<td>0.003 ± 0.002</td>
<td>0</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Total incidents</td>
<td>0.93 ± 0.26</td>
<td>0.14 ± 0.06</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
11.2.5 Change in function and symptoms with CPAP

All items relating to function and symptoms, rated by patients and partners (Table 11.4), showed highly significant improvements with CPAP, except sex drive. These items were scaled from -2 to +2 points, a score of 0 representing no change. Thus average ratings for all items represented improvement following CPAP.

Table 11.4: Patients' reported change in function and symptoms after CPAP

<table>
<thead>
<tr>
<th>Measure</th>
<th>Percentage reporting improvement</th>
<th>Mean ± SEM change in score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient rating</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breathing pauses</td>
<td>94</td>
<td>1.6 ± 0.0***</td>
</tr>
<tr>
<td>Snoring</td>
<td>92</td>
<td>1.6 ± 0.1***</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>84</td>
<td>1.3 ± 0.1***</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>81</td>
<td>1.2 ± 0.1***</td>
</tr>
<tr>
<td>Tiredness</td>
<td>79</td>
<td>1.0 ± 0.1***</td>
</tr>
<tr>
<td>Ability to drive long distances safely</td>
<td>77</td>
<td>1.3 ± 0.1***</td>
</tr>
<tr>
<td>Concentration</td>
<td>68</td>
<td>0.9 ± 0.1***</td>
</tr>
<tr>
<td>Work efficiency</td>
<td>66</td>
<td>0.9 ± 0.1***</td>
</tr>
<tr>
<td>General health</td>
<td>61</td>
<td>0.8 ± 0.1***</td>
</tr>
<tr>
<td>Time taken off work</td>
<td>32</td>
<td>0.5 ± 0.1***</td>
</tr>
<tr>
<td>Sex drive</td>
<td>22</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td><strong>Partner rating</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snoring</td>
<td>95</td>
<td>1.6 ± 0.1***</td>
</tr>
<tr>
<td>Breathing pauses</td>
<td>90</td>
<td>1.4 ± 0.1***</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>79</td>
<td>1.1 ± 0.1***</td>
</tr>
<tr>
<td>Temper</td>
<td>49</td>
<td>0.6 ± 0.1***</td>
</tr>
</tbody>
</table>

***p<0.0001
11.2.6 Problems with CPAP

Patients’ reports of problems with CPAP use are shown in Table 11.5. The frequency of patients reporting some degree of problem was high, but the proportion reporting problems severe enough to limit CPAP use were less than 5% for all items.

### Table 11.5: Percentage of patients reporting problems with CPAP use

<table>
<thead>
<tr>
<th>Problem</th>
<th>Percentage reporting problem</th>
<th>Percentage reporting severe problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal stuffiness</td>
<td>64</td>
<td>4</td>
</tr>
<tr>
<td>Mask leak</td>
<td>63</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dry throat</td>
<td>62</td>
<td>1</td>
</tr>
<tr>
<td>Cold airstream</td>
<td>45</td>
<td>2</td>
</tr>
<tr>
<td>Noise from CPAP unit</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>Mask rubbing</td>
<td>41</td>
<td>1</td>
</tr>
<tr>
<td>Bloating/flatulence</td>
<td>37</td>
<td>&lt;1</td>
</tr>
<tr>
<td>More frequent awakenings</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Red/sore eyes</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Chest wheeze</td>
<td>21</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Difficulty exhaling</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Nosebleeds</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

11.2.7 Change in weight

Weight gain was significant (mean 1 ± 1 kg; p=0.005), although the majority of patients (55%) reported no change in weight.
11.2.8 Principal components analysis

Principal components analysis was conducted within the individual domains of perceived benefits and problems with CPAP.

The items relating to change in function and symptoms with CPAP reduced to two components (Table 11.6), the first having loadings on tired/sleep quality/general health/concentration ability/excessive daytime sleepiness (called 'daytime function') and the second on snoring/breathing pauses (called 'nocturnal symptoms'). It was notable that all seven items in this analysis had high loadings on the first unrotated principal component. This indicates that, apart from the two clearly separable components 'daytime function' and 'nocturnal symptoms', the total score from the seven items may be used as a 'general function' measure.

Table 11.6: Symptoms and function components matrix

<table>
<thead>
<tr>
<th>Component name</th>
<th>First unrotated principal component</th>
<th>Varimax rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Component 1</td>
<td>Component 2</td>
</tr>
<tr>
<td>Tired</td>
<td>0.86</td>
<td>0.86</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>0.81</td>
<td>0.79</td>
</tr>
<tr>
<td>General health</td>
<td>0.77</td>
<td>0.77</td>
</tr>
<tr>
<td>Concentration ability</td>
<td>0.71</td>
<td>0.73</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>0.68</td>
<td>0.72</td>
</tr>
<tr>
<td>Snoring</td>
<td>0.54</td>
<td>0.12</td>
</tr>
<tr>
<td>Breathing pauses</td>
<td>0.61</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Principal components analysis revealed that problems with CPAP use formed three components, with loadings on frequent awakenings/noise/sore eyes (called 'nuisance'), leaking mask/mask rubbing/cold airstream (called 'mask problems') and dry throat/nasal stuffiness (called 'side effects') respectively (Table 11.7). The item describing cold airstream problem loaded at > 0.3 on all three factors, suggesting that it had lower specificity than other variables in this analysis, which loaded at a high and significant level only on one factor each. For this reason the cold airstream item was excluded.

Scores for created variables named 'daytime function', 'nocturnal symptoms', 'general function', 'nuisance', 'mask problems' and 'side effects', were constructed by summing item scores loading on each of these factors. General function, nocturnal

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symptoms and daytime function were all highly significantly improved with CPAP (p<0.0001), with 95%, 95% and 91% of patients respectively reporting improvement on each of these summary scores. Nuisance, mask problems and side-effects were rated as present in some degree by 66%, 72% and 73% of patients respectively.

**Table 11.7: CPAP problems components matrix (varimax rotation)**

<table>
<thead>
<tr>
<th></th>
<th>First unrotated principal component</th>
<th>Varimax rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Component 1</td>
<td>Component 2</td>
</tr>
<tr>
<td>Frequent awakenings</td>
<td>0.62</td>
<td>-0.11</td>
</tr>
<tr>
<td>Noise</td>
<td>0.59</td>
<td>0.10</td>
</tr>
<tr>
<td>Red/sore eyes</td>
<td>0.62</td>
<td>0.13</td>
</tr>
<tr>
<td>Leaking mask</td>
<td>0.55</td>
<td>0.84</td>
</tr>
<tr>
<td>Mask rubbing</td>
<td>0.37</td>
<td>0.81</td>
</tr>
<tr>
<td>Dry throat</td>
<td>0.53</td>
<td>0.14</td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>0.36</td>
<td>-0.13</td>
</tr>
<tr>
<td>Component name</td>
<td>‘Nuisance’</td>
<td>‘Mask problems’</td>
</tr>
</tbody>
</table>

**11.2.9 Rank correlation**

Putative predictive associations between domains of illness severity, sleepiness, road traffic incident rates, change in symptoms and function and problems with CPAP use were assessed with rank correlation (Table 11.8). Subjective CPAP use was not significantly correlated with any objective index of severity of SAHS, but was positively correlated with pre-treatment Epworth sleepiness score and negatively correlated with the degree of nuisance of CPAP therapy reported. CPAP nuisance was negatively correlated with SAHS severity. Improvements in daytime function and nocturnal symptoms correlated with baseline Epworth sleepiness score and reported CPAP use, and negatively with Epworth sleepiness score on CPAP. The frequency of driving incidents before treatment was correlated with Epworth sleepiness score, the frequency of microarousals and the extent of nocturnal hypoxemia.

