Simplified Diagnostic and Management Strategies for the Diagnosis and Delivery of Health Care to those with Obstructive Sleep Apnea

by

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ABSTRACT

Obstructive sleep apnea (OSA) is a prevalent disease. Often resources to provide care for OSA are inadequate, leading to long patient waiting times. Simpler validated methods of care are needed.

In the first study in Chapter 2, the utility of a new high-sampling rate oximeter to diagnose OSA was explored. The home oximetry data collection was robust, with few failures and the data allowed the “rule in” or “rule out” of moderate-severe OSA with high degree of certainty. It is concluded that home oximetry could replace polysomnography (PSG) as a diagnostic test in a significant proportion of patients, thus allowing limited resources available for the care of those with OSA to be re-directed e.g. towards providing therapy.

In Chapter 3, the diagnostic information from the oximeter was used to underpin a study designed to demonstrate that a nurse-led model of care could produce health outcomes in moderate-severe OSA not inferior to physician-led care.

A randomised controlled multi-centre non-inferiority clinical trial was performed. 1,427 patients referred to 3 sleep medical centres with possible OSA were assessed. 195 patients were randomised to 2 models of care. Model A, a simplified model, involved home oximetry to diagnose moderate-severe OSA, auto-titrating constant positive airway pressure (APAP) to set a therapeutic constant positive airway pressure (CPAP), with all care supervised by an experienced nurse. Model B involved 2 laboratory PSG’s, to diagnose OSA then titrate CPAP, supervised by a sleep physician. The

primary endpoint was change in Epworth Sleepiness Score (ESS) measured before and after 3 months of CPAP. A range of other outcome measures were collected.

The change in ESS for nurse-led management (Model A) was not inferior to the physician-led service (Model B) since the lower limit of the two-sided 95% CI did not include -2, the margin of equivalence (difference 0.13, 95% CI -1.52 to -1.25). 11 patients in Model A and 10 in Model B were lost to follow up during the trial. There were no significant differences between Model A and Model B after 3 months of CPAP in any of the other outcome measures, including CPAP adherence at 3 months.

It is concluded that a simplified nurse-led model of care can produce non-inferior results to physician-directed care in the management of moderate-severe OSA.

In Chapter 4 the efficacy of CPAP in normalising or improving subjective and objective sleepiness, quality of life and selected neurocognitive measures was explored. It was shown that only a proportion of patients (60% on ESS, 35% on FOSQ) normalised their scores after 3 months of CPAP therapy. This is important information. As new health care delivery strategies evolve as a result of the data presented in Chapter 3 and elsewhere, it will be crucially important to train new health care professionals in the complexities of OSA management, such that they are aware that the symptoms of patients presenting for OSA investigations can have multiple aetiologies, and may not always resolve by simply applying CPAP.

The data presented in this thesis add to the evidence base in treatment of moderate-severe OSA and will help further evolve health care delivery for this important disease.

PUBLICATIONS ARISING FROM THIS THESIS

Nick A. Antic, Catherine Buchan, Adrian Esterman, Michael Hensley, Matthew T. Naughton, Sharn Rowland, Bernadette Williamson, Samantha Windler and R. Doug McEvoy**.** A randomised controlled trial of nurse led care for obstructive sleep apnea. American Journal of Respiratory and Critical Care Medicine (in review)

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Antic N, Catcheside P, Hansen C, McEvoy RD. Utility of a new high sampling oximeter at the diagnosis of moderate to severe obstructive sleep apnea. TSANZ 2004 Respirology (9) A1-75 2004 (Finalist Young Investigator Award).

Antic N, Catcheside P, Hansen C, McEvoy RD. Utility of a new high sampling oximeter at the diagnosis of moderate to severe obstructive sleep apnea. ATS 2004.

Antic N, Clark R, Hansen C, Hensley M, Naughton M, McEvoy RD. Assessing neurocognitive function in moderate-severe obstructive sleep apnea. ASA 2004.

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Antic N, Hensley M, Naughton M, Rowland, S Windler S, McEvoy RD. A RCT to investigate a simplified diagnostic and management strategy for moderate-severe OSA. ATS 2007.

AWARDS

2003 Finalist Young Investigator Award Australasian Sleep Association.

2004 Finalist Ann Woolcock Young Investigator Award Thoracic Society of Australia and New Zealand.

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DECLARATION

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material published or written by another person except where due reference is made in the text

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GLOSSARY

+LR - positive likelihood ratio

AASM - American Academy of Sleep Medicine

AHI - Apnea-hypopnea index

APAP - autotitrating CPAP

CPAP - continuous positive airway pressure

EDS - excessive daytime sleepiness

EEG - electroencephalogram

EMG - electromyogram

EOG - electrooculogram

ESS - Epworth Sleepiness Scale

FOSQ - Functional Outcomes of Sleep Questionnaire

-LR - negative likelihood ratio

MAP - multivariate apnea index

MAS - mandibular advancement splint

MVA - Motor vehicle accident

MWT - Maintenance of Wakefulness Test

NPV - Negative predictive value

ODI - oxygen desaturation index

OSA- Obstructive sleep apnea

PPV - positive predictive value

PSG - polysomnogram

QALY - quality adjusted life years

SaO_2 - arterial oxygen saturation

SF-36- Short Form 36 (SF-36).

CHAPTER 1 GENERAL INTRODUCTION

1.1 INTRODUCTION

Obstructive sleep apnea (OSA) is characterised by snoring, repetitive upper airway obstructions, oxygen desaturation episodes, arousals from sleep and by excessive daytime sleepiness. There is increasing evidence that OSA increases the risk of motor vehicle accidents, hypertension, and possibly stroke and heart failure [1-4]. More cost-effective clinical pathways of investigation and treatment are required to deal with current referrals and to match the increased demand that is resulting from increasing public awareness of the importance of OSA. Pack 2004 noted;

> "*With the increased recognition of sleep apnea, systems for delivering diagnosis and treatment are overwhelmed. Physicians are trying to cope but, even with creative approaches, waiting lists for diagnosis and treatment are unacceptably long. There is a need to rethink current strategies*."

Later in the same paper he stated;

> *"If we are still doing this in 5 to 10 years from now, we will have failed our patients and failed the funding sources that have supported the research that makes treatment of this disorder so important. The major issue now in this field is access. Let us commit to solving it [5] ".*

Thus the focus of this thesis is to identify and evaluate new diagnostic and treatment strategies for the management of moderate-severe OSA.

1.1.1 OSA, prevalence and significance

Bearpark *et al* showed the prevalence of symptomatic OSA (Sleep Apnea-hypopnea index AHI)> 5 per hour, plus chronic daytime sleepiness) to be 3% in the adult male population of Busselton, in country Western Australia [6]. This Australian estimate of disease prevalence agrees well with the widely quoted Wisconsin prevalence data for symptomatic OSA of 4% of men and 2% of women [7]. A higher proportion of the population experience frequent disordered breathing events (apneas and hypopneas) during sleep while not necessarily perceiving chronic severe daytime sleepiness. One Australian population based study reported a prevalence of 10% for males with apnea-hypopnea index (AHI) >10 events /h [6] and in another study, at least 6% for AHI >15/h [8]. The strongest evidence for adverse outcomes resulting from OSA is in patients with moderate-severe OSA i.e. AHI > 30/hr. Left untreated, severe OSA is associated with a 3-fold increase in fatal and non fatal cardiovascular events [9]. Risk of reduced quality of life, heart failure and stroke and motor vehicle accidents are also increased with an AHI >30/hr [1,3,9-11].

There is less evidence for adverse health outcomes amongst patients with mild disease. However, a recent large study showed that regardless of the presence or absence of excessive daytime sleepiness, mild-moderate OSA (AHI >5-10/hr) was associated with an independent increased risk for systemic hypertension [2]. The longitudinal Wisconsin Sleep Cohort Study

showed a twofold increased risk for incident hypertension over 4 years for AHI 5-15 [2]. The above evidence pointing to possible adverse outcomes from mild OSA has been increasingly promoted to general practitioners and the public and as a result many more patients with mild and perhaps clinically insignificant OSA and simple snoring are being referred. If the evidence for an association between mild OSA and serious morbidity is strengthened in the future this referral trend will likely escalate markedly as epidemiological studies have shown that the numbers of subjects with mild OSA far outweigh those with moderate or severe disease [7]. At present patients with mild OSA still have to be assessed, often in sleep medicine services whose clinical and laboratory resources are already over stretched.

1.1.2 Economic cost of OSA

The overall cost of sleep disorders to the Australian community is large. It was estimated at $US 7,494 million in Australia in 2004 and OSA was the largest disease contributor to these costs [12]. In the USA Sassani *et al* estimated that in 2000, 800,000 drivers were involved in OSA-related MVAs at a cost of approximately US$15.9 billion. They calculated that appropriate diagnosis and therapy could have reduced MVA costs by US$11.1 billion and saved 980 lives [13]. In another study, Albarrack *et al* [14] followed a large group of patients with moderate-severe OSA and their health care expenditure in the 5 years before and after diagnosis and noted that CPAP therapy reversed the trends of increasing health care expenditure in these patients, particularly in those with ischemic heart disease.

1.1.3 CPAP is a highly cost effective therapy for moderate-severe OSA

The cost effectiveness of therapies is usually assessed by the incremental cost effectiveness ratio, which is the ratio of incremental costs associated with therapy divided by the incremental quality adjusted life years gained (QALYs). A ratio of less than US$50,000 is usually considered cost effective [15]. Mar *et al* conducted a study in the Basque Country, Spain [16] to analyse the long-term cost-effectiveness of nasal continuous positive airway pressure (CPAP) treatment in comparison to conventional null treatment. A Markov model was used to represent the natural history of OSA based upon published evidence. Utility values came from a survey of OSA patients. Data on health costs were collected from hospitals. The incremental cost-effectiveness ratio of CPAP treatment was <6,000 Euros (equivalent to $US 5,000) per quality-adjusted life year. On disaggregated analysis, CPAP treatment accounted for 86% of incremental costs; 84% of incremental effectiveness was attributable to improved quality of life.

The key clinical benefit of CPAP treatment is improvement in the quality of life of patients with OSA, but some of the economic modelling [16] has suggested that the issues around less days off work, less motor vehicle accidents and possibly reduced cardiovascular risk all contribute to the compelling financial argument that moderate-severe OSA is a disease that is cost effective to treat. The remaining uncertainties concerning the impact of CPAP on long-term mortality have only a relatively small impact on the economics of treatment. It must be noted that these economic analyses have tended to focus on the economics of managing moderate-severe OSA.

Increasingly greater numbers of patients with mild disease and even simple snoring are presenting to sleep medicine services. For these the cost-benefit of treatment is less certain. The previous research focus on moderate-severe OSA has meant the evidence base for clinical efficacy and cost effectiveness of treating patients with mild disease is relatively lacking. A number of studies have shown small treatment benefits in mild OSA with CPAP and mandibular advancement splints (MAS). Barnes and co-workers reported the results of a randomised placebo controlled crossover trial using CPAP, MAS and placebo to treat mild OSA [17]. They saw improvements in quality of life and subjective sleepiness measures with both therapies, although neurocognitive changes were not greater than placebo using either therapy and there was no consistent therapeutic reduction in 24 hour blood pressure by either therapy [17]. Patients preferred CPAP over placebo but preferred MAS therapy over CPAP. CPAP was more successful at improving sleep indices and oxygen saturation. There remains much uncertainty as to the best approach for those with mild OSA, as currently there have not been studies that show improvement in 24 hour blood pressure, reduction of MVA risk and reduction in cardiovascular morbidity or mortality in those with mild OSA [3,9,17-19]. A recent meta-analysis [20] did show a small but statistically significant reduction in sleepiness using CPAP to treat mild OSA but the changes were of marginal clinical significance with a 1.2 unit reduction on the Epworth Sleepiness Scale (ESS), 2.1 minute fall in mean sleep latency on the Maintenance of Wakefulness Test). A recent Cochrane review commented that data demonstrating the morbidity of mild OSA and the efficacy of CPAP treatment in mild OSA are currently lacking [21]. It is however possible that by

simplifying the management pathways for moderate–severe OSA more laboratory and clinical resources will be available across the spectrum of OSA.

Given the high prevalence of OSA, its marked economic burden on the community, probable widespread under-recognition of the condition and the strong evidence, at least for moderate-severe OSA, for a cost-effective treatment there appears to be a strong economic rationale for increasing sleep medicine services for OSA.

1.1.4 The demand and supply for OSA services in Australia

The traditional method of diagnosing and managing OSA is by overnight diagnostic polysomnography (PSG, sleep laboratory study), followed by specialist advice, further PSG to assess the effectiveness of continuous positive airway pressure (CPAP) or other treatments and ongoing specialist review. This clinical pathway is generally considered the ideal or “gold standard” but there is a serious mismatch between this approach and the current clinical and public health realities with respect to OSA. Sleep laboratory facilities are expensive and limited mainly to tertiary referral centres and there are insufficient sleep study facilities and specialists to deal with the large clinical burden of OSA. There has been steady growth in PSG services in Australia over the last 15 years. This growth has been faster than the overall population growth and faster than the growth in Medicare funding for other diagnostic procedures and classes of medical interventions [22]. While these trends may appear striking, it is quite likely that the growth in diagnostic services may be insufficient to meet the burden of disease, particularly in the

setting of the international trend for increasing prevalence of obesity that is also affecting Australia [23-25]. The per capita provision of PSG and related sleep diagnostic services in Australia (308 per 100,000) is lower than recent estimates from Canada and the United States (370.4 and 427.0 per 100,000, respectively) [26].

In Australia, 68,000 PSG's were performed in 2004 [26]. If one assumes that 2/3 of these studies were for diagnosis, and that conservatively 3% of the adult population have symptomatic OSA requiring medical intervention, then diagnostic services in Australia are capable of investigating fewer than 10% of current cases in any one year. There is a further burden added each year as incident cases of OSA emerge. It is perhaps not surprising therefore that waiting times in Australia to review a newly referred sleep apnea patient in public and private facilities vary from approximately 2 to 6 months. With further delay for diagnostic and treatment PSG's it can take up to 1 or 2 years in some centres from initial referral to the successful establishment of treatment [26].

1.1.5 Epidemiology of OSA around the world.

In a review of the epidemiology of OSA, Young noted the estimated prevalence of OSA varied considerably in 3 main studies (Wisconsin, Pennsylvania and Spain) with very similar designs. For mild OSA (defined by AHI >5), prevalence estimates ranged from 3 to 28%; and for more significant OSA (defined by AHI >15), estimates ranged from 1 to 14% [4,27,28]. There may be distinct racial differences in OSA prevalence. Ip and co-workers reported an OSA prevalence of 25% (AHI >15) in a group of 784 office

workers from Hong Kong. Importantly this study also noted that whereas BMI and other measures of body habitus were associated with OSA the correlations were weaker than those seen in studies of caucasian subjects. It may be that other factors, such as craniofacial features that compromise the upper airway, might play a greater role in the pathogenesis of OSA in Asian populations [29]. Ancoli-Israel and co-workers studied community dwelling adults, age 65 years or greater, by in-home monitoring, and found that the odds of having an AHI of 30 or higher was 2.5 times greater in African-Americans relative to Caucasians, controlling for BMI and other confounding factors [30]. There have not yet been studies in the Australian aboriginal population, but given the high prevalence of metabolic syndrome in this group it is highly likely that there is a significant prevalence of OSA [31]. As obesity prevalence continues to increase in the western world and given the tight linkage between obesity and OSA, the prevalence of OSA is certain to be increasing [24]. Equally, as Western influences continue to emerge in the developing world it is highly likely that the prevalence of OSA will also increase in these cultures. Already the prevalence of OSA in a semi-urban community in Delhi among those aged 30 to 60 has been shown to be similar to the previously quoted prevalence data amongst Wisconsin public servants [32]. This is perhaps not surprising as the prevalence of obesity in North Indian urban slums has been demonstrated to be 28% [33]. As the prevalence of obesity and OSA both continue to grow in developing countries (and the Western world) there is a corresponding increasing need for simplified strategies to diagnose and treat OSA, as it is most unlikely that the resource

intensive and expensive North American traditional sleep medicine models will be widely available in these settings [34].

Perhaps even more concerning than current delays and blocks to OSA services is the under-recognition of OSA. Young *et al* estimated that in 1997 in the USA 93% of female and 82% of male OSA patients were undiagnosed [35]. Similar trends were recently reported for the over 15,000 subjects enrolled in the Sleep Heart Health Study where it was found that only 40% of subjects found to have OSA were previously diagnosed with sleep apnea, and only 30% of these patients were being currently treated [36]. This assertion was borne out by a later survey of people attending primary care practices, which showed that less than 3% of the cases of severe OSA identified in the study had been previously diagnosed [37]. There are no comparable statistics for Australian populations but it is likely the situation would be similar to that in the USA.

1.1.6 World trends in OSA services

Around the world there is great variability in access to sleep medicine services. In the private sector in some countries the wait can be very short. Waiting times in the public sector tend to be much longer [26]. The key statistic is the wait from referral to provision of CPAP therapy, as different services have different access issues. There can be delays at several levels in the management pathway: initial physician review, diagnostic PSG, physician reviewing the results, CPAP titration and then CPAP provision. In a 2004 study it was reported that the mean wait for CPAP provision in the United Kingdom was 14 months, in Canada 24 months, Australia 30 weeks, in

the USA only 20 weeks, but less than 2 months in Belgium [26]. There may also be considerable differences depending on service provision within countries. In Western Canada the overall wait for commencement of CPAP therapy was reported to be 24 months, but only 2-3 months in Ontario [5]. In the USA waiting times for CPAP provision have been reported to be longer in Veteran Administration hospitals than other hospitals [26]. Funding models clearly dictate availability of polysomnography as evidenced by the marked variation in the rate of sleep studies per year across Canada [26].

1.1.7 The historical development of clinical polysomnography

The introduction of clinical sleep laboratories was first seen in the 1970s in the USA [38]. Most of these laboratories evolved from either neurology or psychiatric services or clinical research programs. Sleep measurement was done very precisely and there was a significant focus on EEG measurement. However in time it became apparent that OSA was the most common sleep disorder presenting for clinical investigation and the discovery in 1981 of a simple, highly effective treatment, CPAP [39], markedly accelerated this trend. Because OSA is predominantly a breathing disorder, there has been increasing involvement of respiratory physicians in the field of sleep medicine and they now run most sleep laboratories around the world. In Australia sleep medicine is almost entirely led by respiratory-trained physicians. There are only two Royal Australasian College of Physicians sleep medicine accredited neurologists in Australia and no psychiatrists. Despite Australia not having a tradition of neurology and psychiatry in sleep medicine it has adopted the North American model of PSG-based laboratory investigation.

PSG's are complicated to set up and analyse. The measurement of sleep using EEG/EOG/EMG is a large part of that complexity. There is little doubt that EEG measurement during sleep can be very important, for example in the detection of nocturnal seizure disorders [40], however the vast bulk of PSGs in Australia and internationally are performed to assess OSA. It is reasonable to ask whether EEG/EMG/EOG measurements of sleep are really necessary in this context or do they simply add complexity and costs to the diagnosis, and limit availability of OSA assessment without providing much useful additional diagnostic information? Can simpler diagnostic methods (e.g. nasal flow measurement and/ or oxygen dips during sleep) be validated and used in a more cost effective way? In the United Kingdom, this has been the model adopted in the National Health Service, with some arguing sleep medicine funding should focus more on CPAP provision, education and follow up rather than OSA diagnosis [41], and on finding CPAP responsive disease, although no simple method has been proposed beyond an empirical trial of treatment [41].

1.1.8 Simplified diagnostic strategies for OSA

Both the American Thoracic Society and the American Academy of Sleep Medicine recommend supervised PSG to diagnose OSA and CPAP titration in the laboratory to commence CPAP [42,43]. Therefore, before adopting alternative models to diagnose OSA and commence CPAP, the strengths and weakness of these models against current best practice need to be critically reviewed. The important questions to be addressed are;

1. Can a questionnaire be devised that will diagnose OSA with acceptable sensitivity and specificity?

2. Can portable monitors diagnose OSA accurately? What are the true time and resource implications of using these devices?

3. Can CPAP be commenced in a less labour intensive way than full CPAP titration?

    a. Can Autotitrating CPAP (APAP) be used either to titrate CPAP and set a fixed CPAP pressure, or be used in APAP mode indefinitely thus abolishing the need for CPAP titration?

    b. What are the strengths and weaknesses of performing split diagnostic PSG and CPAP titration on the same night?

    c. Can an empirical algorithm model be used to estimate therapeutic CPAP and commence therapy?

4. What is the optimal mix of professional skills needed to manage OSA? Can nurse led models of care be utilised and is there an evidence base to support this?

5. Can new simplified packages of care for OSA patients be devised by incorporating some or all of the measures above, and will such models lead to acceptable patient outcomes?

Before the introduction of any new model of OSA diagnosis and treatment, careful consideration needs to be given to a) how this will affect service provision at all levels in the OSA management pathway, b) the health funding

models in the target population, and c) appropriate training of health professionals who will be involved in the care of those with OSA including physicians, general practitioners and nursing support staff.

1.1.8.1 Questionnaires

The Berlin Questionnaire was an outcome of the Conference on Sleep in Primary Care, which involved 120 U.S. and German pulmonary and primary care physicians and was held in April 1996 in Berlin, Germany. Questions were selected from the literature to elicit factors or behaviours that, across studies, consistently predicted the presence of sleep-disordered breathing. By consensus, the instrument focused on a limited set of known risk factors for sleep apnea. One introductory question and four follow-up questions concern snoring; three questions address daytime sleepiness, with a sub-question about sleepiness behind the wheel (that is, while driving a motor vehicle). One question concerns a history of high blood pressure. Patients are also asked to provide information on age, weight, height, sex, neck circumference, and ethnicity. Obesity was quantified by calculating body mass index from self-reported weight and height. In a study conducted in a primary care setting in the USA [37], being in the high-risk group determined according to the consensus scoring system predicted an RDI greater than 5 with a sensitivity of 0.86, a specificity of 0.77, a positive predictive value of 0.89, and a likelihood ratio of 3.79. However the Berlin questionnaire may not be as useful for identifying OSA amongst patients already referred to a sleep clinic. The main reason is the high pre test probability of OSA in those referred to a sleep clinic. It is likely that the referring doctor had already asked many of the

relevant questions prior to referral albeit in a less systematic fashion than in the questionnaire. It thus appears that the Berlin Questionnaire may be somewhat useful in primary care, but is less likely to be of value in a tertiary referral setting.

The multivariate apnea index (MAP) has shown similar results in sleep clinic populations. In a research setting it has been used to enrich the population to be studied and it has been shown to have good test-retest reliability (kappa 0.92) [44]. However, it is of questionable value in a tertiary referral setting. Gurubhagavatula and co-workers assessed the efficacy of a two stage process (MAP questionnaire and oximetry) in a group of patients already referred to a sleep laboratory and who were going on to have full PSG as part of their routine clinical care [45]. They found the questionnaire alone not to be very useful, enabling only 8% of patients to be spared full PSG, and concluded the high pre-test probability for OSA in their patient group (69%) reduced its utility. They also noted that the questionnaire might be more useful in primary care. However, the MAP questionnaire has not been systematically studied in primary care and like the Berlin Questionnaire probably contains too many questions for busy primary care doctors to administer (13 in total).

The Epworth Sleepiness Scale (ESS) has been shown to be a valid method of measuring daytime sleepiness, one of the cardinal symptoms adversely affecting quality of life in OSA [46,47]. The ESS is well validated, simple to perform and reproducible. However, it is a questionnaire which focuses on sleepiness and not other common symptoms of OSA such as snoring and

choking arousals. Furthermore, daytime sleepiness is a rather non-specific symptom [48,49]. Therefore the ESS is more useful as an adjunct to management rather than as a primary diagnostic tool in OSA.

1.1.8.2 Home studies to investigate sleep apnea

The performance of a wide variety of portable monitors of varying complexity were systematically reviewed in 2003 [50]. Four types of sleep study system are recognised:

Type 1. Full attended PSG (the gold standard).

Type 2. Less complex PSG but a minimum of 7 channels including EEG. Suitable for home testing and true AHI can be calculated because sleep is measured.

Type 3. Minimum of 4 channels, predominantly focused on cardiorespiratory measurement without EEG.

Type 4. 1-2 channels usually oxygen saturation and/or airflow.

Full home PSG (Type 2) potentially provides precise determination of OSA severity and allows other sleep disorders (e.g. periodic limb movements) to be excluded and full PSG remains the “gold standard” for sleep disorders investigation. However, equipment is expensive, application of transducers and electrodes requires a trained technician, there is an increased risk of losing data, and scoring of records remains manual and time consuming. Multi-channel (Type 3) respiratory monitors are less complex than PSG. However, they remain relatively expensive, and require considerable patient

education and explanation, and technical and medical expertise. Data loss remains a problem in up to 18% of cases [51]. Single or dual-channel (Type 4) monitors have potential advantages over other systems with respect to cost and simplicity but their diagnostic accuracy and reliability in the home environment has not been systematically studied.

In a review by Flemons *et al* [50] the limitations of the literature on portable sleep monitors were highlighted. It was noted that most groups had compared portable monitor vs. full PSG in an attended laboratory setting, and few had commented on the performance of the portable monitor in the unattended setting. Data loss was rarely described, but clearly can be an important issue. In a rural or remote setting where patients may travel for many hours to a central site to pick up and drop off the monitor, a high failure rate would be unacceptable, although might be less of a concern in an urban tertiary centre laboratory. It was also noted that the majority of studies used patient groups with few co-morbidities and there were only limited data in different ethnic groups, or in primary care. With an increasing focus on the identification of sleep apnea in primary care, the possibility of a lower pre-test probability of OSA in the test population, and its impact on the utility of portable diagnostic testing must be considered. For the same test parameters and likelihood ratios a lower pre-test probability will produce a much lower post-test probability and may significantly limit the usefulness of the test [52].

There are other limitations to be considered within regard to Type 3 and 4 monitors. The lack of sleep measurement frequently leads to using “lights out” as the start of recording time and “lights on” as the finish of recording time.

This opens up the possibility of long periods of wakefulness being included in data analysis thereby producing an erroneously low RDI. Slow oxygen saturation sampling rate was noted as a limitation of many older oximetry studies. Flemons *et al* concluded that given the limitations of previous research there is no one universally agreed ideal portable monitor type and the role of portable monitors in general in the diagnosis of OSA requires further study.

To assess the efficacy of portable sleep apnea monitors their technical strengths and limitations must be known, as must the environment the device will be used in. With regard to the latter point, two key questions should be addressed;

1. What is the pre-test probability of OSA in the group being investigated?

2. What tertiary level sleep laboratory back up services exist? For example, a Level 2 monitor produces at least 7 signals to be analysed by an experienced sleep technician and physician and thus has less appeal in a rural and remote area where these services may not exist. It should be noted, however, that in the information technology era it is relatively easy to transmit information via the internet to centralised laboratories for review. However, patient set up remains relatively complex and without skilled people to do this, a complex portable monitor may nevertheless remain an unrealistic option.

1.1.8.3 Manual versus automated scoring of sleep studies

The efficacy and cost effectiveness of non EEG based methods to diagnose OSA would likely be greatest if the severity of OSA could be determined using a computer generated automated analysis of the recorded signals. Most screening devices have such an algorithm, although the quality is variable. The key questions are: a) are they sufficiently accurate to enable the clinician to make important clinical decisions? b) How does their use influence patient outcomes? It is also important to assess how automated these algorithms really are. If time consuming manual interpretation of the recordings is also needed, their appeal and applicability are significantly reduced.

In a study reported by Calleja *et al* [51] manual scoring by an experienced sleep technician was compared to automated analysis of cardio respiratory parameters, without EEG measurement on 79 PSG records. There was a tendency for the automated analysis to considerably underscore the AHI (mean 10.4 vs 34.4 /h with manual scoring). This would lead to an unacceptable false negative rate in OSA diagnosis. Other studies have showed similar results. Fietze reported that automated analysis of the PSG using the Merlin system (Heinen & Loewenstein, Bad Ems, Germany) led to an underestimation of the respiratory disturbance index compared with manual PSG analysis by experienced sleep technicians. Using a cut-off of AHI >5 /hr for the diagnosis of OSAS, the sensitivity of Merlin with the automated analysis was 41% and the specificity 100%. With a cut-off of 15 /h, sensitivity and specificity rose to 91% and 100%. The mean AHI for the studies scored by the Merlin system was about 40% lower than manual PSG

analysis (AHI 17 vs. 24/hr) [53]. A recent concordance study conducted across laboratories in South Australia ranked automated scoring (Compumedics, Series E series, Melbourne, Australia) alongside the manual scoring of 50 experienced sleep technicians. The automated analysis for AHI measurement finished in 37th place in a group of about 50 participants (Dr A. Thornton, personal communication).The "gold standard by which these results were compared was the group mean AHI. A more recent study [54] that used automated analysis of full PSG showed the level of agreement between automated and experienced human scoring to be similar to that between experienced scorers for both sleep staging and AHI. Furthermore the level of agreement was similar to that obtained between scorers in the landmark Sleep Heart Health Study. Thus while the rather complicated and interpretative nature of respiratory event scoring, in particular hypopneas, makes it currently difficult for software to score as well as humans it seems possible that automated systems may in the future be able to score apneas and hypopneas as reliably as well-trained human scorers.

1.1.8.4 Oximetry compared with other ambulatory methods of diagnosis

The use of oximetry as a portable monitor to diagnose OSA has some appeal as oximetry is widely available, simple to operate, highly portable as the devices become smaller, relatively cheap, and automated analysis of data is relatively simple. Most groups who have used oximeters have used the diagnostic information to "rule in" OSA. The proportion of OSA cases that can be "ruled in" by oximetry varied widely in the studies reviewed by Flemons *et al* (32-98%, average approximately 55%) despite little variation in the

prevalence of OSA in the populations studied (40-60%) [55-57]. Oximetry may have less utility to “rule out” OSA, because the technique, as currently applied, lacks sensitivity to detect minor desaturations. What has become recently apparent however is that the “fidelity” of oximetry with respect to the detection of apnea/hypopnea-related desaturations, is critically dependent on the sampling rate and averaging process employed. Most oximeters will automatically revert to a slow sampling and averaging algorithm when used to collect data overnight. The studies mentioned above are cited because they relied solely on oximetry for diagnosis and they were judged as being of moderate to high quality in the recent international review of home monitoring. However, all but one used a slow sampling rate (6-12 seconds) which, because of under-sampling, tends to smooth-out and underestimate desaturation episodes. This limits the ability to confidently “rule in” and “rule out” disease. In fact the one study that used a 1-sec sampling rate showed that 89% of cases were able to be diagnosed (OSA both “ruled in” and “ruled out”) with an overall false positive rate of only 8% [58]. Few current commercially available oximeters will store SaO_2 at 1-2 sec intervals overnight, but many can be simply adapted to do by streaming on-line analogue saturation to an inexpensive data-logger.

1.1.9 Establishing patients with OSA on CPAP

Nasal CPAP is established as the most effective treatment for symptomatic moderate to severe OSA and long-term adherence to treatment in such cases has been reported to be 50-80% [59]. There is less convincing data concerning the efficacy of CPAP in those with mild OSA and variable and

generally sub-optimal CPAP compliance rates are reported in this patient group [19,60,61]. A number of studies have shown that patients with moderate-severe OSA are more compliant than those with mild OSA with the inference being that the more symptomatic a patient is, the more likely they are to tolerate CPAP [61-63]. A recent Cochrane review commented that the data demonstrating the morbidity of mild OSA and the efficacy of CPAP treatment in mild OSA are currently lacking [21].

The gold standard of establishing a CPAP pressure for long term usage is via a laboratory attended CPAP titration where an experienced sleep technician manually adjusts the CPAP pressure to abolish oxygen desaturation, apneas and hyponeas. This is a time consuming and resource intensive process. Laboratory access is often limited and data must be manually scored by a technician during the day and the results interpreted by a physician. There are potentially simpler ways to establish a CPAP pressure for use in the home. These include:

1. Perform split studies (diagnostic and CPAP titration) on the same night.

2. Use APAP devices in the home (unattended) and use data (eg. 90^{th} or 95^{th} centile pressure) to set a fixed CPAP pressure.

3. Use a validated clinical algorithm to set the fixed CPAP level.

4. Use APAP set in automatic mode to provide long term CPAP therapy and thus eliminate the need for a CPAP titration.

The merits and disadvantages of each of these approaches are discussed below.

1.1.9.1 Split studies

An alternative to save laboratory PSG time and resources is to split the PSG into 2 distinct parts [64]. In the first component, diagnostic information is collected. Subsequent to this, CPAP titration is commenced by the technician provided a pre-determined threshold for OSA severity has been met. This does raise the possibility that all stages of sleep may not be sampled, or sleep in all body positions not seen. Ideally supine REM sleep will be sampled prior to any CPAP study [64]. The appeal, however, is that by reducing manual CPAP titration studies, potentially more PSG beds for diagnostic studies can be freed up. Elshaug and colleagues reported a significant improvement of technical efficiency with this approach [65].

For the split study to be an efficacious use of resources, the following issues must be addressed;

(1) Do diagnostic PSG indices (sleep and respiratory) collected on a diagnostic sleep study agree with data collected on a full night study?

(2) Do CPAP pressures from manual titration on a split study protocol agree with full night manual CPAP titration?

(3) How many studies need repeating because OSA control is not achieved during the split CPAP titration?

(4) Are the outcomes for patients commenced on CPAP via a split PSG/CPAP protocol the same as those commenced on CPAP via manual titration in a separate full night study?

With regard to the PSG indices being the same on split study vs. full night study, Sanders *et al* [66] reviewed PSG data from the first half of 48 diagnostic PSGs and compared these indices to the full night PSG data collected on the same patient on the same night. No significant differences were found across a range of measures, with a significant difference noted in REM AHI only (49.1 vs. 44.1 p = 0.03) that may not be clinically significant. An unacceptably low negative predictive value (NPV) was noted for the AHI measurement collected on the first half on the study as compared to a full PSG where OSA was defined as an AHI >5 (NPV 63%) although the positive predictive value was good (92%). These data suggest that a split study might be better used to "rule in" OSA than to "rule out" OSA [67].

Do CPAP pressures from manual titration on a split study protocol agree with full night manual CPAP titration is another key question, and the answer is probably that they do not. Yashamiro *et al* investigated this with a study where a split study was done on the first night, then CPAP titration repeated over the following night [68]. It was of interest to note that the final CPAP pressure was significantly lower in the split night group vs. full night CPAP titration (8.8 vs. 10.3 cmH_2O p <0.001). Sub group analysis showed that the major contributor to this difference in CPAP pressure was in the group with AHI <20. There was no significant difference in recommended CPAP pressures using the two titration methods in patients with AHI >40. Sanders *et al* noted a similar significantly lower CPAP pressure on a split night study vs. subsequent full CPAP titration (10.6 $\pm$ 3.6 vs. 11.8 $\pm$ 3.6 cmH_2O p = 0.002) [66]. They also noted 15 of the 50 patients needed a different interface on their full night CPAP titration and 8 of the 50 patients (16%) were changed to bi-level PAP

on the full night study. Iber and co-workers [69] found an effective CPAP pressure was identified in 78% of CPAP patients following a split night protocol, with repeat CPAP studies being needed in the remainder. They reported a reduction in resource usage with the split night protocol.

1.1.9.2 Home Auto-adjusting CPAP to establish fixed therapeutic CPAP level

Auto-adjusting CPAP devices use flow sensors and algorithms to detect obstruction and adjust CPAP levels across the night or over months, depending on changing needs (e.g. sleep posture change, weight gain) [70]. They have been used to predict a therapeutic, fixed CPAP pressure. The use of these Auto-PAP devices was the subject of a American Academy of Sleep Medicine review, which concluded that Auto-PAP (APAP) can be effectively used to set a fixed CPAP pressure for long term CPAP usage [70]. Reassurance that an APAP technique can be used confidently to set a fixed CPAP pressure first requires that several important questions be satisfactorily addressed. These include:

(1) Does an APAP titration to set a CPAP level produce a similar CPAP pressure to that determined by a manual in-laboratory titration?

(2) Does this APAP titration pressure adequately control OSA? Is the AHI acceptably low after a period of time?

(3) Is the acceptance and adherence to CPAP in those with APAP titration similar to those who commence CPAP by manual titration?

(4) What APAP technology is used and what parameters are used to set a fixed CPAP pressure?

The studies summarized below help to answer some of these questions.

Lloberes *et al* compared pressures set during a partially attended APAP titration to those from a manual titration using a randomised crossover deign and found no difference in final pressures, with a mean APAP pressure of 10.3 cmH_20 vs. manual CPAP pressure 10.1 cmH_20 [71]. Stradling *et al* in a similar study [58], found APAP defined pressures and manual CPAP titration pressures to be very similar (APAP 8.2 cmH_20 manual 8.7 cmH_20). Series *et al* used 2 weeks of unattended APAP titration to fix a CPAP pressure, finding on subsequent review 38/40 patients had an AHI <10 on fixed CPAP on a follow up PSG [72]. Similarly, Teschler *et al* found a mean AHI of 2.5 on a fixed CPAP pressure the night after 2 nights of APAP to set the fixed pressure [73]. The same Auto-PAP technology (Autoset T ResMed, Sydney) and method to set the fixed CPAP level (i.e. 95^{th} centile CPAP pressure generated from the APAP) was used in the study reported in Chapter 3 of this thesis. Use of the 95^{th} centile pressure to set a fixed CPAP pressure was also backed by the study of Gagnadoux and co workers, who found an AHI <10 in 21/24 patients in a laboratory PSG 3 months after starting CPAP, after APAP derived 95^{th} centile pressure was used to set a fixed pressure [74].

Stradling noted in a randomized controlled parallel-group study that the acceptance and adherence of a group of patients who had their CPAP pressure set after APAP titration (unattended but in the laboratory) was slightly, although not significantly, greater than those who had their pressure

set by manual titration [75]. Acceptance in the APAP group was 73%, compared with 64% in the manual group, and 13 patients had discontinued CPAP after 6 weeks from the manual CPAP group compared with only 2 who had their pressure set via APAP. This same study showed equivalent changes in subjective sleepiness as measured by the Epworth sleepiness score in the 2 groups.

It must be noted that a number of these studies had some biases in selection of patients suitable for APAP titration, including the exclusion of patients with complicated medical illnesses. The optimal time needed on APAP to set a fixed CPAP pressure has also not been defined, although the Stradling data suggests that as little as 1 night may be all that is needed to achieve reasonable acceptance and adherence to CPAP [76].

1.1.9.3 Using a clinical algorithm to set the fixed CPAP level

There may well be other simpler ways to commence CPAP therapy than via initial titration. Masa and coworkers investigated another simpler approach to CPAP commencement [77]. 360 patients prescribed CPAP for symptomatic OSA were randomized into three groups: (*1*.) conventional overnight CPAP titration with polysomnographic verification of the efficacy of a final fixed pressure, (*2*.) one-night home autotitration to establish the subsequent fixed pressure, and (*3*.) use of an algorithm-derived fixed pressure and subsequent adjustment according to symptoms (such as continuing snoring). A variety of factors were monitored, but the primary outcomes were symptoms and a repeat PSG on CPAP at 12 weeks. This study found essentially no differences between the three CPAP study groups. The average CPAP pressure was 8.8,

9.1, and 8.4 cmH_2O, in the standard, autotitration and algorithm groups, respectively. The AHI was lowest in the autotitration group, and highest in the algorithm group, commensurate with the different mean pressures, but not significantly so. The arousal index at 12 weeks was effectively identical in the three groups. The Epworth Sleepiness Scale (ESS) values fell to the same levels, and other symptom measures, such as the SF-36, Functional Outcomes of Sleep Questionnaire and EuroQol, showed small and inconsistent differences between the groups. CPAP usage was similar, at 5.2, 5.3, and 5.2 hours/night, in the standard, autotitration, and algorithm groups, respectively.