Most of these significant correlations were modest in size, with r-values approximating 0.2, but stronger correlations were seen between pre-treatment sleepiness and the rates of sleep-related near-miss driving incidents (r=0.54), and between reported CPAP use and symptom improvement (r approximating 0.4).
Table 11.8: Rank correlation between questionnaire study domains

<table>
<thead>
<tr>
<th></th>
<th>AHI</th>
<th>AROUSALS</th>
<th>MINO2</th>
<th>SUBJUSE</th>
<th>PRE ESS</th>
<th>POST ESS</th>
<th>NUISANCE</th>
<th>MASKPROB</th>
<th>SIDE EFF</th>
<th>BNSLP</th>
<th>BMNMON</th>
<th>BMNSLP</th>
<th>BMNMON</th>
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<td>X</td>
<td>X</td>
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<td>0.08</td>
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<td>MINO2</td>
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<td>X</td>
<td>X</td>
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<tr>
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<td>0.22**</td>
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<td>-0.27***</td>
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<tr>
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<td>-0.12</td>
<td>-0.04</td>
<td>-0.15</td>
<td>-0.03</td>
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<td>X</td>
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<td>MASKPROB</td>
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<td>0.00</td>
<td>0.17**</td>
<td>-0.07</td>
<td>0.28***</td>
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<td>SIDE EFF</td>
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<td>0.01</td>
<td>-0.07</td>
<td>0.06</td>
<td>0.11</td>
<td>0.19**</td>
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<td>-0.43***</td>
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<td>-0.20**</td>
<td>-0.20**</td>
<td>0.09</td>
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<td>AHI</td>
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<td>BNMSLP</td>
<td>Sleep-related near-miss incidents before CPAP</td>
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<td>Microarousal index</td>
<td>BNMNON</td>
<td>Non sleep-related near-misses before CPAP</td>
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<td>MinO₂</td>
<td>Minimum oxygen saturation</td>
<td>BMINSLP</td>
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<tr>
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<td>Subjective CPAP use</td>
<td>BMINNON</td>
<td>Sleep-related minor collisions before CPAP</td>
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<td>Pre ESS</td>
<td>Pre-CPAP Epworth sleepiness score</td>
<td>dDAYFUNC</td>
<td>Change in daytime function</td>
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<td>Post ESS</td>
<td>Post-CPAP Epworth sleepiness score</td>
<td>dNOCTSYP</td>
<td>Change in nocturnal symptoms</td>
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<td>Nuisance</td>
<td>Nuisance-type problems with CPAP use</td>
<td>dGENFUN</td>
<td>Change in general function/symptoms</td>
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<td>Side Eff</td>
<td>CPAP side-effects</td>
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</tbody>
</table>

**Table 11.8 Legend**

Cell sample size varies from 117 to 203 patients; p-values are adjusted accordingly.

X: redundant cell

___: non-predictive cell

*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001
11.3 Discussion
This study documents experience and perceptions of CPAP in a large sample of unselected CPAP-users with a wide range of illness severity. Although necessarily limited by its use of mainly self-reported and retrospective information, the study provides evidence of patient-perceived, CPAP-induced improvement across a wide range of function, including sleepiness, driving competence, cognitive function, work efficiency, well-being and nocturnal symptoms. Furthermore, coherent correlations linked pre-CPAP driving competence, use of CPAP and benefit from CPAP to predictive variables.

CPAP Use
Mean objective CPAP compliance demonstrated in this study (5.1 hours/night) was closely in agreement with that of others in cross-sectional CPAP clinic series (Rauscher et al 1993b, Krieger 1992, Pépin et al 1995) which included both new and long-term users. As in other studies employing objective CPAP compliance ratings and subjective reports of CPAP use (Rauscher et al 1993b, Kribbs et al 1993a), patients were seen to overestimate CPAP by approximately one hour. This is illustrated by the tendency for datapoints in the scattergram of objective versus subjective CPAP use (Figure 11.1) to lie below the line of identity.

Self-reported CPAP use was significantly associated with outcome measures assessing post-treatment sleepiness and improvement in function and symptoms, confirming and extending findings of others showing correlations between compliance and subjective change in sleepiness with treatment (Meurice et al 1994, Rauscher et al 1993b).

The observed triangular association between pre-CPAP sleepiness, subsequent compliance and post-treatment sleepiness (Table 11.8) is suggestive of a positively reinforcing loop. Poorer compliance was associated with greater rates of sleep-related collisions after treatment, providing additional corroboration of the benefits of CPAP.

Degree of CPAP compliance was linked only to prior sleepiness and not illness severity, confirming the hypothesis that sleepiness is the primary determinant of CPAP acceptance (Waldhorn et al 1990, Rauscher et al 1991). Apart from the nuisance problem factor (see below), problems with CPAP use were not associated with reduced compliance.
Sleepiness
Subjective sleepiness, assessed by the Epworth sleepiness scale, was significantly improved with CPAP, with average scores after treatment falling within the normal range (Johns 1992). The Epworth sleepiness scale, although subjective and completed retrospectively, may be a relatively robust measure of sleepiness, dealing with memorable real-life situations rather than transient mood states. In addition, the use of retrospective Epworth scores may avoid the unawareness of sleepiness observed in some SAHS patients prior to treatment (Dement et al 1978) and the minimisation of sleepiness by patients keen to continue driving. Sleep onset latency on the MSLT was improved but not normalised by CPAP, as previously reported in the parallel-group pilot study (Engleman et al 1993; Chapter 5), the placebo-controlled crossover study (Engleman et al 1994b; Chapter 6) and by others (Sangal et al 1992b, Bedard et al 1993, Kribbs et al 1993b), with only one study showing normalisation of sleep onset latency with CPAP (Lamphere et al 1989).

Road Traffic Incidents
The survey documents a high prevalence of sleep-related road traffic incidents in untreated patients, with 39% of all driving patients being aware of sleep-related near-miss incidents before treatment (see Figure 11.2). These results are compatible with others' findings of increased accident rates in SAHS patients (Findley et al 1988, George et al 1987). Self-reported mileage-adjusted rates of near-miss incidents were significantly improved after CPAP. Thus the study shows for the first time significant improvement in actual driving competence with CPAP, in keeping with research suggesting that treatment (Findley et al 1989a, Haraldsson et al 1991) may improve driving skills on simulators. Although no significant difference in sleep-related collision rate after CPAP was observed, the low frequency of such events before CPAP in a small population (see Figure 11.2) may contribute to this finding. Road traffic incidents before treatment were significantly correlated with sleepiness as well as polysomnographic measures of sleep fragmentation and hypoxaemia. These findings of putative predictors for driving competence in both sleepiness and illness severity in SAHS extend those of Findley et al (1989b).

Function and Symptoms
CPAP-treated patients reported highly significant improvements in all symptom and function items, except sex drive. These findings are consistent with the objective and subjective improvements in daytime function with CPAP shown by the crossover studies (Engleman et al 1994b; Chapters 6 and 7). Patients in this survey indicated that
daytime impairments were 'better or 'much better, while the crossover studies indicated rather subtle improvements.

The high frequency of reported improvements in daytime function items, especially those relating to concentration, work efficiency, absence from work and ability to drive distances safely, suggests that these areas of function are compromised in a significant proportion of SAHS patients (see Table 11.5). Together with the data on road traffic incidents, the above findings suggest a high cost to community and industry from SAHS and a substantial preventative value for CPAP. The magnitude of reported improvement in daytime function and nocturnal symptoms was related to severity of initial illness. Greater reported improvements in daytime function and in nocturnal symptoms was associated with greater reported CPAP use, greater sleepiness before treatment and lesser sleepiness after treatment.

Problems with CPAP Use
Reported problems with CPAP use, which the majority of patients classified as 'minor' in nature, were remarkably frequent, despite intervention during patient follow-up. Problems with CPAP use have previously been associated with reduced compliance by ourselves (Engleman et al 1993) and by others (Rauscher et al 1993b), but significant relationships between problems and reported CPAP use were limited to the nuisance problem complex. In contrast to nuisance problems, mask problem and side-effect scores were not associated with lower SAHS severity, reported CPAP use or satisfaction with treatment.

Nuisance Problems
The nuisance complex, describing complaints relating to noise, frequent awakenings and sore eyes with CPAP treatment, exhibited an interesting pattern of association with putative determinants and effects (Table 11.8). This problem complex was weakly correlated with milder polysomnographic illness, lower subsequent CPAP use and lesser perceived benefit. One of the nuisance complex items, noise from CPAP units, has been associated with lower SAHS severity (Pépin et al 1995), but not previously with lesser CPAP compliance.

Although high-scorers for nuisance problems had milder initial illness and poorer subsequent CPAP compliance, the evidence from the mild patients participating in the crossover study (Chapter 7) suggests that patients with low indices of illness severity receive objective benefits for cognitive function from CPAP. Thus patients'
unawareness of the benefits of CPAP may be insufficient justification for withholding treatment, although some patients may decline to use it. The lack of correlation between polysomnographic indices of illness severity and CPAP use may well confirm the value of CPAP therapy in ‘heavy snorers disease’ (Lugaresi et al 1989) or ‘upper airway resistance syndrome’ (Guilleminault et al 1993) as well as SAHS. It may be that patient education can aid insight into illness-induced impairment and thus promote improved compliance with and benefit from CPAP.