Stradling *et al* assessed an algorithm to predict CPAP pressure, which was (0.048 x 4% oxygen desaturation dip-rate) + (0.128 x neck size in cm) + 2.1 and compared the CPAP pressure calculated vs. a reference CPAP pressure (average of 30 nights autoset CPAP pressure) [76]. This algorithm produced a small bias, overestimating CPAP pressure by 0.43 cmH_2O. This is not likely to be a clinically significant difference. He also noted considerable night-night variability in the Autoset CPAP pressure over the 30 nights. Hoffstein *et al* used a similar CPAP algorithm to set a fixed CPAP pressure, finding their equation predicted CPAP pressure to within $\pm$ 2 cm of that set by manual CPAP titration in 22/26 subjects [78].

It is important to note that manual titration, considered the gold standard for setting a CPAP pressure, represents only half to 1 full night of a patient trial with CPAP. Given the variability of OSA across multiple nights, this may not be sufficient to set a reliable long-term pressure. Chediak *et al* retrospectively

analysed night-to-night variability in the indices of sleep apnea in a group of 37 men who underwent consecutive polysomnograms (PSGs) in the evaluation of impotence. Fifty-seven percent of the subjects had an AHI >5 on the first PSG, whereas 70% met this criterion on the second study. On both PSGs, 49% of the subjects exhibited an AHI of >10. The AHI varied by 10 or more between the two PSGs in 32% of the cases. Using a threshold AHI of 5 or more to establish a diagnosis of sleep apnea, 22% of the subjects would not have been diagnosed by the first PSG, and the negative rate for the first PSG was 50% [79]. If OSA can vary night-night due to disease variability, different body positions or alcohol consumption, it is not surprising that there is also variability in CPAP pressure requirements over the first month of CPAP therapy [80], raising the question as to whether manual titration of CPAP should really be the gold standard method for commencing CPAP.

Stradling *et al* then went on to assess the clinical efficacy of commencing algorithm based CPAP using retrospective CPAP compliance data from their sleep medicine service [75]. The previous approach had been to use partially attended (in hospital but with ward nurses only responding to emergency calls) APAP pressure to set a fixed CPAP pressure. Comparison between these two groups revealed no significant differences in CPAP compliance (5.1 hrs/night in the algorithm CPAP group vs 5.2 hrs/night in the standard CPAP titration group) after 11 months. There was also no difference between the groups in ESS at 1 and 11 months.

1.1.9.4 Using auto-adjusting CPAP instead of fixed CPAP for long-term care

Another possibility for simplifying sleep services is to use APAP in continuous automatic mode for long term CPAP therapy. This would have the advantage of not needing to spend time and resources to titrate CPAP. Hukins assessed this issue with a single blind crossover trial using fixed pressure CPAP (set from laboratory based CPAP titration study) and APAP in 46 patients [81]. No significant differences were found between the groups in ESS or SF-36 measurements or CPAP compliance. There were less side effects reported and less mask leak in the APAP group (0.08 vs. 0.15 l/min p <0.001). This reduction in leak is likely a function of lower CPAP pressure being delivered over 2 months by the APAP device (7.5 vs. 11.0 cmH_2O p <0.001). These differences did not lead to better patient outcomes in this trial. Ayas and colleagues reported a meta-analysis of studies that assessed the use of APAP vs. fixed pressure CPAP (set by laboratory titration) representing a total of 282 patients. They found no difference in AHI, ESS or CPAP compliance between groups [82]. Again, there was a significantly lower CPAP pressure in the APAP groups of 2.2 cmH_20. More recently, West and co-workers assessed 3 different methods of commencing and using CPAP in patients with OSA (>10 dips/hr on overnight oximetry and ESS >9) [80]. They randomised their patient group to three CPAP treatment strategies.

1. 1 week of APAP to set a fixed CPAP pressure (using the 95^{th} centile pressure).

2. Use of an algorithm based on neck circumference and OSA severity.

3. Use of APAP set in automatic mode.

Outcomes were reviewed in 98 patients at 6 months. There was no significant difference in sleepiness between the three groups either subjectively, using the ESS or measured objectively with maintenance of wakefulness test (MWT). It should be noted that the mean sleep latency in all 3 groups on CPAP was 40 mins. This is surprising and raises the possibility that the MWT results might be limited by a ceiling effect. There were also no significant differences between the CPAP parameters measured after 6 months (residual AHI and leak). CPAP compliance was not significantly different between the 3 groups, but there were trends towards increasing compliance on long term APAP compared to fixed pressure and algorithm based CPAP therapies (5.5 vs. 4.9 vs. 4.0 hrs/night, p=0.23). It is possible that with larger numbers this result may have reached statistical significance. The authors concluded that there is no indication for continuous APAP, although if the study was underpowered there may nevertheless be undetected benefits. Given the known cost effectiveness of CPAP therapy it might be that small differences in CPAP compliance between groups might translate into clinically meaningful differences in patient outcomes over a longer time. This needs further consideration in a larger trial, as does the question of cost effectiveness of the devices given that APAP machines are currently about twice as expensive as standard fixed CPAP machines.

There may be subgroups of OSA patients that do better on APAP. Massie *et al* randomised patients needing higher CPAP pressures (> 10 cmH_2O on initial lab titration) in a single blind crossover design to either APAP or fixed

pressure CPAP and reviewed their outcomes after 6 weeks on each therapy. They found a small but statistically significant increase in CPAP compliance in the APAP group (35 mins/night p= 0.005) [83]. The vitality component of the SF-36 was also significantly higher in the APAP group after therapy. Again average CPAP pressure generated by the APAP machine was lower than the fixed pressure device set pressure. Other components of the SF-36 and the ESS were not significantly different between the two groups.

At this time the use of APAP as a continuous therapy for OSA cannot be justified. The results from these trials have not yet shown any definitive advantage for APAP with respect to important patient outcomes such as daytime sleepiness. Larger trials are needed, which should also include a careful health economic analysis. An important consideration is whether the extra initial expense of the APAP is justified by either better patient outcomes, or the need for less CPAP titration studies, both to set the initial CPAP pressure and to review CPAP pressure requirements if the patient's clinical circumstance change (change in weight, addition of sedating medications etc). APAP might be a good long term therapy but better data is needed.

1.1.9.5 Nurse led models of care

There is increasing interest in nursing led management pathways. Over recent years nurse practitioners and skilled nurse educators/specialist nurses have been used more and more in chronic disease areas such as diabetes and asthma. The efficacy of nurse-led programmes has been subjected mostly to qualitative review. Few of these health care models have been

stringently tested in randomised controlled trials. Some that have been are reviewed below.

New and co-workers reviewed the effectiveness of specialist nurse-led clinics for hypertension and hyperlipidemia provided for diabetic patients receiving hospital-based care [84]. Patients with diabetes and both hypertension and hyperlipidemia were randomised to either usual care or nurse-led clinics. The primary outcome was patients reaching pre-defined clinically acceptable results for both their blood pressure and serum lipids. The nurse-led clinics performed significantly better at achieving these targets than usual care.

Stromberg and colleagues reported a prospective 12-month evaluation of the effect of follow-up at a nurse-led heart failure clinic on mortality, morbidity and self-care behaviour for patients discharged after hospitalisation for heart failure [85]. Patients were randomly assigned to either follow-up at a nurse-led heart failure clinic or to usual care. There were fewer patients with events (death or admission) after 12 months in the intervention group compared to the control group and fewer deaths after 12 months ($p=0.005$). The intervention group had significantly higher self-care scores at 3 and 12 months compared to the control group. The investigators concluded that follow up after hospitalisation at a nurse-led heart failure clinic can improve survival and self-care behaviour in patients with heart failure as well as reduce the number of events, readmissions and days in hospital. The cost effectiveness of such an approach was not measured, although given these results it seems very likely to be a cost effective process.

One of the appealing aspects of developing nurse-led models of care in the area of OSA is that there is already a history of successful high level specialist nurse programs in respiratory medicine, specifically in the fields of asthma and home oxygen delivery. Madge and colleagues performed a prospective randomised control study of an asthma home management training programme in children [86]. They noted a significant decline in hospital readmission rate compared to usual care. The teaching programme included education, written information and telephone advice.

1.1.9.6 Medical workload issues, exploring clinical care by specialist nurses

When one considers the high prevalence of OSA and related sleep disorders, the likely rising burden of disease accompanying the obesity epidemic and the increasing community awareness of sleep disorders, it is clear that there are insufficient specialist respiratory physicians skilled in the management of sleep disorders to meet the clinical need. This is unlikely to change in the short term, even allowing for the possible introduction of smarter and more efficient technologies. Already in many services the delay in obtaining a sleep physician review is as great as or greater than that experienced in accessing PSG. Thus there needs to be consideration of who can “take up the slack”. Two options are specialist sleep medicine nurses and nurse practitioners or increased training and up-skilling of general practitioners. It is likely that both groups will be needed to manage the OSA burden of disease, perhaps increasingly with specialist physicians providing back up/training and being available to manage complex cases. In many sleep medicine services this

process is underway, but there has been little assessment of the patient outcomes under these new treatment models.

Studies have shown that intensive education and attention from skilled nurses improves CPAP adherence. It might be that this process involves supplying good quality written literature and phone support on top of existing education strategies [87,88]. Engleman noted that educational and support interventions have not been as rigorously evaluated as technological advancements, but also noted the difficulty in precisely analysing the impact of some of these programs [87]. High quality education in the form of targeted cognitive behaviour therapy may further increase CPAP acceptance and adherence [88]. Tomlinson and Gibson retrospectively reviewed 150 patients managed by nursing led investigation and CPAP treatment, including laboratory PSG and CPAP titration, and noted 79% of those patients prescribed CPAP continued to use CPAP at 3 months with a mean CPAP adherence of 5.2 hours/night [89]. It was not mentioned if there was any involvement of a respiratory/sleep physician in the process, e.g. offering advice or review of selected patients. It must also be noted that inclusion criteria for this nurse-led program included a significant degree of daytime sleepiness (ESS >10).

In developing new and simplified models of care for OSA it would seem logical to consider expanding the role of the specialist nurse. Specialist nurses and nurse practitioners are being increasingly used in disease management around the world. There are already many nurses in the area of sleep medicine whose skills are probably underutilized. The use of management protocols and a team approach, which would allow a specialist nurse to

review challenging cases with experienced sleep physicians in tertiary referral centres, would likely facilitate any move toward more intensive and autonomous involvement of nurses in OSA management. In time this might also facilitate the move toward more involvement of primary care health professionals in the management of OSA.

1.1.9.7 Testing simplified models of care for OSA

Most studies to date have reported on the effects of a single new technique that might improve efficiency of diagnosis or treatment or reduce cost. Few investigators have integrated several such measures into a simplified care model and subjected that model to critical evaluation. Mulgrew *et al* randomised 68 patients with a high pre-test probability of OSA (OSA defined as AHI >15 episodes/h) identified by sequential application of the Epworth Sleepiness Scale (ESS) score, Sleep Apnea Clinical Score, and overnight oximetry to either standard laboratory based care (PSG and CPAP titration) or a simplified model of care using diagnosis from home oximetry and APAP to set a fixed pressure and control OSA. The physician was integral to both models of care [90]. They found that after 3 months, there were no differences in the primary outcome, AHI on CPAP (median, 3.2 vs. 2.5; difference, 0.8/h [95% CI, -0.9 to 2.3], P = 0.31), between the PSG and ambulatory groups, or in the secondary outcomes, ESS score, or Sleep Apnea Quality of Life Index. Adherence to CPAP therapy was better in the ambulatory group than in the PSG group (median, 6.0 vs. 5.4 hrs/night; difference, -1.12 h/night [CI, -2.0 to 0.2], P = 0.021). It is important to note that this study was designed as a superiority trial and was not powered to demonstrate equivalence or non-

inferiority of the ambulatory versus laboratory models with respect to important quality of life and daytime sleepiness endpoints [91]. Thus the absence of a statistical difference for these parameters between the two models of care cannot be taken to infer that the models were equivalent or that the ambulatory model was not inferior to the laboratory-based model.

On the basis of their results, Mulgrew *et al* suggested a clinical algorithm for use in patients who have a high probability of obstructive sleep apnea, with the caveat that patients who do not fulfil the criteria for high probability in the diagnostic algorithm, or who do not respond appropriately to CPAP, should undergo PSG. They argued that in the context of scarce resources, their ambulatory approach provides an opportunity to expedite care for patients most in need of urgent treatment while conserving PSG resources.

A similar model of care was described by Flemons in a review in the New England Journal of Medicine in 2002 [92]. In this article he acknowledged the long waiting times and limited resources in many sleep laboratories and sleep medicine services. He described an algorithm used in his clinical service in Calgary. This model used intermediate or high neck circumference measurements, availability of full PSG and the presence of daytime symptoms to decide which clinical pathway to follow for each patient. The rationale for the use of neck circumference in such a model resulted from their previous work using neck circumference as a key component of a clinical prediction rule for OSA [93]. Such a model has appeal as an expedient measure if resources are limited. However, there was no outcome based data provided to justify choosing this or any other similar simplified model of care. The study

described in Chapter 3 was designed to help fill this gap in the literature and to provide high level evidence regarding a new, simplified model of care for moderate-severe OSA.

1.1.9.8 Summary of evidence on techniques used to simply the management of OSA

The literature suggests OSA is a prevalent condition with adverse outcomes if untreated and that the current models of care are not adequate to meet demand for services. From the reviewed evidence it seems that questionnaires to diagnose OSA have little use in a tertiary sleep medicine service where the pre-test probability of OSA in patients referred to such services is usually high. It must be noted, however, that clinical assessment of patients both by General Practitioners and Specialists prior to referral does involve clinical questions being used in the assessment of patients. There are portable monitors with varying degrees of complexity that can be used more to “rule in” OSA than to rule it out. While the use of APAP to set a fixed CPAP pressure has a reasonable evidence base, there is less certainty about continuous APAP therapy. Split studies and algorithm based CPAP commencement have strengths and weaknesses. There is an emerging evidence base that nurse led, protocol driven models of care are producing acceptable outcomes in chronic disease programs. There have thus far been very few attempts to combine separate measures such as ambulatory home sleep studies, home protocols for CPAP initiation, and increased nurse specialist involvement in care into a single, simplified diagnostic and management pathway for OSA and to subject this type of model to critical

evaluation. The studies reported in the remainder of this thesis aim to increase knowledge in this important area.

1.2 AIMS OF THESIS

A simpler approach to the diagnosis and management of OSA that will reduce current waiting lists and be more widely applicable, yet at the same time deliver outcomes for patients that are at least equivalent to the present “gold standard”, would likely be of major benefit in this field. The research described in this thesis aims to investigate the effectiveness and cost effectiveness of such a simplified model of care. The model of care compared with the “gold standard” of OSA management uses existing technologies and methods viz. home oximetry for diagnosis and home auto-adjusting CPAP device for initiation of treatment.

The first study (Chapter 2) was designed to test the utility of home oximetry to diagnose moderate-severe OSA. The decision to use overnight home pulse oximetry, rather than another type of OSA monitor, was based on several considerations.

(1) Oximetry is widely available in rural and urban Australia and is simple to operate, highly portable and relatively cheap.

(2) Fully automated computer programs are now available that report the frequency and severity of oxygen desaturation episodes in a matter of seconds or minutes on the following day.

(3) Study failure rate, because of data loss, has been reported to vary between about 7-10% with home oximetry [56,57]. This is likely less than with

more complex multi channel devices, although there are surprisingly few data to evaluate this assertion.

(4) When technical failure does occur it is relatively straight forward to repeat the test the following night.

(5) The reducing size and increasing portability of newer oximeters makes them a suitable and highly portable home diagnostic tool for OSA.

(6) Previous studies have suggested that by setting an appropriate cut-point, oximetry might be able to be used to “rule – in” moderate to severe OSA with a reasonably high degree of certainty (i.e. <5-10% false positive results) in a substantial proportion of patients presenting to sleep apnea clinics.

Having established the practicality of using oximetry in the home in patients naïve to sleep investigations and the most favourable cut-point in saturation dip rate that could be used to “rule in” moderate-severe OSA, the subsequent aim was to use this information in a randomised controlled trial (RCT) in patients with high a likelihood of moderate-severe OSA. This RCT study, the subject of Chapter 3, compared an ambulatory nurse-led model of CPAP treatment with the “gold standard” specialist-led model (i.e. additional in-laboratory PSG studies and hospital initiated CPAP treatment).

The inclusion of auto-adjusting CPAP (to set fixed CPAP levels) in the simplified model of care in the study outlined in Chapter 3 allowed this management arm to be entirely ambulatory. The particular auto-adjusting CPAP device (Autoset, ResMed, Sydney) used is one with the widest usage in Australia and thus all 3 investigating centres had familiarity with the device

and software. The performances of different APAP devices have not been definitively assessed head-head. There have been bench top comparison performed by Farre *et al* on 5 commercially available APAP devices which did show significant variability in the way the APAP devices responded to different breathing patterns [94]. Nolan *et al* assessed the efficacy of three different APAP devices (Autoset Spirit, Breas PV 10i and RemStar Auto) in a randomised crossover trial over a 4 week period. Mean pressure and patient compliance were significantly lower on the Breas PV 10i than on the other APAP devices [95]**.**

The potential advantage of using auto-adjusting CPAP is that such devices are becoming more widely available, are decreasing in price and can be used, for example, in rural or remote areas to commence patients on CPAP. Also, CPAP titration studies currently account for up 30-40% of all PSGs. Thus there is the potential to release significant sleep laboratory resources.

If the findings of study 2 established the effectiveness of these technologies (oximetry and home APAP titration) in the hands of a specialist nurse, it could free up substantial sleep physician and laboratory time for the assessment of complex or difficult sleep cases. Thus the RCT described in Chapter 3 was aimed at establishing the effectiveness of a simplified model of care and reducing the effects of the two major barriers to routine health care in OSA: i.e. limited access to sleep laboratory facilities and limited availability of sleep physician time.

Because of overall funding limitations for sleep services (e.g. UK) or pressure on existing specialist PSG and sleep physician services (e.g. Australia)

components of similar models have already been adopted as standard care in some centres. This has happened without first knowing that these technologies produce equally favourable outcomes for patients to PSG based-methods. Studies have been conducted which show that in the carefully controlled sleep laboratory environment, overnight oximetry and APAP can produce reasonably accurate predictions of sleep apnea severity and the therapeutic CPAP level. However, there are far fewer reports of the reliability of these methods used in the home environment and there are very few proper randomized-controlled studies that focus on medium to long-term patient outcomes such as excessive daytime sleepiness and quality of life.

Chapter 4 of this thesis explores the relationship between the level of CPAP compliance in patients with moderate-severe OSA and the response in several key outcome variables such as daytime sleepiness (ESS, MSLT), quality of life (Functional Outcomes of Sleep Quality (FOSQ) and SF36 questionnaires) and neurocognitive function. It is widely accepted that CPAP is the most efficacious therapy for moderate to severe OSA. What is less well understood is the dose-response curve of CPAP. Individuals exhibit wide variations in sleepiness and neurocognitive and performance measures in response to sleep deprivation [96]. Thus it is likely that for the same CPAP adherence (hrs/night), different patients will experience variable changes in daytime sleepiness and neurobehavioural measures. Weaver et al. went some of the way towards exploring this issue by performing a variety of quality of life, subjective and objective sleep measurements and neurocognitive measures [97]. They found a linear dose response curve for objective and subjective sleepiness measures, but the curve flattened at CPAP use of 7

hours per night for the quality of life measures. They also noted that even amongst those patients using CPAP for >7 hours per night at 3 months, only 30% of patients normalised their multiple sleep latency (MSLT) test results. Only 50% normalised their functional outcome of sleep questionnaire results. It may be that reversal of daytime sleepiness with CPAP might be limited by neural damage associated with exposure to long term hypoxia. In this setting CPAP could overcome sleep deprivation and fragmentation, but grey mater damage might mean that some daytime sleepiness remains [98]. An alternative hypothesis is that these patients present to sleep medicine clinics with multifactorial aetiologies of their daytime sleepiness and treating their OSA reverses only 1 component of this. These issues are furthered explored in Chapter 4.

CHAPTER 2 UTILITY OF A NEW HIGH SAMPLING RATE OXIMETER IN THE DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA IN ATTENDED AND UNATTENDED SETTINGS

2.1 INTRODUCTION

Obstructive Sleep apnea (OSA), a disorder with significant associated morbidity, was shown in 1991 to affect 4% of males and 2% of females between the ages of 30 and 60 years [7]. The prevalence of OSA has likely increased significantly in the last decade due to a sharp rise in obesity [23,99]. The traditional method used to diagnose OSA, and to help assess its severity, is to measure the numbers of apneas and hypopneas per hour of sleep by overnight attended polysomnography (PSG). Respiratory events and sleep stages are usually manually scored. PSG is thus labour and technology intensive, is generally limited to specialized centres and is rarely available in rural and remote areas.

As a result of the high prevalence of disease and the relative scarcity of diagnostic and treatment facilities, waiting times for PSG are frequently long and many patients remain undiagnosed [5]. Alternative strategies for OSA diagnosis and management are clearly needed. One option is the use of home diagnostic studies to complement laboratory studies. A recent systematic review concluded that while home-testing with portable monitors is conceptually appealing, evidence supporting this strategy is frequently lacking

[100]. Particularly lacking is information regarding the performance of such monitors in the home setting.

Oximetry has considerable theoretical appeal as a means of diagnosing OSA in the home. Oximeters are relatively inexpensive and are highly portable. The technology is widely used and understood by the medical profession, data collection is simple and results (i.e. desaturation rates) can be calculated automatically in minutes. The saving of resources by the use of oximeters to reduce the numbers of full PSGs performed has been suggested by other groups [55]. The use of oximetry in the diagnosis of OSA was systematically evaluated as part of the recent review of home monitoring for sleep apnea [100]. Two significant limitations of previous studies were highlighted. First, few studies reported the percentage of data collection failures in the home (unattended) setting, although the available evidence suggests it is less than for more for complex multi respiratory channel home monitoring devices [56,101]. Second, most previous studies used oximeters with limited memory storage capabilities. Sampling rates were limited and stored arterial oxygen saturation values were typically averaged over 6-12 seconds. As a result, oxygen desaturation patterns with such oximeters can be smoothed [57], the frequency of oxygen desaturation dips may be underestimated, and false negative studies are more likely. Newer oximeters with high sampling rates, shorter averaging times and greater storage capacities may reduce these problems [102,103]. However, in some patients, sleep-related upper airway obstructive events may have little if any effect on saturation. It is possible therefore that oximeters may be of greater use in “ruling in” rather than “ruling out” disease.

In this study we investigated the role of a relatively new oximeter that employs a fast sampling rate and an artefact minimization algorithm in the diagnosis of OSA. Our study population consisted of consecutive patients referred to a clinical sleep laboratory for diagnostic sleep study. Our first aim was to assess a) the level of agreement between oximetry desaturation dip rates and PSG defined apnea-hypopnea index and b) the diagnostic accuracy of oximetry desaturation rates in identifying OSA patients at two clinically relevant AHI cut-offs. This aim, we believed, was best achieved by comparing results during simultaneous overnight recordings in a controlled laboratory environment. Our second aim was to ascertain the technical adequacy of oximetry recordings performed at home.

The hypotheses underpinning the study were as follows. 1. Oximetry would have greater diagnostic utility in identifying patients with moderate to severe OSA than patients with mild disease. 2. A detection algorithm measuring minor desaturations (e.g. 2%) would have greatest diagnostic accuracy by virtue of its ability to detect hypopneas that minimally affect oxygen saturation. 3. A simple to use oximeter incorporating robust artefact correction would allow a high rate of technically successful home recordings.

2.2 METHODS

The study protocol was approved by the Research and Ethics Committee of the Repatriation General Hospital and all patients gave written informed consent.

2.2.1 Patient selection

We recruited 121 patients referred to the Adelaide Institute for Sleep Health with a clinical suspicion of OSA who met the following inclusion criteria: (1) 2 or more symptoms of OSA (snoring, observed apneas, excessive daytime sleepiness or choking arousals, (2) age 18-75 years (3) resting arterial oxygen saturation ≥92% whilst breathing room air (4) residence within 75 km of the sleep laboratory. Those with a history of a cerebrovascular accident in the last 12 months, unstable cardiac disease or previous laboratory or home monitoring investigations for sleep apnea were excluded. Because there were many more patients referred to the sleep laboratory than could be accommodated per week in the research study, recruitment was restricted to consecutive patients scheduled to have a diagnostic PSG in Bed 1 and 2 of the sleep laboratory on Mondays and Wednesdays.

2.2.2 Portable oximetry

The portable pulse oximeter used in this study (Masimo Radical, Masimo Corporation, Irvine, CA) is designed to sample at frequencies ranging from once per 2 seconds (0.5 Hz) to once per 10 seconds (0.1 Hz) and to store data from continuous recordings lasting up to 72 hours. In this study, the oximeter was set to average oxygen saturation and sample at 2 second

intervals. It can be powered by mains power or a battery with a life of 12 hours. Stored data can be downloaded as an ASCII file to a PC for subsequent analysis and display. The Masimo Radical proprietary signal extraction technology determines arterial oxygen saturation by separately identifying the arterial and venous blood signals and incorporating adaptive filters for noise cancellation.

2.2.3 Study design

Patients were asked to first attend the laboratory in the afternoon or early evening for an education session by a trained nurse on the use of the Masimo Radical oximeter. This was done either one-to-one or in a small group and took approximately 5 minutes. Patients were instructed to take the oximeter home and to commence recording from lights out after applying the oximeter finger probe, and to remove the probe and turn the oximeter off on rising the following morning. They then returned the oximeter to the laboratory for data download and analysis.

The following night, subjects attended the sleep laboratory and simultaneous supervised polysomnography and Masimo Radical oximetry recordings were made from lights out. The portable oximeter signal was displayed on the PSG monitoring screen as well as the standard laboratory PSG signal, and adjustments were made to the finger probe in the event of excess artefact or poor signal quality. Patients were instructed to take their usual alcohol and prescription medications on both nights and not to vary the quantity or dose. We constructed this protocol to try to replicate the way the oximetry test would be used in real world clinical practice (i.e. before the patients had a full PSG).

I could be argued by some that that the ideal way to perform these tests would be in random order, but that would give those having PSG first some familiarlity with the equipment and monitoring that would not occur if these tests (overnight oximetry) were being performed in clinical practice as stand alone tests.

Full attended PSG (Compumedics Series E, Melbourne, Australia) was performed including: two electroencephalograms (C4-A1 and C3-A2), electrooculograms, submental electromyogram, ECG, airflow at the nose (nasal pressure), chest and abdominal respiratory movement using inductance bands, oxygen saturation (pulse oximetry, Criticare oximeter Model 504, Wisconsin, USA set to an averaging time of 3 sec and sampled at 1 Hz), leg movement sensors, snoring microphone, and body position.

2.2.4 Data analysis

We used the 1999 AASM guidelines [104] for measuring and scoring sleep apneas and hypopneas. The AASM recommendation to use nasal pressure rather than oronasal temperature to measure airflow changes, and to include hypopnea events with less than 50% reduction of flow with either 3% desaturation or arousal, has led to generally higher AHI values than previously reported. BaHammam *et al* [105] reported the AHI to be 27% greater in patients who had their AHI calculated by nasal pressure compared with thermistors on the same night (44.4 ± 37 vs. 35.4 ± 31, $p < 0.001$). Comparable results were found in a similar study, where the AHI was again around 37% higher using nasal pressure compared with thermistors (AHI 37 vs. 27 events/hr) [106] The 1999 AASM report recommended AHI cut off

values of ≥ 5, ≥15, and ≥30/hr for classifications of mild, moderate and severe OSA respectively [104]. However, this classification arose from clinical and epidemiological studies which used older technologies and hypopnea definitions. Having used the more sensitive 1999 AASM-recommended methods to identify respiratory events we have chosen instead in this study to classify OSA as mild if AHI is ≥15/h and moderate to severe if AHI ≥30/h. We believe these classifications more accurately reflect the current state of clinical practice.

Masimo oximetry data were downloaded using Download 2001 software (Stowood Scientific, Oxford, UK) and >2, >3, and >4% oxygen desaturation dip-rates computed. The software defines a desaturation episode by measuring a desaturation (>2, >3 and >4%) followed by a resaturation to within 1% of the initial value. The total number of desaturation episodes are divided by total recording time to compute the desaturation index. An *a priori* criterion of at least 4 hours of technically satisfactory oximetry data was used to define a successful oximetry study.

All PSG's were staged by the same experienced technician blinded to the oximetry results using previously published consensus criteria for scoring respiratory events [104], arousals and sleep stages [107]. Airflow was assessed using nasal pressure except if this signal was of poor quality, in which case the sum of uncalibrated thoracic and abdominal effort signals was used.

2.2.5 Statistics

The agreement between home and laboratory oximetry dip rates and between laboratory oximetry dip-rate and PSG-defined AHI was assessed using Pearson correlation and Bland-Altman plots [108]. Receiver operator characteristic (ROC) curves were constructed from oxygen saturation dip rates obtained in the laboratory to determine the utility of oximetry to diagnose OSA defined by AHI cut rates of ≥15/h and ≥30/h. Separate ROC curves were constructed for >2%, >3%, >4% dip-rates to assess the effect of changes in the threshold used to define a desaturation episode on diagnostic utility. Areas under Receiver Operating Characteristic curves were compared using the method of DeLong *et al* (AccuROC version 2.5, Accumetric Corporation, Montreal, Canada). Likelihood ratios were calculated to determine the diagnostic usefulness of positive and negative oximetry results. For a positive result the likelihood ratio is calculated from the formula true positives/false positives, and for a negative result, true negatives/false negatives. A likelihood ratio > 10 for a positive result means that such a result will lead to a large increase in disease probability and a likelihood ratio < 0.1 for a negative result produces a large decrease in disease probability [52]. Student's t-test was used to compare home versus laboratory derived oximetry dip rates. A p value <0.05 was considered significant.

2.3 RESULTS

2.3.1 Study population

All patients who satisfied the inclusion/exclusion criteria were invited to participate. One patient refused and one was excluded because he was found to be hypoxemic at the time the oximeter was allocated. The anthropometric and PSG findings of the remaining 119 patients who completed the study are provided in Table 2.1. Patients were typical of a sleep apnea clinic population being predominantly male, obese and middle aged with just over one-third having moderate to severe disease (AHI ≥30/hr).

Table 2.1. Patient anthropometric characteristics and PSG data.

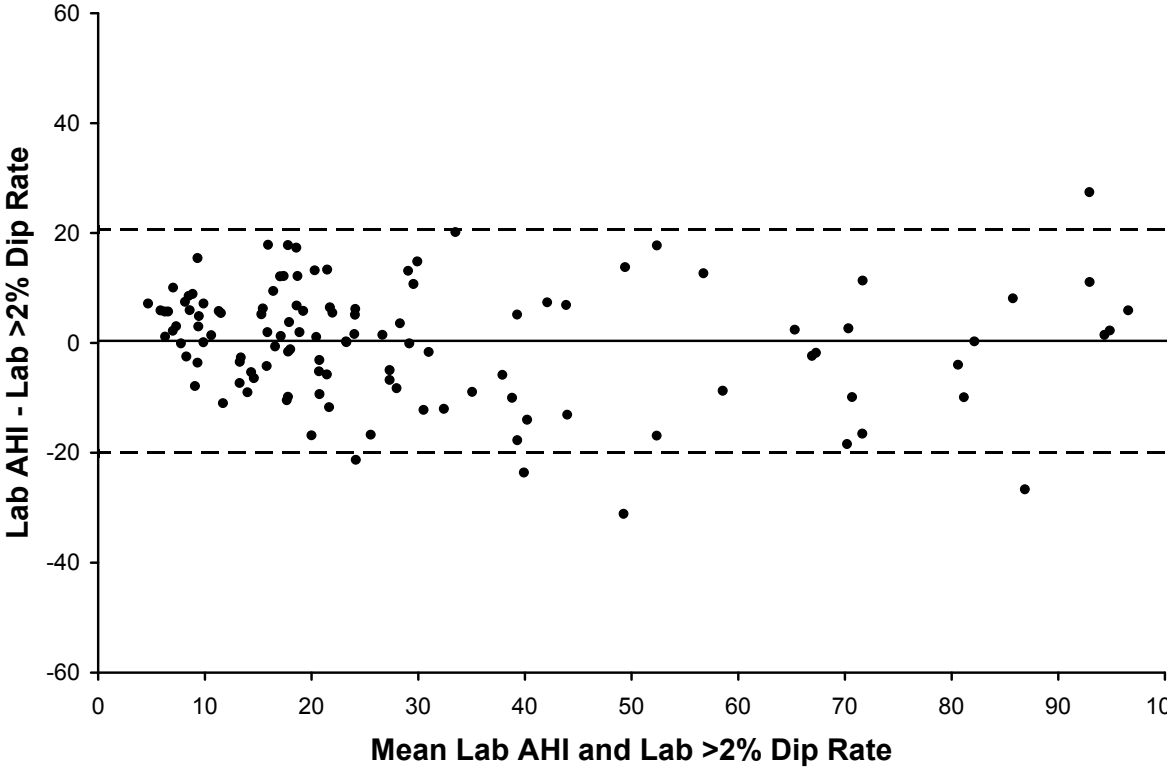
Males	73%
Females	27%
BMI (kg/m^2)	31.9 ± 5.9
Neck circumference (cms)	41.4 ± 3.6
ESS	9. 7 ± 5.0
Age (yrs)	51.2 ± 12.2
Total Sleep Time (mins)	306 ± 78.0
PSG-AHI (events/h of sleep)	32.2 ± 27.6
Proportion of population with AHI ≧15	68.1%
Proportion of population with AHI ≧30	36.1%

Values are means + SD, n=119

2.3.2 Agreement between Laboratory oximetry and PSG-defined respiratory events

The Bland Altman plot showed good agreement between the laboratory oximetry dip-rate and PSG derived AHI without evidence of significant bias across the range of OSA severity (figure 2.1). The Pearson correlation coefficient for oximetry dip rate (>2%) versus AHI was also high ($r = 0.93$, $p < 0.001$).

Figure 2.1. Bland-Altman plot Laboratory AHI vs. Laboratory >2% oximetry dip-rate



Bland-Altman plot of in laboratory PSG AHI versus in laboratory >2% oximetry dip rate. Horizontal lines indicate average bias and 2 SD limits of agreement. N=119.

2.3.3 Diagnostic usefulness of oximetry test results

The areas under the ROC curves for oximetry dip rates defined by desaturations of >2%, >3%, and > 4% are given in table 2.2. The ROC curves for oximetry > 2% dip rate for OSA defined as either AHI ≥ 15/h or AHI ≥ 30/h are shown in Figure 2.2. Areas under the AHI≥30/h ROC curves were significantly greater (p =0.03) than for AHI ≥15/h indicating superior diagnostic utility for moderate- severe OSA than for mild OSA. There were no significant differences between the areas under the ROC curves for >2%, >3% and >4% desaturation dip rates, indicating similar diagnostic utility between dip rates. For simplicity, all subsequent results are shown for >2% dip rates only. These reflect the current “Chicago Criteria” as they measure oxygen desaturations as $\geq$ 3 (i.e. the same as >2%)

Figure 2.2. Receiver Operator Characteristic Curves for >2% laboratory dip-rate where OSA is defined as AHI ≥ 15 and ≥30

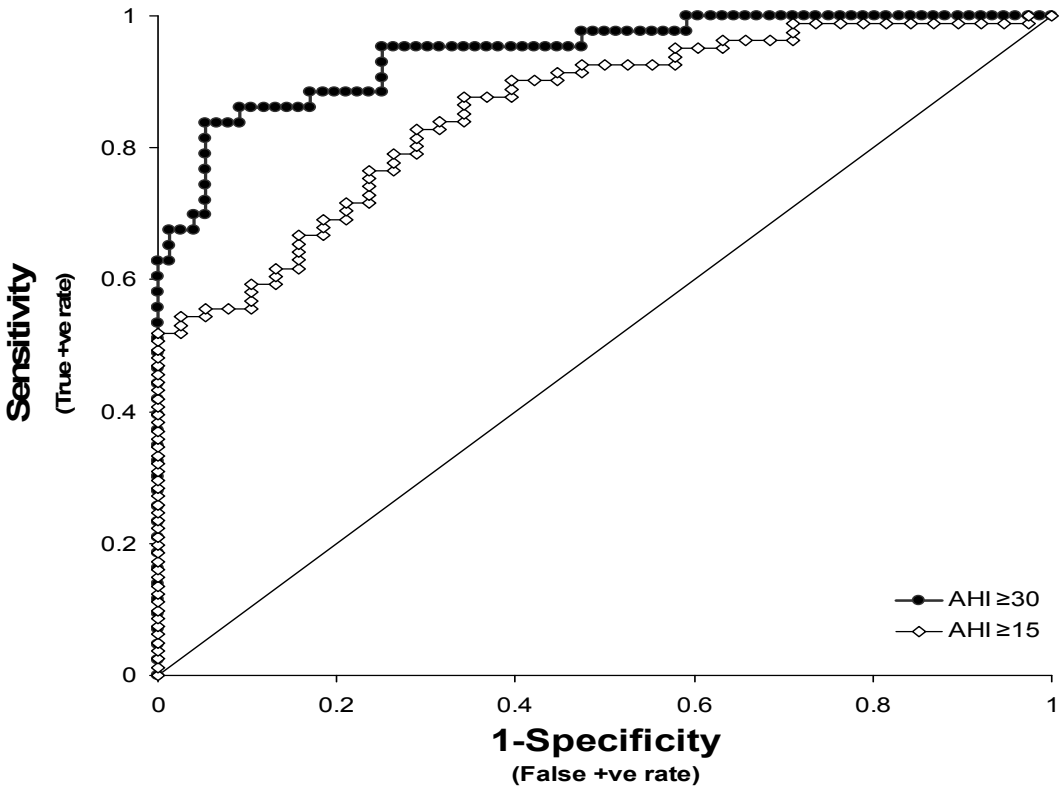


Table 2.2. Areas under the ROC curves ±SEM for oximetry using three different desaturation threshold values and two different OSA diagnostic cut points for AHI

	AHI ≥15/hr	**AHI ≥30/hr**
> 2% Dip-rate	0.86 ± 0.03*	0.94 ± 0.03*
> 3% Dip-rate	0.85 ± 0.02	0.95 ± 0.02*
> 4% Dip-rate	0.84 ± 0.02	0.95 ± 0.17*

*__AHI ≥15/hr__ vs. __AHI ≥30 p <0.05__

2.3.4 Diagnosing OSA using a single oximetry dip rate cut point

The sensitivities, specificities, positive and negative predictive values and positive and negative likelihood ratios for oximetry test cut offs corresponding to the optimum points on the ROC curves (i.e. the points nearest the top left hand corner of the Figure 2.2) are given in Table 2.3. Oximetry test classification using a single diagnostic cut-point had reasonable utility for diagnosing moderate to severe OSA (AHI ≥30). The optimal dip-rate of 27.4 /h identified 86% of cases (sensitivity 86%) with a specificity of 91%. The positive predictive value of a positive test result in this instance was high (84%), as was the positive likelihood ratio (9.3). In our clinic population there was a prevalence (i.e. pre-test probability) of moderate to severe OSA of 36%. Thus the post-test probability of disease, having returned a positive test result, would be 84% and represents a potentially useful change for clinical decision making [52]. The pre-test probability of not having moderate to severe OSA was 64%. The corresponding negative likelihood ratio of 0.15 was reasonably low and indicates that the post-test probability of not having disease, having returned a negative test result, is reduced to 21%, a potentially useful reduction for clinical decision making. Only 11% of cases were misclassified using this method, 7 false positives and 6 false negatives.