In summary, this questionnaire-based study documents high rates of road traffic incident rates before CPAP, which were significantly reduced by treatment. The high frequency of positive responses to items rating change in function since CPAP suggests that untreated SAHS carries substantial costs to community and industry. These positive ratings however substantiate accepted wisdom that CPAP therapy improves a wide range of function and symptoms, and corroborate the findings of improved daytime function following CPAP demonstrated in the crossover study (Chapter 6). Reported CPAP use was influenced by sleepiness before treatment but not by prior illness severity or CPAP-related side-effects and mask problems. Greater reported CPAP use was associated with better resolution of sleepiness and greater improvement in daytime function and nocturnal symptoms.
Chapter 12:  
CONCLUSIONS AND PROSPECTS FOR FUTURE RESEARCH 

The research studies presented within this thesis provide a contribution to the knowledge of the effects of CPAP therapy on daytime function on two levels. These studies suggest that objective and subjective improvements in symptoms, daytime sleepiness, cognitive performance and psychological well-being are experienced by patients with SAHS after CPAP therapy. Thus, although CPAP is a relatively intrusive and expensive treatment, the clinical usefulness of CPAP therapy is corroborated by these studies. On a secondary level, the studies in this thesis provide an organic record of the refinement of methodological techniques and measures useful in this particular area of study, and of issues requiring further investigation.

The pilot parallel-group study (Chapter 5) improved on previous studies by employing a control for repeated testing. This trial showed improvements in excessive daytime sleepiness and psychological well-being with CPAP, but failed to show an improvement in cognitive performance. This led to the adoption of a rigorous study design to control for inter-individual variability, learning effects and expectation of benefit from treatment, and to the inclusion of sleep-loss sensitive performance measures. The randomised, placebo-controlled crossover study (Chapter 6) in turn showed improved symptoms, excessive daytime sleepiness, cognitive performance and psychological well-being with CPAP. These findings of CPAP-related benefits for all areas of daytime function were corroborated by reports from a cross-section of CPAP users (Chapter 11). These two studies, one using objective measures and the other focusing on perceived benefits, provided cross-validation of the benefits of CPAP. Each suggested, whether with a driving-based vigilance task or through self-reports of road traffic incidents, that driving impairment might be improved by CPAP. These and the findings of improved work efficiency and work absenteeism in the CPAP users’ survey (Chapter 11) provide support for the contention that CPAP reduces costs to state and industry from SAHS.

The clinical applications of CPAP therapy were examined by the crossover study of patients with mild SAHS (Chapter 7), which indicated objective and subjective benefits for symptoms, cognitive performance and well-being from CPAP in symptomatic patients with AHI 5 to 15 per hour slept. This may indicate that therapeutic trials of CPAP are merited in such patients. The higher levels of sleep
fragmentation in the better CPAP users within this range of SAHS severity may also support the role of sleep fragmentation in inducing daytime deficits in SAHS.

The CPAP compliance rates, objectively measured in these prospective studies of new CPAP users (Chapters 6 and 7), were disappointingly low, although synchronous studies showed similar findings (Kribbs et al 1993a, Reeves-Hoché et al 1994). Self-reported CPAP compliance rates in the survey of CPAP users (Chapter 11) were not related the commonly-experienced problems of mask discomfort, but did show a weak association with the degree of nuisance-type complaints from users, emphasising the inconvenient nature of the therapy. Nevertheless, the surprisingly low objective compliance rates of CPAP users in the randomised crossover studies of daytime function still resulted in demonstrable improvements in daytime function. The precise relationship between CPAP use and benefit is still ill-understood, and requires further examination. Further work is also required to identify the determinants of CPAP compliance, so that use of therapy can be optimised.

Both parallel-group and crossover studies showed a relatively small improvement in objective daytime sleepiness, as measured by the MSLT, with CPAP. Sleep onset latencies remained in the range associated with moderate sleepiness following therapy. This observation finds agreement in studies conducted before (Fry et al 1990, Gaddy and Doghramji 1991) and synchronously (Sangal et al 1992b, Bédard et al 1993, Kribbs et al 1994b) with those reported in this thesis. It remains to be seen whether this lack of normalisation is due to insensitivity in the MSLT instrument, or to persistent but lessened sleepiness after CPAP. The use of alternative tests of sleepiness, such as the maintenance of wakefulness test, may help clarify this issue.

Although cognitive improvements with CPAP were demonstrated in the crossover study (Chapters 6 and 7), the study design did not elucidate whether these improvements were complete or partial, and if other cognitive abilities remained impaired. Further investigation is required to identify the type and scale of improvements in cognitive performance following CPAP.

Further prospective and quantitative investigations of the effects of CPAP on driving ability are also required. Driving impairment was self-reported in the crossover study (Chapter 6) and patient survey (Chapter 11) studies, and retrospective in the survey, compromising the quality of these data. Prospective and quantitative studies would help evaluate the scale of benefit from CPAP.
The study of auditory evoked potentials indicated trends towards improvement in neurophysiological function following CPAP, while the ambulatory blood pressure study suggested that selective benefits from CPAP in lowering blood pressure might be gained by SAHS patients at risk of cardiovascular accidents. In the auditory evoked potential study, limited sample size might well have contributed to a Type 2 statistical error. Larger samples may yet show that evoked potential measures, linked through other research to both sleepiness and cognitive function, cross-validate the improvements in these domains of function with CPAP therapy. Another fruitful area of research, raised during the course of these thesis studies, might be to examine whether patients with mild SAHS may also gain protection from cardiovascular morbidity and mortality from CPAP.

The study of correlates of daytime function (Chapter 10) indicated that severity of the nocturnal events of SAHS was modestly related to daytime sleepiness and to cognitive impairment, but did not identify whether daytime impairment is more closely related to sleep fragmentation or hypoxaemia. The best overall correlates of daytime impairment were AHI and a factor score representing overall severity of nocturnal measures, supporting the contention (Gould et al 1988) that the primary breathing pauses which lead in turn to oxygen desaturations and to microarousals are the best currently available measure of severity of SAHS.

The reversibility of impairments observed in the studies of daytime function (Chapter 5, 6 and 7) might support the view that these are most closely related to the sleep fragmentation of SAHS. However, no relationships between microarousal frequency and daytime function were observed in the correlational study of nocturnal determinants (Chapter 10). The lack of correlations between microarousal index and the daytime deficits of SAHS may lead to queries of the suitability of current techniques used to measure sleep fragmentation. The commonly-used electroencephalographic measure of microarousal index varies in definition between centres, and objective research is required to validate optimal criteria. Recent interest has focused on the autonomic arousals accompanying apnoea termination (Davies et al 1993, 1994b, Rees et al 1993, 1995, Rees and Calverley 1995), which may or may not lead to electroencephalographic arousals. Such 'sub-cortical' arousals may prove a future useful index of nocturnal physiological events in SAHS, and possibly also to daytime impairment (Sahloul et al 1995).
The studies of this thesis confirm the clinical efficacy of CPAP in improving the daytime impairments associated with SAHS. Although inconvenient, CPAP results in objective and subjective benefits to users. Until therapeutic advances supersede this valuable treatment, it is necessary for scientists and clinicians to further describe the effects of this treatment, and to work towards maximising its use and its benefits in patients with SAHS.
ABBREVIATION


Aguirre M and Broughton RJ. Complex event-related potentials (P300 and CNV) and MSLT in the assessment of excessive daytime sleepiness in narcolepsy-catalepsy. Electroencephalogr Clin Neurophysiol 1987;67:298-316


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APPENDIX A:

CPAP PATIENT QUESTIONNAIRE
Name:  

Date of Birth:  

Date questionnaire completed:  

Roughly how many nights per week do you use CPAP?  

_____________________ nights/week  

On the nights that you use CPAP, how many hours do you manage to use the CPAP therapy?  

_____________________ hours/night  

The following symptoms may be associated with the sleep apnoea syndrome. Please tick a single column for each symptom to indicate if CPAP therapy has made any difference to these.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>MUCH WORSE</th>
<th>WORSE</th>
<th>NO CHANGE</th>
<th>BETTER</th>
<th>MUCH BETTER</th>
<th>NEVER PRESENT EVEN BEFORE CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNORING</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BREATHING PAUSES (when asleep)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAYTIME SLEEPINESS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Have any of the following factors been affected by CPAP therapy (please tick one column for each factor)?

<table>
<thead>
<tr>
<th>Factor</th>
<th>MUCH WORSE</th>
<th>WORSE</th>
<th>NO CHANGE</th>
<th>BETTER</th>
<th>MUCH BETTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONCENTRATION</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIGHT-TIME SLEEP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WORK EFFICIENCY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIREDNESS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GENERAL HEALTH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Are you in employment at the moment (please circle appropriate answer)?  

YES  NO  

If you answered yes above, please tick one column below to tell us whether your ability to attend for work has changed since starting CPAP.

<table>
<thead>
<tr>
<th>Days Off Work</th>
<th>MUCH MORE FREQUENT</th>
<th>MORE FREQUENT</th>
<th>NO CHANGE</th>
<th>FEWER ABSENCES</th>
<th>MUCH FEWER ABSENCES</th>
</tr>
</thead>
</table>

220
Has your sex drive changed since starting CPAP (please tick a single column)?

<table>
<thead>
<tr>
<th></th>
<th>GREATLY REDUCED</th>
<th>SLIGHTLY REDUCED</th>
<th>NO CHANGE</th>
<th>SLIGHTLY INCREASED</th>
<th>GREATLY INCREASED</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEX DRIVE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Has your weight changed since starting CPAP (Please circle one answer and fill in weight change if appropriate)?

<table>
<thead>
<tr>
<th></th>
<th>WEIGHT DECREASED</th>
<th>WEIGHT IS THE SAME</th>
<th>WEIGHT INCREASED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BY ______ kg</td>
<td></td>
<td>BY ______ kg</td>
</tr>
</tbody>
</table>

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This question refers to your usual way of life both before and since starting CPAP. Even if you have not done some of these things recently, try to work out how they might affect you now and in the past. 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

<table>
<thead>
<tr>
<th>SITUATION</th>
<th>SLEEPINESS BEFORE STARTING CPAP</th>
<th>SLEEPINESS SINCE STARTING CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watching TV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting inactive in a public place (e.g. a theatre or meeting)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In a car while stopped for a few minutes in traffic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Occasionally CPAP therapy may be associated with side effects. Please tick a single column for each side effect to inform us if you are suffering these problems and if they affect your ability to benefit from CPAP.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Not a Problem</th>
<th>Minor Problem</th>
<th>But able to continue using CPAP</th>
<th>Unable to continue using CPAP</th>
<th>Problem present even before starting CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal stuffiness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry throat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red/sore eyes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mask leak</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Cold airstream</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Nosebleeds</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mask rubbing</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Difficulty exhaling</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>More frequent awakenings</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Excessive noise from CPAP unit</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Bloating of stomach or excessive wind</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest wheeze</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Do you drive (please circle appropriate answer)? 

YES  NO

We would like to know more about your experience of driving both before and since starting CPAP. This information is entirely confidential and will not be passed to insurers, police or other authorities. Please complete all of this section you are a driver, but leave blank if you do not drive.

Approximately how many miles per year do you drive? 

Is driving involved in your occupation (please circle appropriate answer)? 

YES  NO

Has your ability to drive longer distances safely changed since starting CPAP? Please tick a single column.

<table>
<thead>
<tr>
<th>MUCH WORSE</th>
<th>WORSE</th>
<th>NO CHANGE</th>
<th>BETTER</th>
<th>MUCH BETTER</th>
<th>NEVER A PROBLEM EVEN BEFORE CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABILITY TO DRIVE LONG DISTANCES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

We would like to investigate whether CPAP is reducing road accidents caused by sleepiness. The definition of accident types is presented below:

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

In the 5 years before you started CPAP, how many of each of the following events happened to you?

<table>
<thead>
<tr>
<th>NEAR MISS ACCIDENT</th>
<th>MINOR ACCIDENT</th>
<th>MAJOR ACCIDENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events in all</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of these caused by sleepiness</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Since you started CPAP, how many accidents or near-misses have you been involved in?

<table>
<thead>
<tr>
<th>NEAR MISS ACCIDENT</th>
<th>MINOR ACCIDENT</th>
<th>MAJOR ACCIDENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events in all</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of these caused by sleepiness</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PLEASE CHECK THAT ALL APPROPRIATE SECTIONS OF THIS FORM ARE FILLED IN

THANK YOU FOR YOUR HELP
PLEASE ASK YOUR SPOUSE OR PARTNER TO FILL IN THIS FORM
CPAP PARTNER'S QUESTIONNAIRE

Your Name: Date questionnaire completed:

Your partner's name: Partner's date of birth:

The following symptoms may be associated with the sleep apnoea syndrome. Please tick a single column for each symptom to indicate if CPAP therapy has made any difference to your partner's health.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>MUCH WORSE</th>
<th>WORSE</th>
<th>NO CHANGE</th>
<th>BETTER</th>
<th>MUCH BETTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNORING</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BREATHING PAUSES (when asleep)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DAYTIME SLEEPINESS</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>TEMPER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How likely is/was your partner to doze off or fall asleep in the following situations, in contrast to just feeling tired? This question refers to your partner's usual way of life before and since starting CPAP. Even if your partner has not done some of these things recently, try to work out how they might affect him/her now and in the past. 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

<table>
<thead>
<tr>
<th>SITUATION</th>
<th>SLEEPINESS BEFORE STARTING CPAP</th>
<th>SLEEPINESS SINCE STARTING CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watching TV</td>
<td></td>
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</tr>
<tr>
<td>Sitting inactive in a public place (e.g. a theatre or meeting)</td>
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</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
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<td></td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
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</tr>
<tr>
<td>Sitting and talking to someone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In a car while stopped for a few minutes in traffic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

THANK YOU FOR YOUR HELP
APPENDIX B:

PUBLICATIONS AND PRESENTATIONS OF WORK INCLUDED IN THESIS
Appendices

Original Papers


Compliance with continuous positive airway pressure therapy in patients with the sleep apnoea/hypopnoea syndrome. Engleman HM, Martin SE, Douglas NJ. Thorax 1994; 49: 263-266

The effect of continuous positive airway pressure therapy on daytime function in the sleep apnoea/hypopnoea syndrome. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Lancet 1994; 343: 572-575

Manuscript submissions under consideration by journals


Abstracts and Presentations


Placebo-controlled crossover trial of daytime function after CPAP therapy for the sleep apnoea/hypopnoea syndrome. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Proc of the British Sleep Society, Dublin, Sept 1993


Randomised, placebo-controlled crossover trial of the effects of CPAP on auditory evoked potentials in patients with the sleep apnoea/hypopnoea syndrome. Engleman HM, Martin SE, Chiswick A, Douglas NJ. Proc of the British Sleep Society, Bristol, September 1994


Daytime sleepiness, cognitive performance and mood after continuous positive airway pressure for the sleep apnoea/hypopnoea syndrome

Heather M Engleman, Katherine E Cheshire, Ian J Deary, Neil J Douglas

Abstract

Background—Patients with the sleep apnoea/hypopnoea syndrome often receive continuous positive airway pressure to improve their symptoms and daytime performance, yet objective evidence of the effect of this treatment on cognitive performance is lacking.

Methods—A prospective parallel group study was performed comparing the change in objective daytime sleepiness as assessed by multiple sleep latency, cognitive function, and mood in 21 patients (mean (SE) number of apnoeas and hypopnoeas/hour 57 (6)) who received continuous positive airway pressure for three months and 16 patients (49(6) apnoeas and hypopnoeas/hour) who received conservative treatment for a similar period.

Results—Both groups showed significant within group changes in cognitive function between baseline and three months, but when comparisons were made between groups the only significant difference was a greater improvement in multiple sleep latency with continuous positive airway pressure. However, the improvement in sleep latency with continuous positive airway pressure was relatively small (3.5 (0.5) to 5.6 (0.7) min). The group treated with continuous positive airway pressure was divided into those who complied well with treatment (>4.5 hours/night) and those who did not. Those who complied well (n = 14) showed significant improvement in mean sleep latency and also in depression score compared with the controls but no greater improvement in cognitive function.

Conclusion—This study confirms significant improvements in objective sleepiness and mood with continuous positive airway pressure, but shows no evidence of major improvements in cognitive function.
Patients had only non-caffeinated drinks on CPAP (n = 21) and control (n = 16) the days of testing. Because patients with the sleep apnoea/hypopnoea syndrome tend to have arousals associated with apnoeas and hypopnoeas soon after sleep onset, the definition of sleep onset used in the multiple sleep latency test was modified to one 20 second epoch of any sleep stage. This definition of sleep onset in such patients has since been accepted by the American Sleep Disorders Association. The psychometric battery was designed to incorporate tests of a wide range of neuropsychological function, including general level of function, visuomotor skill, concentration ability, vigilance, memory, and mood. A standardized alternative to the word list in the auditory verbal learning test was used in the repeat testing session to obviate learning related improvements in score. The administration of the national adult reading test rendered an estimate of premorbid performance IQ. This estimate was subtracted from the performance IQ score obtained from the Wechsler adult intelligence scale performance subtests to calculate an “IQ decrement” score for each patient. Overall change in cognitive function score for each individual was assessed by using a summed Z score of each patient’s performance in all cognitive tests in the battery.