Oximetry, using a single desaturation rate cut-point, was on the other hand of limited use for diagnosing mild OSA (AHI ≥15) as given in Table 2.3. The single cut point nearest to the top left corner of the ROC curve (dip-rate 18.6 /hr) corresponded to a specificity and sensitivity of 76%. Thus it is more difficult to rule in or rule out mild OSA. Twenty four percent of patients were misclassified at this cut point.

Table 2.3. Ruling in and ruling out OSA using a single > 2% desaturation dip rate cut-point

	AHI ≥15	AHI ≥30
Optimal oximetry cut point (dips/hr)	18.6	27.3
Sensitivity	76%	86%
Specificity	76%	91%
PPV	86%	84%
NPV	61%	92%
+LR	3.2	9.3
-LR	0.31	0.15
True positives	52%	31%
True Negatives	24%	58%
% of patients misclassified (i.e. false + and false -)	24%	11%

Abbreviations

PPV positive predictive value

NPV Negative predictive value

+LR positive likelihood ratio

-LR Negative likelihood ratio

2.3.5 Increasing diagnostic certainty by using different oximetry dip rate cut-points to “rule in” and “rule out” OSA

We considered *a priori* that clinically useful high-certainty “rule in” and “rule out” cut points could be defined where, respectively, the false positive (1-specificity) and false negative (1-sensitivity) rates for the test were 5% or less. Table 2.4 summarizes the diagnostic performance of oximetry for mild OSA and for moderate-severe OSA using these “rule in” and “rule out” oximetry cut-points. For moderate-severe OSA 78% of patients were diagnosed (both with and without the disease) with a very high level of certainty (post-test probability of having disease if test is positive of 91% and post test probability of having disease if test is negative of 9%). The level of certainty when ruling out mild disease was less than for moderate-severe OSA as there was a 19% post-test probability of disease if the test was negative. However the post-test probability of having disease if the test was positive remained high (96%). Thus oximetry was better at “ruling in” rather than “ruling out” mild OSA.

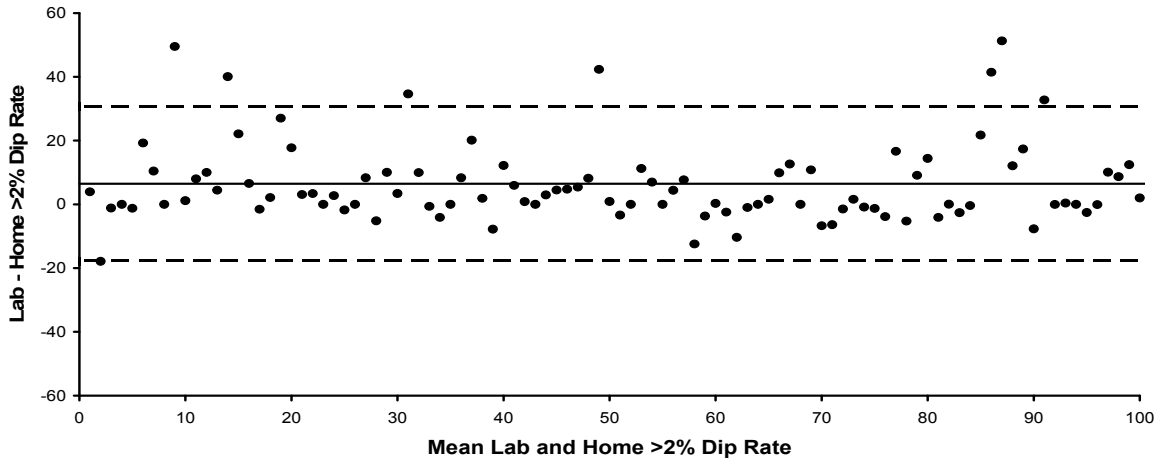
Table 2.4. Ruling in and Ruling out OSA using two different > 2% desaturation dip rate cut-points

	Rule in		Rule out	
Diagnostic Criteria for OSA	AHI ≥15	AHI ≥30	AHI ≥15	AHI ≥30
Optimal oximetry cut point	26.9 /hr	30.1 /hr	11.6 /hr	23.5 /hr
Sensitivity	55%	84%	95%	95%
Specificity	95%	96%	42%	75%
PPV	96%	90%	78%	68%
NPV	49%	91%	81%	97%
+LR	10.6	15.9	1.6	3.8
-LR	0.47	0.18	0.11	0.06
% of patients "ruled in"	38%	30%		
% of patients "ruled out"			13%	48%

2.3.6 Home oximetry – technical reliability and comparison with laboratory results

Oximetry was well performed in the home by patients. Data collection failed in only 2 patients (i.e. technical success rate 98%). Home and laboratory derived dip-rates were highly correlated (r 0.89, $p<0.001$ at the >2% dip-rate), although the Bland-Altman plot (Figure 2.3) showed the mean laboratory derived dip-rates to be approximately 5 dips/hr higher than home dip rates ($p=0.01$).

Figure 2.3. Bland-Altman plot Home dip-rate vs. Lab dip-rate



Laboratory and home oximetry oxygen desaturation dip-rates

2.4 DISCUSSION

The findings of this study add significantly to the existing literature on the use of oximetry in OSA and provide support for its more widespread use as a means of increasing access to diagnostic services and reducing costs. Oximetry dip rates were in close agreement with PSG-defined AHI during simultaneous laboratory recordings. Oximetry measurements had high diagnostic utility at ruling in and ruling out moderate-severe OSA. The area under the ROC curve for an AHI ≥30 was very high at 0.94, which compares favourably with other diagnostic tests in internal medicine. For example, various clinical models for predicting pulmonary embolism that are currently used in practice have produced areas under the ROC curve of 0.72 to 0.95 when compared with the gold standard for pulmonary embolism diagnosis, pulmonary angiography [109,110]. Oximetry data collection in the home by patients was robust with few failed studies and the automated oxygen saturation dip-rate calculations required minimal technician time.

As predicted, oximetry had greater diagnostic value “ruling in” and “ruling out” patients with moderate-severe OSA than it did in diagnosing patients with mild disease. It is important to note, however, that the AHI threshold of 30 events/ hour we used to define moderate-severe OSA was based on the Chicago criteria for measuring respiratory events, which is equivalent to an AHI of approximately 15-20 events/hour using earlier methods and the current US Medicare definitions for event scoring [54,104]. Thus it represents a highly relevant clinical definition of sleep disordered breathing. Patients who fall above this level of sleep disordered breathing are generally more

symptomatic [28], have a much greater risk of long term morbidity [9] and adhere to and benefit from CPAP therapy to a much greater extent [63] than do patients who fall below this level.

A number of studies have been published comparing the diagnostic utility of oximetry compared with PSG. The Flemons *et al* systematic review [100] reported that of these studies only two met Level 1 evidence criteria [55,102]. Both studies defined OSA at an AHI cut-off of ≥15 using thermistors to measure flow, and one of the studies [102] defined hypopneas as a reduction of flow associated with a ≥ 4% oxygen desaturation. Thus, their definition of OSA (i.e. AHI ≥15) is likely to have been similar to that used in the present study (AHI ≥30, Chicago criteria). Vasquez *et al* reported a sensitivity of 98% and specificity of 88%, with a positive LR ratio of 8.2 and negative LR of 0.04. Chiner *et al* found a similarly high specificity (93%) for oximetry but lower sensitivity of 63% with a positive LR of 8.9 and negative LR of 0.24 [55]. Our results comparing oximetry with PSG are in close agreement with these earlier studies but extend the findings by also investigating the reliability of oximetry recordings in the home.

The circumstances in which oximetry is applied are important to consider before deciding how best to use the results of our study. If one is practicing in an area without an existing sleep laboratory, it might be appropriate to use a single cut point (Table 2.3) to rule in or rule out OSA. This carries with it a greater risk that some patients will be misclassified. In our study 11% of moderate-severe OSA patients were misclassified, with 6% false positives and 5% false negatives. However, it is worthwhile considering further the

implications of this approach. We believe a 6% false positive rate to be acceptable, and likely includes patients with a lower but still clinically relevant AHI who are likely to benefit from therapy. Applying a safe treatment such as CPAP that may lead to some clinical benefit is not a great concern [19]. The impact of the small number of false negative studies (5%) could be further reduced by incorporating clinical review into the assessment. Oximetry test negative patients who are very sleepy could either proceed onto a definitive test (PSG) or alternatively undergo a trial of therapy. Either way, we consider the potential concerns regarding the small number of patients misclassified are outweighed by the benefits of accurate and more rapid assessment in approximately 90% of patients without the need for long waiting times and potentially large travel distances required for PSG. Such an approach might also be an ideal fit for the developing world, where, as western influences increase, the prevalence of obesity and OSA are increasing ahead of sleep laboratory facilities [32,33].

If the test is performed by a sleep clinic operating in an urban centre with an existing PSG facility, and the aim is to reduce a long PSG waiting list, the option exists to use two cut points as seen in Table 2.5. Here there is the opportunity to both “rule in” and “rule out” OSA in a high proportion of patients with a very high degree of clinical certainty. Positive cases could proceed directly to treatment, the negative case could be reassured they do not have OSA, and patients with indeterminate test results (in our clinic a manageable 22% of all patients) could be assessed on a case by case basis and referred on for full laboratory PSG assessment if clinical circumstances warranted (e.g.

significantly sleepy, commercial driver or significant co-morbid cardiovascular risk).

Our hypothesis that sensitivity-specificity analyses based on minor desaturations (e.g. >2%) would show greater diagnostic accuracy was not supported. This may indicate that minor hypopneas, that contribute to AHI with potentially minimal impact on oxygen saturation, remain undetected with >2% cut-off, or that the majority of events contributing to AHI are detected irrespective of the dip-rate cut-off. Strong correlation and close agreement between PSG-determined AHI and oximeter based >2% dip-rate suggests that the same events largely underlie both of these measures.

Oximetry data collection was very simple in this study. We found that patients who had never previously had a sleep study investigation were easily instructed in the use of the oximeter during a 5-minute session. Recording failures in the home were exceedingly rare, and review and download of oximetry data and automatic calculation of desaturation dip rate took only 5-10 minutes per patient. Our definition for a technically adequate study was that the oximetry recording should be signal artefact free for >4 hours. Less than 2% of studies performed in the unattended home setting were deemed a failure. This compares most favourably with other groups that have reported data collection loss to be 7-9% using oximetry in the unattended home setting [56,101]. It is possible that the artefact correction algorithm incorporated into the Masimo Radical oximeter contributed to the low failure rate.

The ease of data collection is most important as it likely contributes to a low failure rate and may enable the sleep health care professional to study a

number of patients in a short time frame, and to perform additional tasks such as patient introduction to CPAP. If data collection failures are common they decrease the efficiency and cost effectiveness of a home diagnostic service, with studies needing to be repeated. This is particularly problematic in rural and remote areas where patients may have travelled large distances for their test, only to need them repeated.

Bland-Altman plots and simple correlation statistics showed that the home and sleep laboratory oximetry recordings were in general in quite close agreement and were highly correlated. It was evident that the laboratory dip-rate recordings were somewhat higher than home dip-rates. The recording times for both measurements were the same (from lights out). With many electrodes attached during a diagnostic polysomnogram, patients often report that it is more comfortable to sleep on their back. This may have led to an increase in the laboratory dip rate compared to the home dip rate measurements since body position is known to affect the AHI [111] . Position sensors were not applied to the patient in the home setting so it is not possible to confirm this possibility; however, similar findings have been reported in other studies comparing home and laboratory PSG [112,113].

There are significant potential cost savings afforded by using home oximetry as a diagnostic test for OSA. Using two dip-rate cut-points to “rule in” and “rule out” OSA could save 78% of PSG’s from being performed. Applied to a referral base of 1,000 patients in Australia this would save approximately $403,260 in PSG costs (about $517 per test rebate from Health Insurance Commission of Australia). However 1,000 extra oximetry studies to assess

these patients need to be factored in. There is no Health Insurance Commission rebate for this test, but a similar rebate used calculates each oximetry study at $98 per test (i.e. $98,000 in oximetry studies over a year). Oximeters and software need initial purchase, at around $16,000 for 3 oximeters plus software. This calculation still leads to a cost saving of $289,260 per 1,000 studies performed.

2.4.1 Methodological limitations

There are some limitations worth considering in this study. We excluded patients who were hypoxemic (resting saturation <92%). However, only one patient was excluded on this basis. All our patients had been referred to a tertiary sleep laboratory with a clinical suspicion of OSA. As a result the pre-test probability for moderate-severe OSA was relatively high (36%), but was very similar to other published studies assessing portable monitors [100]. If the oximeter was used with the same cut-offs in a different setting such as general practice where the pre-test probability for moderate OSA would likely be lower, the post-test probability of OSA for the same likelihood ratios would fall significantly. Post-test probability would probably be lower again if the device was used to screen asymptomatic patients (e.g. pre-employment screening). To use the oximeter in these settings to rule in OSA would likely require a different cut point, one that had a higher specificity and therefore higher positive likelihood ratio. Incorporation of a questionnaire to increase the pre-test probability of OSA and/or a detailed clinical examination may add to the assessment process in these circumstances.

Patients had to make two trips to the laboratory, one to pick up and another to return the oximeter. It might be possible to have the oximeter delivered to the patient but this would add cost and one to one education would not be possible which could lead to more data collection failures.

2.4.2 Conclusion

Our study has shown oximetry has the potential to “rule in” and “rule out” moderate-severe OSA with a high degree of certainty in most patients referred to a tertiary sleep clinic. It seems important to have an oximeter with a high sampling rate (0.5-1 Hertz) although we did not assess more than one oximeter in this study Oximetry has less diagnostic utility in patients with mild OSA. We do not foresee oximetry replacing full PSG where such facilities already exist, but rather as a procedure that has the potential to significantly shorten existing waiting lists and reduce costs. However, in countries or regions that do not currently have PSG laboratory services, home overnight oximetry may be a cost-effective stand-alone alternative means of diagnosis. An important task in sleep clinics is the early identification and treatment of patients with moderate to severe OSA. Such patients generally have the greatest morbidity and respond best to treatments such as CPAP [114]. Thus oximetry could be used to substantially improve access to diagnostic services for most patients, whilst reducing health care expenditure.

CHAPTER 3 A RANDOMISED CONTROLLED TRIAL OF SIMPLIFIED DIAGNOSIS AND NURSE LED CARE FOR OBSTRUCTIVE SLEEP APNEA

3.1 INTRODUCTION

Obstructive sleep apnea (OSA) is characterised by snoring, repetitive upper airway obstructions, oxygen desaturation episodes, arousals from sleep and by excessive daytime sleepiness. OSA increases the risk of motor vehicle accidents, hypertension, and possibly stroke and heart failure [1-3,7]. Some of these risks can be reduced by continuous positive airway pressure (CPAP) treatment [3,9]. More cost-effective clinical pathways of investigation and treatment are required to match the increased demand for services that is resulting from increasing public awareness of OSA. Pack, in a review article in 2004 [5] noted;

> *"With the increased recognition of sleep apnea, systems for delivering diagnosis and treatment are overwhelmed. Physicians are trying to cope but, even with creative approaches, waiting lists for diagnosis and treatment are unacceptably long. There is a need to rethink current strategies".*

In the early 1990's the prevalence of symptomatic OSA in developed countries as assessed by an apnea-hypopnea index (AHI) >5 per hour, plus chronic daytime sleepiness in adults, was found to be approximately 3-4% for

men and 2% for women [7,115]. Whilst more recent prevalence studies in these populations are lacking, it is almost certain that the prevalence of OSA has increased in parallel with the rise in obesity [23-25]. The prevalence of OSA in developing countries has recently been shown to be similar to early estimates for developed countries, and will likely climb rapidly with the increasing adoption of western lifestyles [32].

In many countries, when OSA is suspected the usual practice is to refer the patient to a specialist physician at a sleep centre for clinical assessment and attended overnight, laboratory-based polysomnography (PSG). If OSA is confirmed the patient mostly returns to the laboratory for another PSG to determine the therapeutic CPAP level although, if the AHI is high, therapeutic CPAP level may be tested in the second half of the diagnostic study i.e. ”split study”. The patient is subsequently reviewed by a physician and a CPAP nurse or technician involved for the commencement of treatment. Even in developed countries this clinical pathway is often quite drawn out due to a relative scarcity of qualified personnel and laboratory facilities. In 2004 it was reported that the mean wait from referral to CPAP provision for OSA patients in the United Kingdom was 14 months, in Canada 24 months and Australia 7-8 months [26]. In developing countries such as China and India the situation is considerably worse with services being sparse or non-existent in most regions. Scarce health resources and a large and rising burden of disease mean that unless simpler, more cost-effective management strategies are developed, many patients with OSA will be denied effective treatment.

A number of strategies to assist in the earlier detection and treatment of OSA have been suggested but have either not been properly evaluated or not widely accepted. Home diagnosis using simplified portable respiratory monitors, some combined with automated scoring algorithms to reduce labour-intensive data analysis, has been suggested as an alternative to PSG. However, the quality of many of the studies designed to evaluate the accuracy of such devices has been brought into question [50]. Very few studies have tested the reliability of these monitors in the home and virtually no studies have compared patient outcomes when clinical decisions were based on the findings of portable monitors versus PSG. Home-based, auto-adjusting methods of CPAP titration (APAP) have been more thoroughly assessed with respect to patient outcomes and have generally been found to produce similar results to in-laboratory manual titration [58,70,78]. The use of APAP to titrate CPAP has, however, not been universally adopted. Many studies have excluded patients with co-morbid illness raising questions about the generalisability of results. Setting CPAP pressure empirically using a predictive equation has also been reported but without long term patient outcome follow up data [76]. Ways of overcoming physician workforce shortages in sleep apnea services have not been systematically studied. A nurse led model of care in OSA management has been described [89], but was not subjected to randomised controlled trial evaluation. In other chronic diseases (e.g. heart failure and asthma) protocol-based specialist nurse care models have proven to be highly effective [85,86] and anecdotal evidence is that the skills of sleep nurses and technicians can be harnessed to markedly improve CPAP treatment outcomes for OSA patients [87].

The present study was designed as a randomised controlled study in which a package of care incorporating each of these newer management strategies (simplified home diagnosis, CPAP titration with APAP to set a fixed CPAP pressure and overall care supervised by a specialist nurse) was compared with the more traditional physician-directed, in-laboratory PSG, hospital-based program of care. We used oximetry for home OSA diagnosis, as we had previously evaluated this and found it to have reasonably high diagnostic utility in "ruling in" moderate to severe OSA (see Chapter 2) [116].

3.2 METHODS

The study was conducted as a randomised controlled open-labelled non-inferiority clinical trial. Patients were recruited at 3 separate sleep medicine services, the Adelaide Institute for Sleep Health (Adelaide, SA Australia), Alfred Hospital (Melbourne, Victoria Australia) and John Hunter Hospital (Newcastle, NSW Australia). Approval was granted by the Ethics Committee at each site and the study was registered with the Australian Clinical Trials Registry.

3.2.1 Participants

Referrals to the sleep medicine services at all 3 sites were reviewed. Patients referred with a clinical suspicion of OSA were interviewed to assess their eligibility for the trial. Inclusion criteria were (a) Epworth Sleepiness Scale (ESS) $\geq$8, (b) history of snoring "most nights" or "every night", (c) age 18-75 years and (d) patient willing to trial CPAP. We excluded patients with (a) unstable cardiovascular diseases (e.g. recent unstable angina, myocardial

infarction, stroke or TIA within the previous 6 months or severe left ventricular failure), (b) neuromuscular disease affecting or potentially affecting respiratory muscles, (c) moderate to severe respiratory disease (i.e. breathlessness affecting activities of daily living) or documented hypoxemia or awake SaO_2 <92% or (d) psychiatric disease that limited the ability to give informed consent or complete the study. Patients were recruited between March 2004 and September 2006 and followed for 3 months after randomisation.