Table 2 Psychometric battery

<table>
<thead>
<tr>
<th>Tests of general function and of memory</th>
<th>WAIS subtests—information, arithmetic, block design, digit symbol substitution TrailMaking tasks A and B Auditory verbal learning test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premorbid level of function</td>
<td>National adult reading test</td>
</tr>
<tr>
<td>Processing time</td>
<td>Inspection time test</td>
</tr>
<tr>
<td></td>
<td>Simple unprepared reaction time</td>
</tr>
<tr>
<td>Concentration</td>
<td>Paced auditory serial addition test (presentation rates 2 and 4 s) Driving simulator</td>
</tr>
<tr>
<td>Mood</td>
<td>Hospital anxiety and depression scale</td>
</tr>
</tbody>
</table>

WAIS—Wechsler adult intelligence scale.

Results

All patients

Comparison of treatment groups at baseline

There were no differences in psychometric function at baseline in the two groups. However, the mean sleep latency on the multiple sleep latency test was longer in the conservatively treated group (fig: p = 0.01).

Within group changes in scores from first to second assessment

Both groups showed significant improvements in scores in a wide range of psychometric function tests (table 3). There was also significant lengthening of sleep latency in the multiple sleep latency test on the group treated with continuous positive airway pressure.

Comparison of change in scores from first to second assessment between the two groups

There was no significant difference between the two groups in changes in any of the
Effect of continuous positive airway pressure on sleep apnoea

Table 3 Mean (SE) significant within group changes * from first to second assessment

<table>
<thead>
<tr>
<th>Test</th>
<th>CPAP group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change</td>
<td>Change</td>
</tr>
<tr>
<td>Information (no correct)</td>
<td>1.4 (0.4) &lt; 0.01</td>
<td>0.9 (0.4) 0.05</td>
</tr>
<tr>
<td>Digit symbol substitution (no correct)</td>
<td>3.6 (0.9) &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>IQ:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TrailMaking task B (s)</td>
<td>21.1 (0.0) 0.05</td>
<td></td>
</tr>
<tr>
<td>PASAT (no correct):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4s</td>
<td>4.3 (1.9) 0.01</td>
<td></td>
</tr>
<tr>
<td>2s</td>
<td>5.3 (1.7) 0.01</td>
<td></td>
</tr>
<tr>
<td>Driving response time (s)</td>
<td>-6.2 (2.4) &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Sleep latency (min):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.1 (0.8) 0.01</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>1.3 (0.5) &lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

CPAP—continuous positive airway pressure; PASAT—paced auditory serial addition test. *All significant changes were in the direction of improvement in the tests concerned.

Discussion

This study shows that treatment with continuous positive airway pressure results in improvements in objective sleepiness and may improve mood in good compliers, but we were unable to show any improvement in cognitive performance. We thus confirm the findings of Lamphere et al of an improvement in objective daytime sleepiness with continuous positive airway pressure, although our changes are much less dramatic than those of Lamphere et al. In part, this may reflect differences in criteria of defining sleep onset during the daytime naps, which we defined as a first 20 second epoch of any sleep stage rather than the first minute of any sleep stage to detect short sleep episodes rapidly disrupted by apneic arousals. Our data showing a moderate improvement in sleep latency with continuous positive airway pressure come midway between the dramatic improvements reported by Lamphere et al and the lack of improvement with continuous positive airway pressure or uvulopalatopharyngoplasty, or both, recently reported by Sangal et al. Although our different criteria for sleep onset might change the absolute value of multiple sleep latency in comparison with earlier studies, it is difficult to see how this could adversely affect our ability to detect improvement with continuous positive airway pressure. We have confirmed the results of Derderian et al that the treatment may improve mood.

There has been a relative paucity of data on the effects of continuous positive airway pressure on cognitive performance. In a prospective report Bearpark et al found improvements in scores in visual memory, verbal fluency, and mental set flexibility on retesting after 4–5 months of continuous positive airway pressure, but their study had no control group to evaluate the effects of learning on performance. Similarly, Charbonneau et al have reported improved cognitive function with the treatment in an uncontrolled study. Our finding of within group improvements in cognitive performance on retesting in both groups shows that a learning curve exists for cognitive function tests. It also indicates the need for control groups in such studies and shows that the conclusions of Bearpark et al and Charbonneau et al that continuous positive airway pressure improves psychometric function cannot be drawn from their studies. Our studies are consistent with the observation of Walsieben et al, who found no improvement in cognitive function after two nights of continuous positive airway pressure treatment in a small study (n = 7).

The lack of demonstrable improvement in cognitive function in our study could be due to our choice of psychometric performance tests, to the wide interindividual variability, to poor compliance with treatment, or to the fact that there genuinely is no improvement in cognitive function which might be permanently impaired in patients with the sleep apnoea/hypnoea syndrome. We chose the psychometric function tests to reflect the abnormalities that we have previously detected in patients with the syndrome and to cover a wide range of cognitive functions. Our patients were well within the operating range for all the cognitive function tests and thus the lack of an improvement was not due to there being no room for improvement in their results. We believe that the battery of psychometric function tests (p > 0.2). Mean sleep latency lengthened significantly in the treated group compared with the control group (p < 0.02; fig). Similarly, the treated group had a trend to greater improvement in the shortest of the five sleep latencies during the multiple sleep latency test (p > 0.05).

GOOD COMPLIERS

The hidden time clocks in the continuous positive airway pressure units allowed an average nightly usage to be calculated for each patient. The mean (SE) usage for the group was 5.9 (1.4) hours per night. We divided the group treated with continuous positive airway pressure into those who complied well with treatment and used their units for more than 4.5 hours per night (n = 14) and those who used it for less than 4.5 hours per night. The results for the good compliers were compared with those for the controls. The good compliers again showed significantly greater improvements in mean sleep latency compared with the conservatively treated patients (visit 1: 3.4 (0.5) minutes, visit 2: 5.5 (0.4) minutes; p < 0.05) and shortest sleep latency (visit 1: 1.3 (0.3) minutes, visit 2: 2.4 (0.3) minutes; p < 0.05). The good compliers also showed a significantly greater improvement in depression score (p = 0.05) but no significant improvements in any cognitive function assessment compared with the control group.

There was no difference between the treated and control group in the change in weight during the study period (treated gained 1.4 (0.6) kg, control gained 1.6 (1.3) kg).
tests used is fairly comprehensive. Nevertheless, Findley et al have shown improvement in a long and repetitive task designed to simulate driving, although it remains to be seen whether this reflects improved cognitive function, a decrease in daytime microsleeps, or improved performance with greater familiarity with the task. We believe that the large interindividual variability in cognitive function may have resulted in our failure to find differences in a parallel group design such as we used. We are thus initiating a crossover study of the effect of continuous positive airway pressure or placebo on objective daytime sleepiness, cognitive function and mood.

Compliance with treatment was somewhat disappointing in our study, with a mean use of continuous positive airway pressure of 5-9 hours/night. We suggest, however, that this probably reflects use in the community and is certainly in keeping with other recent studies which have objectively examined compliance in patients with the sleep apnoea/hypopnoea syndrome. 1, 11

This study shows that there are significant improvements in both objective daytime sleepiness and mood with continuous positive airway pressure in patients with the sleep apnoea/hypopnoea syndrome, but we found no evidence of major improvements in cognitive function with such treatment.

We thank Sisters C Hoy and M Vennelle and Ma K Stedul and H Bierneck for technical and nursing help and Mrs E Doan for preparing the manuscript.

Compliance with CPAP therapy in patients with the sleep apnoea/hypopnoea syndrome

Heather M Engleman, Sascha E Martin, Neil J Douglas

Abstract

Background - Continuous positive airway pressure (CPAP) therapy is the treatment of choice for the sleep apnoea/hypopnoea syndrome. Compliance with this relatively non-invasive therapy has not been well studied.

Methods - Usage of CPAP was investigated in 54 patients with sleep apnoea/hypopnoea syndrome (median 36 (range 7-129) apnoeas/hypopnoeas/hour slept) over the first 1-3 months after starting CPAP therapy. In all cases CPAP usage was monitored by hidden time clocks that indicated for how long the machines were switched on - that is, the CPAP run time. In 32 patients the time at which the CPAP mask pressure was at the therapeutic level of CPAP pressure set for that patient - that is, the mask time - was also monitored. In all patients objective daytime sleepiness was assessed by multiple sleep latency before and after CPAP therapy.

Results - The mean (SE) nightly CPAP run time was 4.7 (0.3) hours. There was no correlation between run time and severity of the sleep apnoea/hypopnoea syndrome as assessed by apnoea/hypopnoea frequency or multiple sleep latency, and no correlation between CPAP usage and improvement in multiple sleep latency. Thirty two patients in whom mask time was recorded had therapeutic CPAP pressures for 89% (3%) of their CPAP run times. Patients who experienced side effects from CPAP used their CPAP machines significantly less than those who did not.

Conclusions - Patients with sleep apnoea/hypopnoea syndrome used CPAP for less than five hours/night on average with no correlation between severity of sleep apnoea/hypopnoea syndrome and CPAP usage. Patients who complained of side effects used their CPAP therapy less. It is recommended that, as a minimum, CPAP run time should be regularly recorded in all patients receiving CPAP therapy.

(Pt 1994;49:263-266)

Recent evidence indicates that the sleep apnoea hypopnoea syndrome has a prevalence in middle age of 2% in women and 4% in men, approaching the approximately 6% prevalence of asthma in the middle aged population. The treatment of choice for the sleep apnoea hypopnoea syndrome is continuous positive airway pressure (CPAP) therapy via the nose.

Compliance with therapy in patients with airflow obstruction is relatively poor. Despite the fact that CPAP therapy is more invasive than the use of bronchodilator inhalers, and that CPAP therapy carries a relatively high initial capital cost, there have been few studies of compliance with CPAP therapy in patients with the sleep apnoea hypopnoea syndrome and no studies in a British population. We have therefore studied CPAP use in such patients, and have also examined whether there were correlations between indices of severity of the sleep apnoea hypopnoea syndrome and objective measures of compliance.

Methods

Usage of CPAP was studied in 54 patients during the first 1-3 months after initiation of CPAP therapy.

Patients

Of the 54 patients studied, 48 were men. The mean (SE) age was 51 (1.3) years and body mass index was 33 (1.1) kg m⁻². Each had at least two major symptoms of the sleep apnoea hypopnoea syndrome plus at least five apnoeas/hypopnoeas hour of sleep recorded by overnight polysomnographic monitoring performed with our usual equipment and scoring techniques. These patients were deliberately selected to provide a wide range of frequencies of apnoeas/hypopnoeas (median 36 (range 7-129) hour slept).

All patients had multiple sleep latency tests performed in the baseline state and again, off CPAP, after the last night of CPAP therapy. Sleep onset was defined by the first 20 second epoch of any sleep stage.

CPAP THERAPY

Following an initial positive clinical sleep study, all patients had the rationale for CPAP therapy explained to them and the CPAP equipment demonstrated. They then had an overnight CPAP titration sleep study in which the CPAP pressure was adjusted to the minimum pressure that normalised breathing pattern and minimised electroencephalographic arousals, defined as an episode of alpha or theta rhythm for at least 1.5 seconds associated with a transient increase in electromyographic tone, however brief. In the morning the patients' further queries about CPAP therapy were
answered and they were allowed home with an appropriately set CPAP unit and a correctly fitting mask or intranasal system. The importance of all night use of the CPAP machines was stressed. The patients were given a telephone number to contact if they experienced any problems with their CPAP machines or side effects, and were phoned after two weeks on CPAP to check their progress.

PROTOCOLS
The first 22 patients studied received Respironics Sleep Easy II or Sleep Easy III CPAP units with hidden time clocks which indicated for how long the machines were switched on—the "CPAP run time." These time clocks were read when the machines were issued and re-read after three months. These patients were taking part in a parallel group study of the effect of CPAP on daytime function.11

The 32 subsequent patients were issued with ResCare Sullivan APD 1 CPAP units which had been modified by building in two time clocks. The first, as in the Sleep Easy II and III machines, indicated the CPAP run time. The second was linked to a pressure sensitive switch connected via a polythene tube to the CPAP mask, this tube passing along the CPAP hosing.14 The pressure sensitive switch was set so that it was activated when the pressure in the mask was more than 2 cm H2O below the therapeutic level of CPAP pressure set for that patient, thus monitoring the time spent at an effective CPAP pressure—the "mask time." These patients were taking part in a crossover trial of CPAP therapy; their time clocks were read when the CPAP units were dispensed and again one month thereafter.

STATISTICAL ANALYSIS
Correlation analysis to determine significant associations and multiple regression analysis with forward stepwise entry of variables to assess the relative contributions of different factors were conducted using the SPSS-X package.15

Results
The mean (SE) nightly CPAP run time for the 54 patients was 4.7 (0.4) hours. There was no correlation between CPAP run time and frequency of apnoeas + hypopnoeas (fig 1), baseline multiple sleep latency time (MSLT; fig 2), or body mass index, nor was there any correlation between change in MSLT following therapy and CPAP run time (fig 3). Separate analyses of the data from the two component studies showed that none of these correlations were significant.

The 32 patients in whom mask time was recorded had therapeutic CPAP pressures for 89% (3%) of their CPAP run times (fig 4). The patient in whom appropriate CPAP pressure was only achieved for 24% of the night was subsequently found to have displaced the cap from one of the sensing ports on his CPAP mask.
**CPAP compliance in sleep apnoea hypopnoea syndrome**

A total of 13 of these 32 patients (41%) contacted our staff to report problems associated with the use of their CPAP units. Nine complained of nasal congestion and were prescribed steroid nasal spray to relieve this side effect, two experienced dryness of the upper airway which was treated by humidification of the CPAP airstream, and five patients disliked the pressure effects of the CPAP system. Average CPAP mask time was higher in the patients reporting no problems with CPAP than in those reporting problems (4.1 (0.6) v 2.4 (0.4) hours: night; p=0.02), with a trend (p<0.1) between patients reporting no problems (4.3 (0.6) v 2.8 (0.6) hours: night).

The therapeutic CPAP pressure assessed for each patient during the CPAP titration run and given to these patients during the studies correlated significantly with the frequency of apnoea+hypopnoeas (p<0.001), collar size (p<0.001), the male sex (p<0.02), and body mass index (p<0.05). Multiple regression showed that the most important variables in determining CPAP pressure were collar size (p<0.003) and apnoea+hypopnoea frequency (p<0.02), which together explain 53% of the variance in prescribed CPAP pressure.

**Discussion**

The average duration of CPAP use (4.7 hours/night) seems disappointing. However, these results have to be compared with those obtained by similar objective methods in other chronic conditions. For example, asthmatic patients have been shown by electronic monitoring devices to use their chronic treatment as instructed on only 37% of days, and anti-epileptic treatment was taken as prescribed on 39% of days in another study.

The results in our study are very similar to those in a contemporaneous study performed in two centres in North America for which the average duration of CPAP used by 35 patients with sleep apnoea hypopnoea syndrome was 4.9 (2.0) hours: night, and the CPAP was received at the appropriate pressure for 91% of the CPAP run time. The subjects in that study only used their CPAP units for 66% of the nights, however, and we therefore deduce that their average CPAP use was 3.2 hours.

Similar results have been reported by another North American group. CPAP run times averaging 5.1 hours night were obtained in a French sample of 45 patients. Our results extend these observations by examining correlates between CPAP usage and severity of the sleep apnoea hypopnoea syndrome, and indicate that there was no correlation between any measure of severity of the sleep apnoea hypopnoea syndrome and objective CPAP use. This somewhat surprising result means, not only that patients with severe sleep apnoea hypopnoea syndrome cannot be relied upon to comply with their therapy, but also that some patients with mild sleep apnoea hypopnoea syndrome in terms of apnoea+hypopnoea frequency or objective daytime sleepiness (MSLT) use their CPAP therapy regularly. Our results also extend these previous observations by reporting results in British patients in whom CPAP units were provided free of charge. Theoretically this might reduce motivation to use CPAP in comparison with patients who had to pay for their own units, but our CPAP usage is similar to that in North America.

CPAP therapy is obtrusive, and it is not surprising that patients do not use it all night every night. However, the results in this study indicate that CPAP usage is extremely variable between patients and that, on average, CPAP use is less than five hours night. Even with this level of compliance, however, these patients have reported improvements in symptoms and we have identified statistically significant improvements in objective daytime sleepiness which, in the first sample of 22 patients, rose to 5.5 (0.4) minutes from a preCPAP level of 3.5 (0.7) minutes. It thus seems likely that the patients titrate their own CPAP use to provide an acceptable balance between the inconvenience of CPAP and the benefits of therapy.