3.2.2 Interventions

3.2.2.1 Home oximetry

All patients who met these criteria and consented to the study had overnight home oximetry (Masimo Radical oximeter, Masimo, Irvine California, USA). The oximeter was set to average, acquire and store finger SaO_2 data at 2-sec intervals. The stored oximetry data was reviewed the following day to remove artefact and analysed using commercial software (Download 2001, Stowood Scientific Oxford, Stowood Scientific UK) to produce >2% dip rates for SaO_2. If the patient had a dip-rate of >27 /hr at the >2% level they were randomised into one of the 2 arms of clinical care. This dip-rate cut-point was established in a preliminary study reported in Chapter 3 [116] to give the highest diagnostic sensitivity for moderate to severe OSA (PSG-determined AHI $\geq$30) while keeping the false positive rate at 10% or less. This corresponded to a positive predictive value for the test of 92% and positive likelihood ratio of 9.3.

Model A (the simplified nurse-led model of care) was supervised by a specialist nurse experienced in sleep disorders and the management of CPAP patients. Home Auto-titrating CPAP (Autoset T, ResMed, Sydney, Australia)

was used for 4 consecutive nights in the patient's home. The Autotitrating mode was set between 4 and 20 cms H_2O. The CPAP machine data was downloaded to a computer, reviewed by the specialist nurse and the median 95th centile CPAP pressure for the 4 days recorded. This was determined *a priori* to be the appropriate fixed CPAP pressure for Model A. The nurse then converted the patient to a fixed CPAP device (S6 Elite lightweight ResMed), with in-built compliance meter and optional humidifier, and set the pressure accordingly. The nurse dealt with CPAP complications as appropriate (e.g. initiated humidification or nasal steroids, or changed masks) under protocol. Patients who failed or refused CPAP during the trial period were referred to a sleep specialist for further advice and initiation of alternative treatments as appropriate. The patients were seen routinely at set up and again at 1 and 3 months. Phone consultation and extra reviews were possible at the discretion of the nurse.

Model B (traditional physician-directed care) consisted of full laboratory PSG to confirm the diagnosis of OSA and identify any additional sleep disorder (e.g. periodic limb movements of sleep). CPAP was the primary treatment recommendation and manual laboratory CPAP titration during PSG was undertaken the night after the diagnostic PSG. Sleep specialists (12 overall and at least 3 in each centre) supervised and reported the PSG's, interviewed and examined the patient, and prescribed the CPAP pressure. The timing of physician follow up after CPAP was decided by the responsible physician. There was no restriction placed on the physician and they were free to diagnose and treat co-morbidities during the trial (e.g. PSG diagnosed periodic limb movements of sleep) whereas the Nurse in Model A was

restricted to protocol based management. Usual nursing CPAP support was offered in Model B (independent of the Model A nurse) to set patients up on CPAP after their CPAP PSG titration, and review at 1 and 3 months.

PSG's were conducted using Compumedics E Series equipment (Melbourne, Australia) at the Adelaide and Melbourne sites. The Newcastle site used Sensormedics equipment (Sydney, Australia) and had data transferred to an EDF file to enable conversion to a Compumedics file for review. PSG included a standard sleep montage: EEG, EMG, EOG and respiratory signals of thoracic and abdominal effort and their sum (inductance coils), nasal airflow (pressure transducer) and oximetry. PSG records were transferred to the Adelaide site for scoring by a single experienced sleep technician. Sleep architecture was scored in the standard fashion [107] and sleep apneas and hypopneas scored using recently agreed international standards and definitions [104].

In both arms of care extra nursing consultations and phone advice were possible. The time to complete these extra consults was recorded. The same fixed pressure CPAP machine was used in Models A and B. Additional investigations, treatments or advice for OSA or other coexisting sleep disorders were recommended at the discretion of the treating specialist. The investigation and management of these two arms of care were conducted over equal time periods.

3.2.3 Objectives

We set out to answer the question “Can a simplified model of care produce outcomes that are not inferior to current best practice for diagnosis and management of moderate-severe OSA?”

3.2.4 Outcome measures

The primary endpoint was the change in Epworth Sleepiness Score (ESS) as measured before and after 3 months of CPAP therapy [46,47]. Several secondary outcome measures were also collected as follows: 1. Short Form 36 (SF-36). The SF-36 score has been used widely in OSA studies [83,117,118]. Subscales in the SF-36 of mental health and vitality were separately analysed as these have been shown to be the most sensitive to CPAP therapy in previous randomised controlled trials [118]. 2. Functional Outcomes of Sleep Questionnaire (FOS-Q). This is a sleep specific self-report questionnaire designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living. It has excellent internal validity and test-retest reliability [119]. 3. CPAP adherence as measured objectively by in-built CPAP meter for the 3 month duration of the trial. 4. Maintenance of Wakefulness Test (MWT) after 3 months of therapy [120]. The MWT was performed only at the conclusion of the study as it was felt that to ask the patients to do this test also at the beginning of the study would have adversely affected recruitment, particularly given the other complexities of data collection. 5. Detailed neurocognitive testing before and after 3 months of CPAP using Brain Resource Company Integneuro testing via a touch screen computer with linked headphone set to provide instructions (BRC, Sydney

Australia). 6. A questionnaire of general patient satisfaction with investigation and treatment (VSQ-9) [121]. This questionnaire consists of 9 items corresponding to different aspects of the patient's experience, such as office waiting time, amount of time spent with the health care provider, and personal manner of the health care provider. Items are rated on a 5-point scale from poor to excellent.

3.2.5 Sample size

The study was powered to demonstrate non-inferiority of nurse-led management compared to specialist directed care with respect to change in ESS, the primary outcome measure. A sample size of 86 patients in each group achieves 90% power to detect non-inferiority using a one-sided, two-sample t-test. The margin of equivalence was set at 2, i.e. a difference of this size or less on the ESS scale was not considered to be clinically important. The true difference between the means was assumed to be 0. The one-sided significance level (alpha) of the test was set at 0.025. It was assumed that the common standard deviation for change in ESS in moderate-severe OSA is 4 [122]. In order to allow for 10% drop-out over the course of the study, we aimed to recruit 100 patients in each group.

3.2.6 Randomisation

The randomisation sequence was undertaken by a third party not involved in the trial at any investigating centre. Block randomisation within each centre was used with a block size of 20. Patients were randomised to one of two models of Care: Model A and Model B (Figure 3.1).

3.2.7 Allocation concealment and blinding

All the questionnaires and measurements were administered by research assistants who had no involvement in the clinical care of the patients and who were blinded to group allocation.

3.2.8 Statistical analysis

Primary statistical analysis was a comparison of change scores at three months between groups using an independent samples t-test. The lower limit of the two-sided 95% Confidence Intervals was used to determine non-inferiority. Data were analysed with patients assigned to their randomised group, with no attempt to adjust for compliance.

3.3 RESULTS

3.3.1 Participant flow

The patients' pathway through the clinical trial is summarised in Figure 3.2. Once patients were contacted and gave informed consent, 195 of 882 met inclusion and exclusion criteria. The majority of those who were not eligible for the trial (424) did not have an oximetry dip-rate of >27 dips/hr. All patients that were excluded were returned to their same position on the sleep clinic waiting list to be reviewed at a later date.

Figure 3.1. Design of Clinical Trial

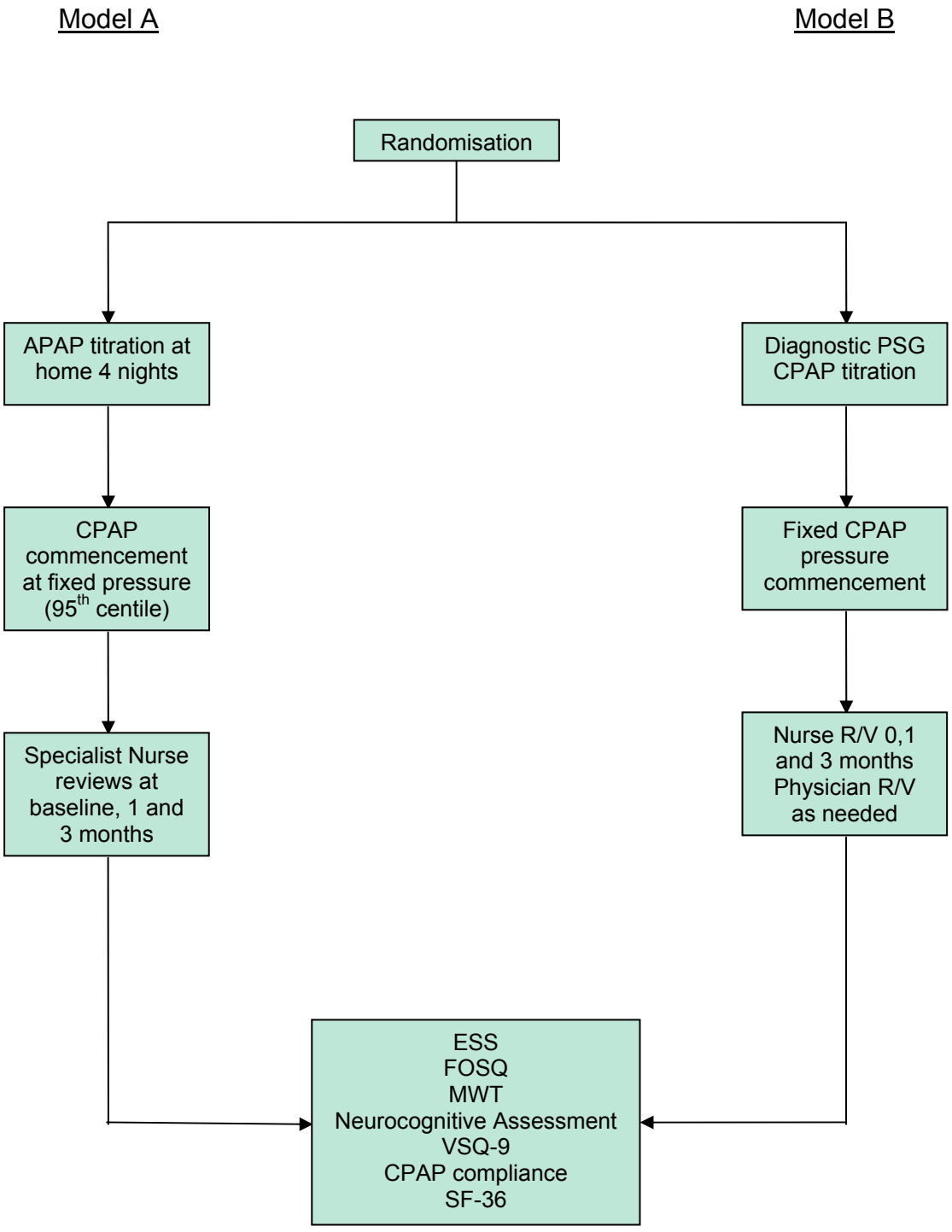
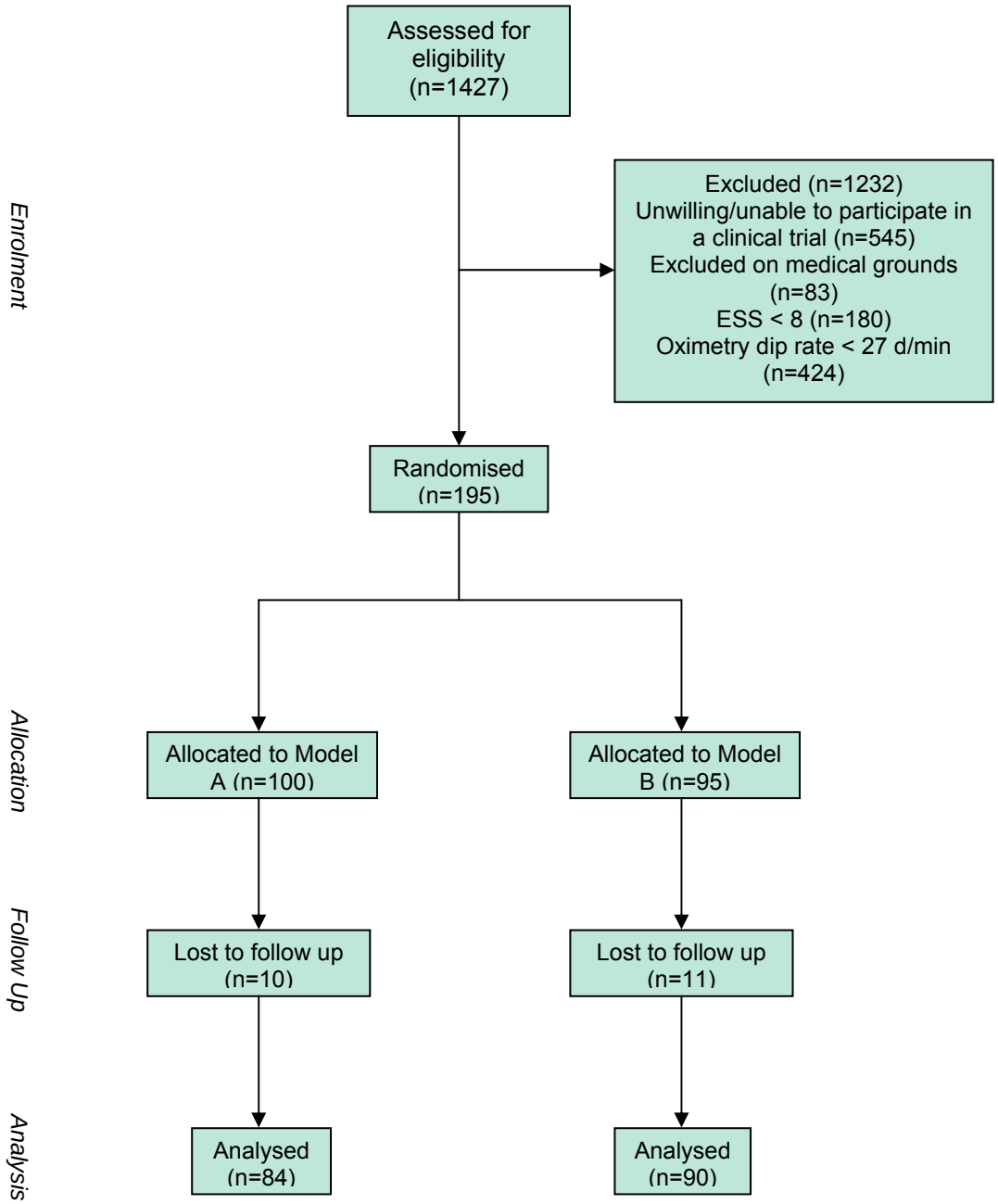


Figure 3.2. Study Flow Diagram



3.3.2 Baseline data

195 patients were randomised to the two arms of care. Key anthropometric variables are summarised in Table 3.1. These results confirm that the characteristics of the patient population were typical of those with moderate-severe OSA and that the two groups were similar at baseline with respect to key anthropometric variables.

Table 3.1. Group characteristics at baseline.

	Model A (Nurse led) (n=100)	Model B (Specialist led) (n =95)
ESS	13.7 ± 0.4	13.4 ± 0.4
BMI	35.1 ± 0.7	34.0 ± 0.6
>2% dip-rate	49.2 ± 2.1	52.5 ± 2.7
Age	49.9 ± 1.2	50.3 ± 1.3
Neck circumference	44.1 ± 0.4	44.0 ± 0.4
% males	72%	76%
% Females	28%	24%

Values are means ± SEM, unless otherwise indicated.

3.3.3 Outcomes

3.3.3.1 Daytime sleepiness (ESS and MWT)

The primary outcome measure of change in ESS for nurse led management (Model A) was not inferior to the specialist managed led service (Model B) since the lower limit of the two-sided 95% CI did not include -2, the margin of equivalence (Table 3.2).

There was no significant difference in mean sleep latency as measured by MWT protocol providing confirmatory objective evidence that daytime sleepiness after CPAP was not different between the 2 groups.

3.3.3.2 Quality of Life (FOS-Q, SF-36 including Energy Vitality and Mental Health)

There were no significant differences between Model A and Model B after 3 months of CPAP in any of the quality of life indices (Table 3.2). These included total FOS-Q score after treatment, and change in FOS-Q score after therapy (post-pre). SF-36 scores were analysed as sub-scale scores after 3 months of CPAP, and change in SF-36 scores before and after 3 months of CPAP, with mental health energy and vitality components considered the primary measurements, since these have been shown to be the most responsive in previous CPAP trials in OSA [83,118]. There were no significant differences between the 2 groups in any of the SF36 subscales.

3.3.3.3 CPAP Adherence

There were no statistically significant differences in CPAP adherence at 3 months between Model A or Model B (Table 3.2). These results were analysed as a per protocol analysis. There were 11 patients who dropped out in Model B compared with 10 in Model A. Other patients were not using CPAP after 3 months, but returned for final assessment and here their CPAP adherence was recorded as zero hours/night.

Table 3.2. Outcomes after 3 months

Outcome	Model A – Nurse led			Model B – Physician led			Mean Difference (MD)	SE (MD)	95% CI (MD)
	N	Mean	SEM	N	Mean	SEM			
ESS change	90	4.02	0.52	84	4.15	0.47	-0.13	0.70	-1.52 – 1.25
FOSQ change	89	-13.61	2.02	81	-13.22	1.96	-0.38	2.83	-5.97 – 5.20
SF36 Vitality change	89	-16.12	2.17	81	-15.31	2.06	-0.81	3.01	-6.75 – 5.12
SF36 Mental Health change	89	-4.81	1.46	81	-5.09	2.11	0.27	2.53	-4.71 – 5.27
CPAP compliance	94	4.11	0.28	83	4.56	0.30	-0.45	0.41	-1.26 – 0.36
MWT (mins)	65	30.18	1.24	61	31.68	1.08	-1.49	1.65	-4.76 – 1.78

Values are Mean + SEM. CPAP compliance reported in hrs/minutes

3.3.3.4 Nursing and physician consultations

In Model A, the Specialist Nurse discussed 12% of patient cases with a sleep physician. 12% of Model A patients were reviewed by a physician during the trial, usually because of problematic non-adherence to therapy. When considering total time spent (unscheduled and scheduled) CPAP Nurses spent about 50 minutes extra with the patients in Model A than in Model B, but there was an average of 2.36 physician consultations per patient in Model B compared with 0.18 in Model A (Table 3.3).

Table 3.3. Patient consultations, medical and nursing, and patient preference data

	Model A	Model B	P value
Number physician visits (per patient)	0.2 ± 0.1	2.4 ± 0.1	<0.001
Scheduled nursing time per patient (mins)	153.0 ± 3.9	103.3± 4.2	<0.001
Unscheduled nursing time per patient (mins)	8.4 ± 1.5	11.4 ± 2.5	0.31
VSQ-9 (total score)	3.73 ± 0.05	3.76 ± 0.05	0.68
Executive Maze (total number of completed mazes)	8.66 ± 0.56	9.75 ± 0.53	0.20

Values are mean ± SEM, Model A, N=100, Model B, N=95.

3.3.3.5 Patient satisfaction

Total patient satisfaction with treatment as measured by the VSQ-9 was not significantly different between the 2 groups (Table 3.3). Each of the 9 questions in the VSQ-9 is scored individually, with the overall satisfaction with treatment being one of those 9 questions. 5 of the 9 questions showed patient satisfaction with Model A was greater than Model B ($p < 0.05$), including time waited, personal manner, explanation, information provided and time spent with the health professional.

3.3.3.6 Neurocognitive Tests

A single measurement is presented here, the Executive Maze: total number of completed mazes within the allocated time. This measurement was felt to most accurately represent executive function measurement, a component of neurocognitive dysfunction often affected in moderate-severe OSA. There were no significant differences between the 2 groups (Table 3.3).

3.4 DISCUSSION

This is the first study which has compared a simplified package of care (incorporating nurse-led home diagnosis and CPAP therapy) for patients with moderate-severe OSA with physician led current best practice in OSA management. The main finding of the study was that the simplified model of care was not inferior to the usual specialist sleep physician-led, hospital-based model with respect to our primary outcome measure, the mean change in ESS after CPAP treatment. The lower limit of the confidence interval of the difference between the two models was well within the *a priori* determined range of clinical significance for ESS (i.e. 2.0).