The patients in whom mask time was monitored achieved satisfactory mask pressures for an average of 89% of the run time. These APD CPAP units had built-in delay timers which allowed the patients to ramp up their CPAP pressure, achieving therapeutic CPAP pressure within 20 minutes of the machine being switched on. One would therefore anticipate that optimal CPAP pressure would only be achieved for 93% of the night in patients using a 20 minute delay on one occasion if the machine was switched on for the average 4.7 hours night. It thus seems that these patients are achieving satisfactory CPAP pressures for most of the time during which the CPAP machines are switched on, with the one noticeable exception of the patient whose pressure monitor port cap was displaced. Thus, while monitoring the time at the appropriate CPAP pressure is the ideal method of monitoring compliance and manufacturers should work towards this end, recording the time for which the machine is switched on appears to give a good measure of CPAP use. We would recommend that, as a minimum, the machine run time should be regularly recorded in all patients receiving CPAP therapy.

Our study documents a relatively high inci-
dence (41%) of problems relating to CPAP use such as side effects and pressure intolerance. Such problems may have a serious impact on CPAP compliance rates, with mask times in patients reporting problems reduced to 60% of those found in patients not complaining of problems with CPAP. These findings emphasise the need for adequate follow up care and problem management for patients prescribed CPAP.

The patients reported formed part of two separate studies. We have reported their compliance data in this paper in order to allow aggregate data to be used to assess correlations (or lack of them) between CPAP use and severity of the sleep apnoea-hypopnoea syndrome. We do not believe that the difference in the study protocols will have influenced the results. In particular, our own evidence is that usage in the first month predicts CPAP use in the subsequent two months, an observation recently confirmed by others.

This study also shows that effective CPAP pressure relates to apnoea+hypopnoea frequency and also, independently, to neck size. This latter observation confirms the importance of neck size in the sleep apnoea-hypopnoea syndrome.

4 Hoeb CR, Clark TJJH, Cochrane GM. Compliance with inhaled therapy and morbidity from asthma. Respir Med 1990; 84: 9-70.
Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome

Heather M Engleman, Sascha E Martin, Ian J Deary, Neil J Douglas

Summary
Continuous positive airway pressure (CPAP) is the treatment of choice for the sleep apnoea/hypopnoea syndrome (SAHS); it is usually given with the aim of improving daytime cognitive function, mood, and sleepiness. However, its efficacy has not been validated by controlled trials. We have carried out a randomised, placebo-controlled, crossover study of objective daytime sleepiness, symptoms, cognitive function, and mood in a consecutive series of 32 SAHS patients with a median apnoea plus hypopnoea frequency of 28 (range 7–129) per hour slept.

Patients were treated with 4 weeks each of CPAP and an oral placebo, which they were told might improve upper airway muscle function during sleep. Assessments on the last day of each treatment included a multiple sleep latency test and tests of symptom scores, mood profiles, and cognitive performance. The patients had significantly less daytime sleepiness on CPAP than during the placebo period (mean sleep latency 7.2 [SE 0.7] vs 6.1 [0.7] min, p = 0.03). There were also improvements with CPAP in symptom ratings (2.1 [0.2] vs 4.3 [0.3], p<0.001), mood (p<0.05 for several measures), and cognitive performance, which showed improved vigilance (obstacles hit in Steer Clear “driving” test 76 [5] vs 81 [6], p<0.01), mental flexibility (trail-making B time 66 [5] vs 75 [5] s, p<0.05), and attention (p<0.05).

Objectively monitored CPAP use averaged only 3.4 (0.4) hours per night, but this study provides evidence of improved cognitive performance even at this low level of CPAP compliance.

Lancet 1994; 343: 572–75

Introduction
The sleep apnoea/hypopnoea syndrome (SAHS) affects 2–4% of men and 1–2% of women in middle age. The main clinical features are disordered respiration during sleep, daytime sleepiness, impaired daytime cognitive performance, and dysphoric mood; patients have increased mortality and morbidity from cardiovascular events and road traffic accidents. The treatment of choice for SAHS is continuous positive airway pressure (CPAP), given in an attempt to improve daytime sleepiness, cognitive function, and mood, but there have been few adequate studies of the efficacy of this expensive and obtrusive therapy. Findings on the effect of CPAP on sleepiness have differed; one uncontrolled study reported striking improvements, whereas a parallel-group study found only minor changes. We have examined the effect of CPAP therapy on cognitive function, sleepiness, and mood in SAHS patients in a placebo-controlled crossover study.

Patients and methods
Design
CPAP therapy (Sullivan APD-1 units, ResCare, Abingdon, UK), used throughout sleep, was given for 4 weeks, and oral placebo (ranitidine 300 mg homologue [inactive], Glaxo, Greenford, UK; two tablets at bedtime) for 4 weeks. The treatment order was randomly allocated and there was no intervening washout period. Subjects were told about the mechanisms of action of CPAP therapy and that the placebo tablets might improve upper airway muscle function in sleep. Sham CPAP therapy is not possible, because a nasal mask without effective CPAP would worsen both sleep and gas exchange. The study was approved by the Lothian Health Board Ethics Subcommittee.

Subjects were recruited from consecutive outpatients referred for investigation of SAHS, who had at least two symptoms of the syndrome. All patients in the consecutive series underwent a clinical sleep study by our standard procedure with monitoring of the electroencephalogram, electro-oculogram, electromyogram, thoracic and abdominal respiratory effort, oronasal flow, and oximetry to establish a minimum frequency of apnoeas and hypopnoeas of 5 or more per hour of sleep. We approached consecutive patients who satisfied this criterion, who had no coexisting disorder causing excessive sleepiness, and who lived within 50 miles of the laboratory. Of the 43 patients invited to join the study, 35 accepted (3 could not afford the required time off work, 5 were on CPAP treatment, and 2 had another sleep disorder). Their remaining subjects, 15 had been assigned placebo as the first treatment and that the placebo tablets might improve upper airway muscle function in sleep. Sham CPAP therapy is not possible, because a nasal mask without effective CPAP would worsen both sleep and gas exchange. The study was approved by the Lothian Health Board Ethics Subcommittee.

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treatment, and 17 CPAP first. The 26 men and 6 women had a median apnoea plus hypopnoea frequency of 28 (range 7–129) per hour of sleep, a mean age of 49 (SE 1.5) years, and a mean body-mass index of 33 (1.8) kg per m².

Assessments

The last day of each treatment period was spent in the laboratory. Objective daytime sleepiness was measured with the multiple sleep latency test (MSLT), in which the subject is given five 20 min daytime nap opportunities, the first at 1000 hours and the others every 2 hours until 1800 hours. Electroencephalographic monitoring detects sleep, and the time from lights-out to the first 20 s period of any sleep stage is the sleep onset latency. Each test was done at the same time of day during the two study sessions to reduce practice effects further.

An in-house symptom questionnaire asked patients to rate the presence or absence and frequency of symptoms of SAHS—chooking during the night, morning headaches, morning confusion, frequent waking during the night, daytime sleepiness, sleepiness in the evenings, snoring, and sleepiness while driving.

Mood questionnaires were selected to assess the impact of illness in terms of psychological distress (hospital anxiety and depression scale and general health questionnaire-28), the quality of specific aspects of life, excluding sleep quality (Nottingham health profile part 2), and the mood dimensions of energetic arousal, tense arousal, and hedonic tone (UWIST mood adjective checklist). Mood and symptom questionnaires were administered in the early part of the day, when endogenous mood symptoms tend to be most severe.

Before the study, subjects attended a 5 h session of familiarisation with the psychometric battery, to introduce the mood and psychiatric questionnaire, and to reduce subsequent test-retest improvements in cognitive test scores. At this session patients were educated in CPAP use and masks were fitted.

Compliance with CPAP therapy was monitored by reading hidden timeclocks in the CPAP units. The timeclocks counted both the total number of hours that machines were switched on ("runtime") and the total hours that the CPAP pressure was within 2 cm water of that prescribed ("masktime"). Subjects were asked to avoid caffeine-containing drinks before attending for assessments, and were offered only decaffeinated drinks during the assessment day. At the final assessment, subjects were asked to state which treatment they preferred.

Analysis

All statistical analyses were done with SPSS-PC (SPSS Inc, Chicago, USA). McNemar’s test for repeated measures was used to assess the significance of frequencies of individual symptoms on the symptom questionnaire and psychiatric cases identified by mood questionnaires. The binomial test was used to test the significance of patients’ treatment preference. The distributions of outcome variables were examined and non-normal distributions found in 5 cases—floor effects for the number of RVIPT misses, tense arousal, and general health questionnaire—28 score, and ceiling effects for scores for hedonic tone and the 4 s PASAT. Placebo and CPAP scores for these variables were compared by the paired Wilcoxon’s test. All other dependent variables were normally distributed and were examined with two-way analysis of variance (ANOVA), comparing assessment scores on the two treatments, with treatment order as a between-subjects factor and treatment as a within-subject factor; variables judged likely to affect treatment response were entered as covariates.

Results

The mean number of symptom complaints was significantly lower on CPAP therapy than on placebo (2.1 [SE 0.2] vs 4.3 [0.3], p <0.001). There were also significant differences between the CPAP and placebo periods in daytime sleepiness (13 vs 26 patients reported daytime napping, p = 0.001) and snoring (3 vs 30, p <0.0001). 20 (63%) of the 32 patients decided after weighing benefit of treatment and ease of use that their preferred form of treatment was CPAP, and 12 preferred tablets. This bias towards CPAP was not significant (p = 0.22).

Mean CPAP runtime for patients in the study was 3.7 (0.4) h per night and an effective CPAP pressure was delivered to the mask for 3.4 (0.4) h, a mean 89 (3)% of the time that units were run.

CPAP had a significant effect on objective daytime sleepiness. The mean and minimum sleep onset latencies in the MSLT were significantly longer on CPAP than on placebo (mean 7.2 [0.7] vs 6.1 [0.7] min, p = 0.03; minimum 3.5 [0.4] vs 2.9 [0.4] min, p = 0.05).

CPAP improved cognitive function (table) as assessed by tests of mental flexibility (trailmaking B), learning efficiency (digit symbol substitution), and vigilance (SteerClear). In addition, CPAP reduced IQ decrement in comparison with placebo. There was an improvement in PASAT 2 s presentation rate performance on CPAP (p <0.001 on ANOVA) but there was also an order effect (p <0.02), indicating a potential carry-over effect of treatment. We therefore compared PASAT 2 s data from the first assessment only, with a resulting loss of statistical power, and found no significant difference between CPAP and placebo (p = 0.11).

Despite the familiarisation session, several of the cognitive test scores showed learning effect interactions (SteerClear task, p <0.001); trailmaking B, p <0.019; correct responses on the RVIPT, p <0.01; digit symbol substitution test, p <0.034; 2 s PASAT, p <0.003).

However, the treatment-order randomisation meant that these learning effects did not influence the analysis of effects of treatment type.

CPAP produced significant improvements in all mood questionnaires (table). In the Nottingham health profile...
quality of life questionnaire there were improvements with CPAP ($p<0.01$) in the patients' ratings for social life, sex life, and ability to carry out domestic chores. CPAP significantly improved the self-rated levels of energetic arousal ($p<0.001$), but there was no significant change in tension or hedonic tone (an index of pleasant/unpleasant mood).

Using the hospital anxiety and depression scale as a screening device to identify psychiatric “cases”," we identified 10 patients with anxiety and 8 with depression while taking placebo. Only 4 patients were found to have anxiety and 4 depression during the CPAP period, but the differences were not significant ($p=0.11$ and 0.22, respectively). The number of patients identified as psychiatric cases with the general health questionnaire$^{18}$ was 11 during placebo treatment and 5 on CPAP ($p=0.16$).

Apnoea plus hypopnoea frequency, an index of SAHS severity, and CPAP masktime, an index of CPAP compliance, were entered as putative covariates in the analyses of variance. There were significant covariates for only a very few outcome variables, and their inclusion did not lead to any systematic effects becoming non-significant in any case. Increased CPAP use was correlated with greater improvements in symptom scores ($p<0.03$), quality of life (Nottingham health profile, $p<0.03$), and concentration (PASAT 2 $a$, $p<0.02$).

**Discussion**

This study showed, for the first time within a controlled investigation, objective and subjective improvements in daytime function after the introduction of CPAP therapy for SAHS. The total number of reported symptoms, including both daytime and night-time symptoms, was lower on CPAP. The reported improvements in daytime sleepiness on the symptom questionnaire were objectively corroborated by the increase in MSLT sleep onset latencies during the day.

The lengthening of MSLT sleep onset latency on CPAP was small compared with increments found by others,$^{36}$ and even the improved sleep latencies were below the normal range for healthy adults.$^{13}$ However, the improvement is similar to that in other open or parallel group studies of the effects of CPAP on MSLT.$^{32,33}$ It is possible that patients with SAHS become accustomed to falling asleep rapidly and that this ability, which is measured by the MSLT, is retained after treatment. However, the persistence of low sleep latencies after CPAP treatment is a cause for concern and further work is needed to clarify whether better compliance with CPAP treatment might result in greater improvements in sleep latencies. Another feature supporting the improvement in sleepiness measures was the increase in energetic arousal scores from the UWIST mood adjective checklist, a well-validated instrument measuring the dimensions of mood.$^{36}$ Energetic arousal level is related to activation in the reticular activating system of the brainstem, which modulates wakefulness/drowsiness.$^{30}$ The measures of objective sleepiness and subjective energy levels may therefore have a common biological basis.

The results of the cognitive assessments suggest reliably for the first time that CPAP treatment improves vigilance, mental flexibility, and coding speed, all areas of function known to be compromised in SAHS.$^{34,35}$ and significantly reduces the degree of cognitive deficit (IQ decrement). Although CPAP did not significantly change verbal fluency or memory, the cognitive tasks showing CPAP-related improvements in performance were those that require simultaneously rapid and co-ordinated responses. Langan et al.$^{42}$ found, similarly, that scores on complex, timed cognitive tasks were sensitive to the effects of diabetic hypoglycaemia, whereas memory and verbal performance were not affected. The processes precipitating cognitive impairment in diabetes and SAHS may not be identical, but the modest deficits found in both disorders may be best measured with complex, timed tasks.

Mood assessments showed striking improvements in psychological distress and quality of life on CPAP. Since both the questionnaires we used include anxiety subscales, they cross-validate each other. With both questionnaires the number of patients identified as psychiatric cases was smaller during the CPAP period; however, no differences achieved significance. Patients' mean score for the general health questionnaire fell in the pathological range on placebo but was well within the normal range on CPAP.

Previous research on mood after CPAP in SAHS has shown improved scores for psychological distress. Derderian et al.$^{26}$ in a small parallel-group study of untreated and CPAP-treated SAHS patients, found significantly improved depression and fatigue factors. A larger uncontrolled study of depression questionnaire responses from SAHS patients also found significantly improved scores after CPAP,$^{37}$ but neither study took account of the effect of expectations of post-treatment improvement. Our study, by using a placebo period, controls for such expectations.

Our findings of widespread learning effects on repeated cognitive testing, despite efforts to familiarise subjects and boost performance to the top of the learning curve, cast doubt on the reliability of preliminary results from uncontrolled studies of improved cognitive performance after CPAP.$^{38,39}$ Our study controlled for the effects of learning through the use of a randomised, crossover design.

Use of an oral tablet placebo for CPAP is not ideal, but we believe that this is the best available placebo. The potential value of the tablet treatment was emphasised to patients, with the approval of the local ethics committee. At recruitment, many patients expressed the hope that the tablet treatment would prove more beneficial, and after the study 12 stated that they preferred tablets. This finding indicates the level of belief in the placebo therapy. However, most of the patients, some of whom had mild SAHS, preferred the more obtrusive option of CPAP.

Objectively monitored CPAP compliance rates are disappointingly low in the light of instructions to use the units every night, but the monitored usage is very similar to that found in North American patients.$^{30}$ The minimum therapeutic usage of CPAP is as yet unknown, but it seems likely that patients may adjust their CPAP use to a level that produces subjective benefits in daytime function. Our results imply that full-night use may not be necessary to reduce daytime cognitive performance deficits. The low compliance and the lack of significant preference for CPAP indicate, however, that improvements in therapy for SAHS are needed. Further study will identify the severity of SAHS at which CPAP is a beneficial and acceptable therapeutic option. Because of the strong evidence linking SAHS with reduced road safety,' these objective data lend weight to the argument for aggressive treatment of SAHS.

We thank Ms Kristyna Stedul, Ms Sian Finch, Sister Marjorie Vennelle, and Sister Carol Hoy for technical assistance.

This study was supported by a grant from the British Lung Foundation.