There were also no significant differences between Model A and B after 3 months of CPAP therapy across a range of other measures including objective sleepiness, general and disease-specific quality of life measures, neurocognition, patient satisfaction and CPAP adherence after 3 months.

Mulgrew and colleagues recently described a similar simplified model of care involving home diagnosis and commencement of CPAP although it differed from the present study in that physicians were involved in both arms of care [90]. Their study showed no differences in patient outcomes between the two groups (simplified vs. best OSA practice) but was underpowered to show that the simplified model of care they used was either equivalent or non-inferior to standard care [91]. The generalisability of their study findings is also open to question as only 68 (3%) of a possible 2,215 patients participated in the trial.

It is important to note that the simplified model of care employed in the present study was underpinned by a) knowledge of the pre-test probability of

OSA in our referrals, b) the expertise of very experienced CPAP Nursing staff in OSA management, c) tertiary sleep laboratory back up, in terms of interpretation and quality control for oximetry data and APAP data and d) sleep physician input if needed.

We felt it important for the Specialist Nurse to be able to cross-consult in circumstances when they were uncertain about the management of the patient. Twelve patients had a sleep physician review as a result of unsatisfactory progress in Model A. Nine of these reviews were a once only consultation. While this represents a small percentage of all patients managed by the nurse, it underscores the need for this simplified model of care to be conducted either within a tertiary sleep medicine service or with patient access to same. We do not recommend the simplified management approach occur autonomously. How this occurs in a rural or remote setting needs consideration, but the opportunity for internet data transfer and teleconferencing/consultation makes it possible for a tertiary sleep medicine service to oversee this model of care even in a remote setting.

It is also important to note that the patients included in this study had been referred to a sleep medicine clinic for assessment of OSA. Thus the pre-test probability of moderate-severe OSA was high. We found it to be 36% in a similar previous study in our centre which fits with reports from other sleep disorders services. If such a simplified diagnostic and management approach was to be used in another setting (e.g. primary care) consideration would be needed as to which diagnostic test and cut-point would be appropriate, as the pre-test probability of OSA would be lower as would the post-test probability if

the same oximetry dip-rate was used [52]. The experience and skill of those providing clinical care must also be considered. Whilst nurse rather than sleep physicians provided care in Model A, these were all highly skilled and expert in the management of OSA and CPAP usage.

3.4.1 Health Economic Considerations.

If 450 patients referred to a sleep medicine service were to be screened using these methods in Australia, a cost saving of 13% is possible assessing direct research costs and assuming that the laboratory has the necessary equipment and software. 450 patients would need an ESS measured and oximetry testing to find 100 patients suitable for Model A as 22% of those patients who returned paperwork and gave informed consent to participate in the trial were eligible to be randomised after the ESS and oximetry results were known. The costs involved in Model B are about $1,200 per patient, accounting for PSG, CPAP titration and physician review (Health Insurance Commission, Australia). This money is saved in the 100 Model A patients, but this cost saving is partly offset by the need to perform 450 oximetry studies at approximately $100 each, the extra nurse time (50 minutes more per patient in Model A vs. B), and the occasional need for physician review in Model A. Applying costings from the Health Insurance Commission of Australia, this leads to a cost saving of approximately $71,000 in Model A per 450 patients. The monetary savings, non-inferior patient outcomes, increased efficiency and reduced patient waiting times all contribute to the appeal of Model A care.

If oximetry data were used both to “rule in” and “rule out” moderate-severe OSA, the impact of a simplified model of care could be much greater, both in

terms of health economics and a reduction in OSA waiting lists. Using both “rule in” and “rule out” cut points on oximetry could potentially identify up to 50% of patients having a true negative oximetry study [116]. This could increase the cost saving per 450 patients from $71,000 to $350,000 as half of the patients may not need to go onto PSG and physician review. This equates to a saving of $780 per patient.

Table 3.4 Direct Research Costs of both models of care for 100 patients

	Model A(Nurse led)	Model B (physician led)
Nursing assessment time (including screening)	467 hours @$30/hr $11649	190 Hours @$30/hr $5700
Diagnostic tests	450 @ $100/each $45000	200 PSGS @ $517 $103,400
Physician Consultation	20 visits @ $100/each $2000	2.40 visits @ $100/each $24000
Total	$61000	$132,000

Note We have used Health Insurance Commission rebates (no gap) for PSG and physician consultation estimates

3.4.2 Methodological Limitations

Once informed consent was provided only 22% of patients met inclusion/exclusion criteria (Figure 3.2). Nevertheless being able to triage and manage nearly a quarter of patients referred with OSA could help considerably with OSA waiting lists. We targeted symptomatic patients with moderate-severe OSA as it is this group of patients most likely to be adherent to CPAP [63], and who have the greatest risk of adverse health outcomes related to OSA [1,9].

At the conclusion of the trial we did not perform a PSG on patients in Model A to assess the effectiveness of CPAP in controlling oxygen desaturation during sleep. Given one of our inclusion criteria was an awake oxygen saturation of ≥92% it seems unlikely that significant sleep hypoventilation as a result of obesity or other medical problems such as kyphoscoliosis or chronic lung disease would be present in our patient group. Nevertheless, it is possible that CPAP may not have normalised oxygen saturation in all patients.

3.4.3 Conclusion

In conclusion, this study has shown that a simplified diagnostic and management model to investigate and treat moderate-severe OSA can produce patient outcomes with respect to daytime sleepiness that are not inferior to current best practice that includes in hospital PSGs and physician review. This simplified model of care could be used in existing sleep medicine

clinics to reduce the PSG and physician waiting lists by 20-25% (a greater reduction is possible if an OSA “ruling out” algorithm is added) and thereby importantly improving patient access to OSA services, perhaps the major challenge facing sleep medicine services around the western and developing world. Simplified diagnostic and management strategies need to be carefully integrated into an overall package of care. If resources are not adequate to meet the clinical need, the inclusion of different approaches to OSA diagnosis and management may not reduce the wait between referral and CPAP delivery in the home. For example a simplified diagnostic approach will have little impact if there are insufficient public funds to supply therapeutic equipment and too few skilled health professionals to fit CPAP and manage therapy. Nevertheless, we believe this overall package of care involving simplified OSA diagnosis, APAP titration in the home and the expansion of the sleep medicine workforce using skilled CPAP nurses working under protocol (with the back up of sleep medicine services if needed) has the potential to add significantly to the field of sleep medicine and improve access to care for those with OSA.

CHAPTER 4 THE EFFECT OF CPAP IN NORMALIZING DAYTIME SLEEPINESS, QUALITY OF LIFE AND NEUROCOGNITIVE FUNCTION IN MODERATE-SEVERE OSA

4.1 INTRODUCTION

The preceding chapters have focused on the development and evaluation of simplified methods of diagnosing and treating OSA with the ultimate aim of improving access to care and improving clinical outcomes for patients. However, it is important when developing new programmes of care for OSA patients to have a clear understanding of what can realistically be expected of current treatments in terms of reversal or improvement in patient symptoms. This chapter uses data obtained during the RCT reported in Chapter 3 in an attempt to address this question. It explores the relationship between the level of CPAP compliance in patients with moderate-severe OSA and patient responses in several key outcome variables such as daytime sleepiness (ESS, MWT), quality of life (Functional Outcomes of Sleep Quality, FOSQ, and SF36 questionnaires) and selected neurocognitive function measurements.

CPAP has been shown to reduce daytime sleepiness in OSA and is widely accepted as the most efficacious therapy for OSA. Patel and colleagues performed a meta-analysis showing that CPAP reduced the Epworth Sleepiness Scale score an average of 2.94 points more than placebo

(P<0.001) in those with OSA. Patients with moderate-severe OSA had a greater fall in ESS than those with mild OSA [114].

What is less well understood is the dose-response curve of CPAP and the proportion of patients that return to normal function after CPAP therapy. These are most important questions as it is known that;

1. CPAP adherence varies widely amongst patients,

2. Many patients present with EDS as their primary presenting symptom but it is likely that OSA is not always the dominant aetiology for EDS and thus CPAP therapy may only partially improve the EDS, and

3. Symptoms due to pre-existing hypoxic brain injury as a result of untreated OSA may not be reversible with effective CPAP therapy, even if CPAP adherence is optimal.

The average CPAP adherence varies widely in clinical cohorts. Weaver *et al* reported amongst a sample of 32 patients using CPAP that half were consistent users of CPAP, applying it >90% of the nights for an average of 6.22 hrs/night, while the other half were intermittent users who had a wide range of daily use averaging 3.45 hrs/night [123]. To further complicate the clinical picture, individuals exhibit wide variations in sleepiness and neurocognitive and performance measures in response to sleep deprivation [96]. Thus it is likely that the same CPAP adherence (hrs/night) will impact differently on sleep apnea-related daytime sleepiness and neurobehavioural deficits in different patients. Additionally, patients present to sleep medicine clinics with multifactorial aetiologies for their daytime sleepiness; daytime

sleepiness might only be partly related to OSA (or not at all). Thus, treating OSA may reverse only one component of a patient's sleepiness.

The issue as to what causes excessive daytime sleepiness (EDS) was assessed by Bixler and colleagues, using the Penn State cohort, a random sample of 16,583 men and women from central Pennsylvania, ranging in age from 20 to 100 yr with about 10% of the sample randomly chosen for a one night diagnostic sleep study in the sleep laboratory [48]. Using logistic regression to explore factors that were independently associated with daytime sleepiness, the authors found that depression was the most significant risk factor for EDS followed, in decreasing levels of importance, by body mass index, age, typical sleep duration, diabetes, smoking, and finally obstructive sleep apnea. They noted daytime sleepiness was more prevalent in those under 30, postulating that chronic sleep restriction and depression may be large contributors to EDS. These findings are most relevant to our study, because if a patient's EDS (often the main presenting complaint) does not resolve with CPAP, other casual factors such as depression, obesity and chronic sleep restriction must be considered.

The same investigating team had noted in an earlier study that obesity itself may be associated with EDS independent of OSA [98,124,125]. They studied 73 obese patients without sleep apnea, upper airway resistance syndrome, or sleep hypoventilation syndromes. Mean BMI was 45.4 kg/m². This group was compared to a control group of 45 controls matched for age, with a mean BMI of 23.5 kg/m². AHI was not significant difference between the two groups (5.2 /hr in the obese group, compared with 5.5 /hr in the control group). All patients

and healthy controls were monitored in the sleep laboratory for 8 hours at night and at 2 daytime naps, each for 1 hour the following day following a modified multiple sleep latency format. 57% of the obese group reported an ESS >10/24 compared to 2% of the control group. The obese group had more fragmented sleep, with more NREM sleep and less REM sleep than the control group, and the obese group demonstrated a significantly shorter sleep latency during the first daytime nap compared to the control group (13.7 mins compared to 22.7 mins $p < 0.01$). Their second sleep latency was also significantly shorter. The authors concluded that obese patients compared with controls were sleepier during the day, their night-time sleep was disturbed and that EDS in individuals with obesity may be related to a metabolic and/or circadian abnormality.

It may also be that reversing the daytime sleepiness with CPAP might be limited by previous brain injury caused in OSA patients by exposure to long-term nocturnal intermittent hypoxia, hypertensive vascular injury, repeated arousal or some combination of all three. In this setting CPAP could overcome sleep deprivation and fragmentation, but residual grey matter damage might mean that some daytime sleepiness remains [98,125].

Weaver *et al* went some of the way towards exploring these issues by performing a variety of quality of life, subjective and objective sleep measurements and neurocognitive measures before and after CPAP therapy in a group of patients with severe OSA. They found a linear dose response curve for objective and subjective sleepiness measures, but the curve

flattened at CPAP use of 7 hours per night for the quality of life measures. She also noted that even amongst those patients using CPAP for >7 hours per night at 3 months, only 30% of patients normalised their multiple sleep latency (MSLT) test results. Only 50% normalised their functional outcome of sleep questionnaire results [97]. Thus, even the most optimally treated OSA patients may not experience a complete reversal of daytime symptoms and functional abnormalities.

While dose-response relationships are perhaps to be expected, these data support that there are important differences in dose-response sensitivity to treatment and the degree of normalisation amongst key clinical outcomes. Given that clinical decisions must ultimately be guided by a firm understanding of the dose response relationships in the key clinical outcome measurements such as daytime sleepiness and functioning and neurocognitive performance, this study was designed to further explore the impact of CPAP adherence on clinical outcomes in OSA.

To better understand the impact of CPAP adherence in OSA patients we have conducted a similar study in patients with moderate-severe OSA to that reported by Weaver and colleagues, but have expanded the number of daytime functional measures to include several tests of cognition and measures of general as well as disease specific quality of life. We have also explored the relationship between CPAP and the maintenance of wakefulness test.

4.2 METHODS

The study was conducted as a multi-site effectiveness study. Patients were recruited at 3 separate sleep medicine services, the Adelaide Institute for Sleep Health (Adelaide, SA Australia), Alfred Hospital (Melbourne, Victoria Australia) and John Hunter Hospital (Newcastle, NSW Australia). Approval was granted by the Research and Ethics Committee at each site and the study was registered with the Australian Clinical Trials Registry.

The study population, methods of patient recruitment, sleep studies and CPAP treatment were as described in Chapter 3.

4.2.1 Outcome Measures

A number of differing endpoints relevant to OSA were collected. These included 1. Epworth Sleepiness Score (ESS). 2. Short Form 36 (SF-36), which has been used widely in OSA studies. Subscales in the SF-36 of mental health and vitality were separately analysed as these have been shown to be the most sensitive to CPAP therapy in previous randomised controlled trials. 3. Functional Outcomes of Sleep Questionnaire (FOS-Q). This is a sleep specific self-report questionnaire designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living. It has excellent internal validity and test-retest reliability. 4. CPAP adherence as measured objectively by in-built CPAP meter for the 3 month duration of the trial. 4. Maintenance of Wakefulness Test (MWT) after 3 months of therapy. 5. Detailed neurocognitive testing before and after 3 months of CPAP using Brain Resource Company Integneuro testing via a

touch screen computer with linked headphone set to provide instructions (BRC, Sydney Australia).

4.2.2 MWT

The MWT protocol followed the procedure described by Mitler, i.e. four tests are performed at two hourly intervals commencing 1.5 – 3 hours after the patient has awoken [126]. The patient was required to sit in a comfortable chair in a quiet room. Light intensity (illumination) was set at 1 Lux (as measured by a light meter). Patients were dressed in normal, comfortable daytime clothes and smoking disallowed for 30 minutes prior to each test. Patients were asked to cease alcohol and caffeine consumption for 24 hours prior to the test. Any vigorous activity was suspended 15 minutes before each test and the patient encouraged to go to the toilet. The study concluded if 40 minutes had elapsed with no sleep seen or three consecutive 30 second epochs of stage 1 sleep or any 30-second epoch of stage 2, 3, 4 or REM sleep were noted. Between tests, patients were asked to get out of the chair and study room and careful attention was paid by the technical staff to prevent patients from dozing. Sleep latency was defined as the elapsed time from lights out to the first epoch scored as sleep (this criterion is reached when sleep occupies >50% of any epoch). The absence of sleep during any trial was scored as a sleep latency of 40 minutes. In a manuscript from our laboratory, normative values for a group of patients from the community without sleep disordered breathing were described [120]. Mean sleep latency to the first epoch of unequivocal sleep during the 40-minute trial MWT was 36.9 ± 5.4 (SD) minutes. The lower normal limit, defined as 2 SD below the

mean, was therefore 26.1 minutes. The MWT was performed only at the end of the 3 months of CPAP therapy as we felt the requirement for a full day of testing both on randomisation and conclusion of the trial would limit recruitment given the other complexities of data collection.

4.2.3 Neurocognitive Testing

Detailed neurocognitive testing was performed before and after 3 months of CPAP using Brain Resource Company Integneuro testing via a touch screen computer with linked headphone set to provide instructions (BRC, Sydney Australia). Because the testing process required some manual dexterity and significant comprehension of English, some patients were excluded from the neurocognitive testing process on the basis of the following exclusion criteria: 1. Previous significant head injury (loss of consciousness of more than 15 minutes in the last 5 years. 2. Illicit drug or alcohol abuse (more than 8 standard drinks per day on most or all days of the week). 3. Significant active psychiatric illness (e.g. major depression, active psychosis). 4. Manual dexterity problem (i.e. broken arm, hemiplegic and thus unable to perform tests). 5. English not the primary language spoken at home. Key data such as age, sex and years of education was collected to enable comparison with a BRC database of matched controls. The tests performed as part of the assessments of patient outcomes were different to the baseline tests to limit the potential for a learning effect.

4.2.4 CPAP adherence

Patients were reviewed by an experienced nurse at the 1 and 3 month mark in both groups. The CPAP machine data was downloaded to the Autoscan

program (Resmed, Sydney, Australia) and mean hours of CPAP use (hrs/night) collected. CPAP adherence figures quoted are average CPAP usage across the entire 90 day CPAP trial.

4.2.5 Quality of Life Measures

These were collected at the 0 and 3 month mark and included SF-36, FOSQ and ESS. The forms were filled out directly onto a computer by the patient. Patients without computer skills filled out hard copy forms. Supervision of the self-administered questionnaires was by a research assistant not otherwise directly involved in the trial.

4.2.6 Statistical Methods

For the majority of comparisons involving CPAP compliance, patients were grouped into average nightly CPAP compliance categories of ≤2, >2 to <4, ≥4 to <5, ≥5 to <6, ≥6 to <7 and ≥7 hours per night. Chi² tests were used to test for differences in the distribution of patients between CPAP compliance categories in groups A versus B, and to examine potential differences in the proportion of males between groups (A vs. B and OSA vs. Controls for neurocognitive data). Group (A vs. B), pre- vs. post-CPAP treatment effects, and the effect of compliance category on the various outcome measures were examined using ANOVA for repeated measures, with treatment as a within-subject repeated factor and compliance category (grouped according to nightly hours of use) as a between subject factor. Where applicable, treatment effects within compliance category sub-groups were identified on the basis of non-overlapping 95% confidence limits. Neurocognitive measures were compared between age-matched controls and OSA patients pre- and post-

CPAP treatment using independent sample t-tests adjusted for multiple comparisons using the Dunn-Sidak procedure. Values are reported as mean ± SEM, unless otherwise indicated. P-values <0.05 were considered significant.

4.3 RESULTS

Baseline characteristics of the patient groups are shown in Table 4.1. The group consisted of a working age, predominantly male population representative of a typical clinic population of patients with moderate-severe OSA. The ODI (oxygen desaturation index) was consistent with moderate-severe OSA and there was significant self reported sleepiness. There were no differences in any parameter between Groups A and B.

Table 4.1. Patient Characteristics

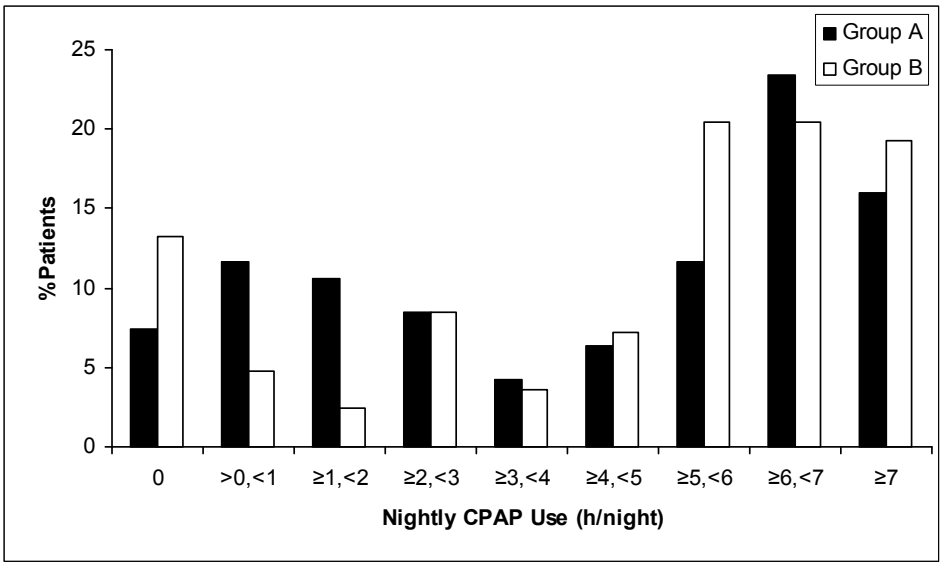
	All Participants n = 174	Group A n = 90	Group B n = 84
Characteristics at Baseline			
Men (%)	74.9	71.6	78.6
Age (y)	50.1 ± 12.0	49.7 ± 11.5	50.6 ± 12.7
BMI (kg/m²)	34.7 ± 6.8	35.3 ± 7.3	34.1 ± 6.1
Weight (kg)	105.2 ± 22.0	107.3 ± 24.0	103.0 ± 19.2
Height (kg)	174.1 ± 8.9	174.4 ± 9.3	173.9 ± 8.6
Neck Circumference (cm)	44.1 ± 4.2	44.1 ± 4.4	44.1 ± 4.0
ODI (2% dips/h)	50.9 ± 24.8	49.6 ± 21.4	52.4 ± 28.3
ODI (3% dips/h)	36.2 ± 22.1	34.9 ± 19.6	37.5 ± 24.7
ODI (4% dips/h)	28.0 ± 21.4	27.0 ± 19.2	29.3 ± 23.7
SaO_2 Nadir (%)	73.2 ± 13.8	74.6 ± 13.2	71.6 ± 14.3
ESS Score	13.4 ± 4.0	13.8 ± 3.9	12.9 ± 4.1
FOSQ Total Score	14.9 ± 2.6	14.5 ± 2.7	15.3 ± 2.5
SF 36 Total Score	99.0 + 8.6	99.0 + 7.6	99.0 +8.1
Nightly CPAP Duration (h)	4.3 ± 2.7	4.1 ± 2.7	4.6 ± 2.7

With the exception of the proportion of males in each group, all values are mean ± SD.

4.3.1 CPAP adherence

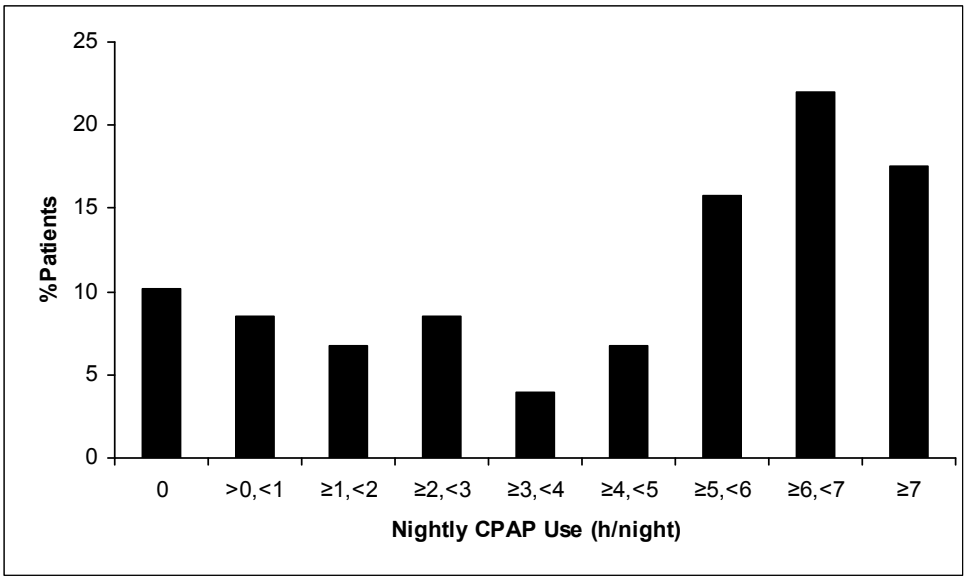
As might be expected, there was considerable variability in CPAP adherence across the patient group, with a coefficient of variation of CPAP compliance in excess of 50% (Table 4.1 and Figures 4.1 and 4.2). There were no significant differences in compliance or the distribution of patients between compliance categories between Group A (nurse led) and Group B (physician led), such that data from both groups were combined for the remaining analyses.

Figure 4.1. CPAP adherence Model A and Model B



Values are mean CPAP compliance in hrs/minutes Total n=174 (≤2 n=46; >2, <4 n=21; ≥4,<5 n=12; ≥5,<6 n=26, ≥6,<7 n=39; ≥7 n=30).

Figure 4.2. CPAP adherence (whole group)



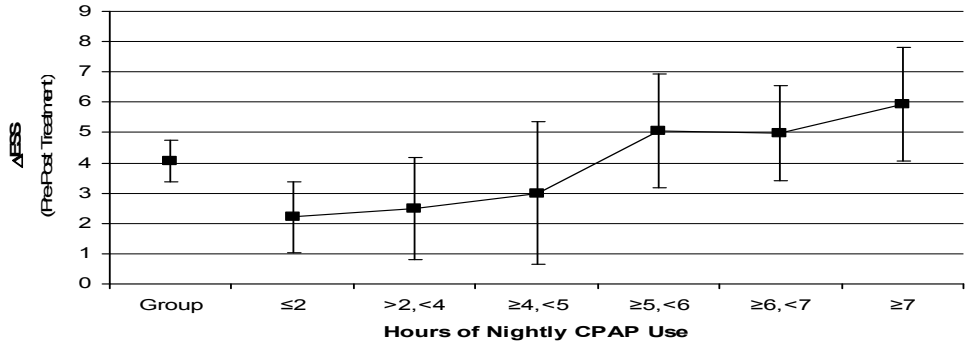
Values are mean CPAP compliance in hrs/minutes Total n=174 (≤2 n=46; >2, <4 n=21; ≥4,<5 n=12; ≥5,<6 n=26, ≥6,<7 n=39; ≥7 n=30).

4.3.2 ESS

ESS showed substantial and dose-dependent improvement following CPAP treatment ($p<0.001$, Figure 4.3), with significantly greater improvement in more adherent patients (compliance and treatment by compliance effects $p=0.018$ and $p=0.004$ respectively). 80.6% of all patients using CPAP >7 hours per night had a normal ESS post-treatment (Table 4.3), compared to 52.4% amongst those using CPAP for between 2-4 hours/night. Across the whole patient cohort only 59.5% exhibited a normal ESS after treatment. Even with very good CPAP compliance not all patients normalised their ESS.

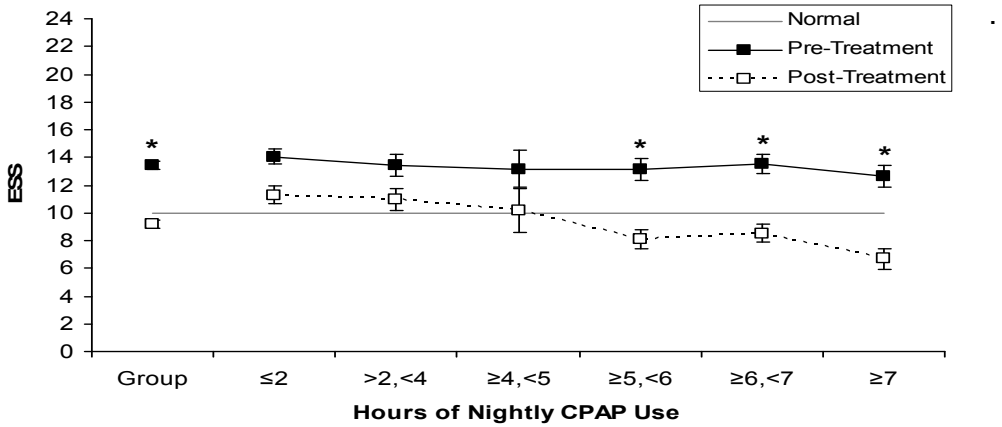
Among those who had abnormal ESS ($\geq$10) pre-treatment, only 48% normalised their ESS over the 3 months, and only 66% of those who used CPAP >5 hours/night over the 3 months achieved a normal ESS at the conclusion of the trial (Figure 4.5 and Table 4.2).

Figures 4.3. Pre-post treatment change in ESS as a function of compliance category



Values are mean ± SEM. Total n=174 (≤2 n=46; >2, <4 n=21; ≥4,<5 n=12; ≥5,<6 n=26, ≥6,<7 n=39; ≥7 n=30).

Figure 4.4. Pre and post treatment ESS as a function of compliance category



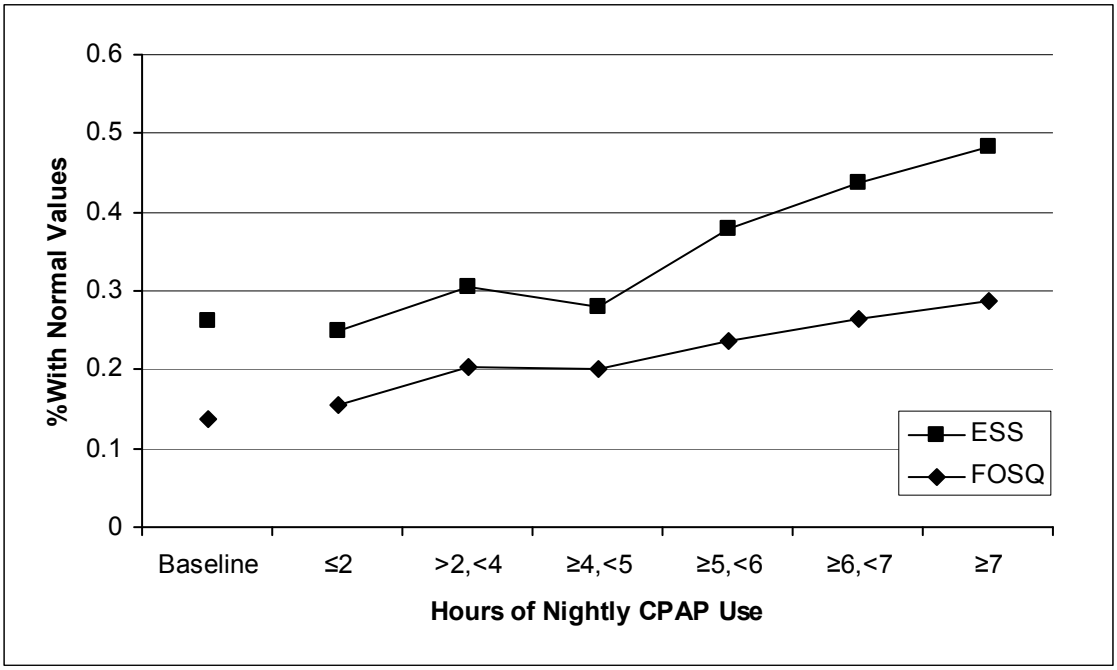
Values are mean ± SEM. Total n=174 (≤2 n=46; >2, <4 n=21; ≥4,<5 n=12; ≥5,<6 n=26, ≥6,<7 n=39; ≥7 n=30). The unbroken horizontal line corresponds to the ESS cut-off value usually used to distinguish normal from abnormal results [46].

Table 4.2. Percentage of patients with normal values pre- and post treatment and according to CPAP compliance

Measure (normal cut-off)	Pre-Treatment	Post-Treatment Mean CPAP Hours Per Night						
		≤2	>2 - <4	≥4 - <5	≥5 - <6	≥6 - <7	≥7	Total
	%Patients Normal	%Patients with normal values after treatment						
ESS (≤10)	26.2 (44/168)	35.9 (14/39)	52.4 (11/21)	41.7 (5/12)	76.9 (20/26)	64.1 (25/39)	80.6 (25/31)	59.5 (100/168)
MWT (≥26.3 min)	-	60.9 (14/23)	71.4 (10/14)	60.0 (6/10)	61.9 (13/21)	80.0 (24/30)	68.0 (17/25)	68.3 (84/123)
FOSQ Total (≥17.9)	13.9 (23/166)	27.0 (10/37)	33.3 (7/21)	25.0 (3/12)	34.6 (9/26)	35.9 (14/39)	48.4 (15/31)	34.9 (58/166)
		%Patients with abnormal pretreatment values achieving normal values after treatment						
ESS (≤10)	26.2 (44/168)	25.0 (8/32)	41.2 (7/17)	12.5 (1/8)	70.6 (12/17)	58.6 (17/29)	71.4 (15/21)	48.4 (60/124)
FOSQ Total (≥17.9)	13.9 (23/166)	15.4 (4/26)	27.8 (5/18)	18.2 (2/11)	32.0 (8/25)	32.4 (12/37)	38.5 (10/26)	28.7 (41/143)

Values are presented as percentages with parenthetical numbers depicting the number of patients showing normal values versus the total number of patients within the relevant category.

Figure 4.5. Total cumulative proportion of patients achieving normal ESS and FOSQ values with increasing compliance derived from data within each compliance category shown in Table 4.3 (above).

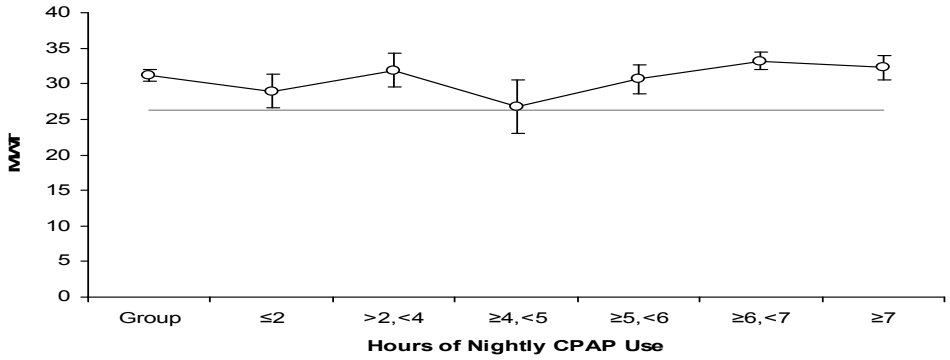


Values are the % of patients returning to normal ESS/FOSQ with mean CPAP compliance Total n=174 (≤2 n=46; >2, <4 n=21; ≥4,<5 n=12; ≥5,<6 n=26, ≥6,<7 n=39; ≥7 n=30).

4.3.3 MWT

Approximately 70% of patients exhibited normal (>26.1 min) post-treatment MWT mean sleep latency and there was no effect of CPAP adherence category on MWT results (p=0.36) (Figure 4.6).

Figure 4.6. Average MWT sleep latency following CPAP treatment as a function of compliance category.

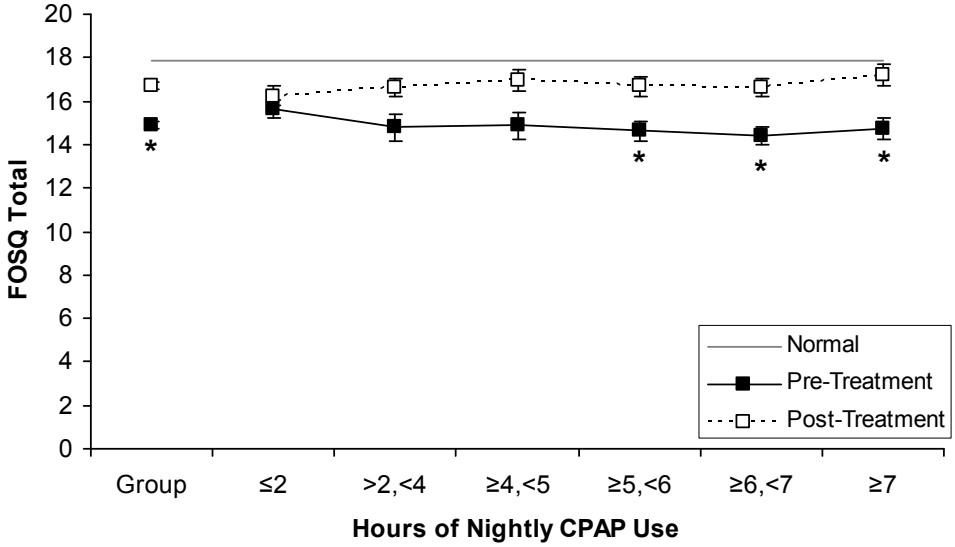


Values are mean ± SEM. Total n=123 (≤2 n=23; >2,<4 n=14; ≥4,<5 n=10; ≥5,<6 n=21, ≥6,<7 n=30; ≥7 n=25). The unbroken horizontal line corresponds to the MWT mean sleep latency cut-off value used to distinguish normal from abnormal results [120].

4.3.4 FOSQ

FOSQ scores showed significant improvements post-treatment in all domains (activity, vigilance, intimacy, general productivity and social outcome and total score, all $p<0.001$). There were no significant main effects of compliance category on any FOSQ outcome measure. However, FOSQ total and activity level scores showed significant treatment by compliance interactions ($p=0.021$ and $p=0.002$ respectively), indicating greater improvements in more adherent patients, with a similar trend in general productivity ($p=0.053$). In the absence of published normative data for the FOSQ [97], a the cut-off value of ≥17.9 as described by Weaver *et al* 2007 (based on unpublished normative data) was used. Using this cut-point, only 35% of all patients achieved normal FOSQ scores post-treatment (Table 4.2). One of the 30 questions administered as part of the FOSQ was inadvertently excluded. This was the question relating to “difficulty maintaining telephone conversation” in the General Productivity subscale. Given the repeated measures design and that scores in each subscale (and overall) are averaged, it is unlikely that this omission affects the interpretation of the results in any meaningful way.

Figure 4.7. Pre-post treatment total FOSQ scores as a function of compliance category

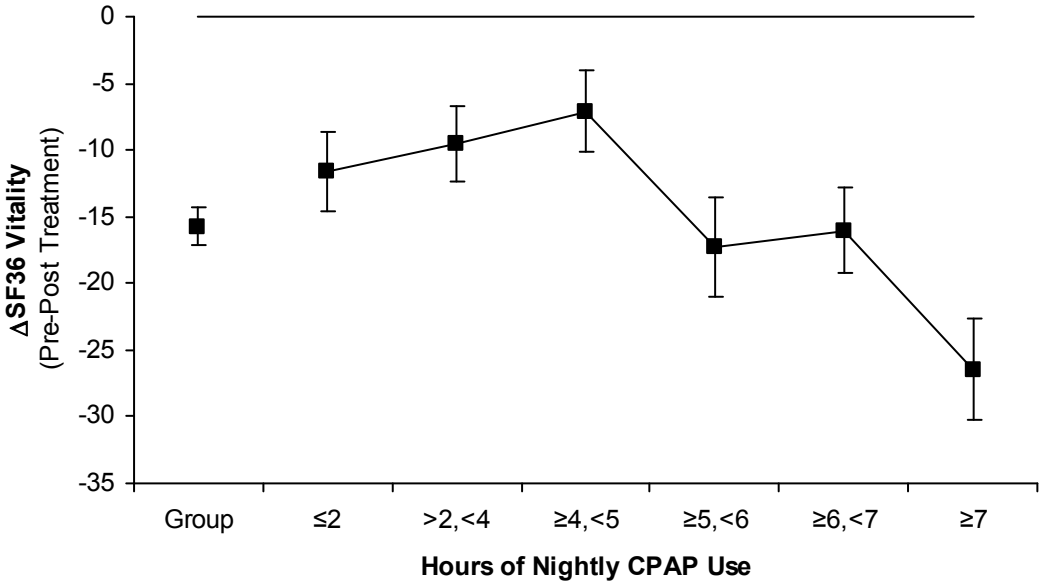


Values are mean ± SEM. Total n=174 (≤2 n=46; >2,<4 n=21; ≥4,<5 n=12; ≥5,<6 n=26, ≥6,<7 n=39; ≥7 n=30). The unbroken horizontal line corresponds to the FOSQ cut-off value used by Weaver et al to distinguish normal from abnormal results [97].

4.3.5 SF36

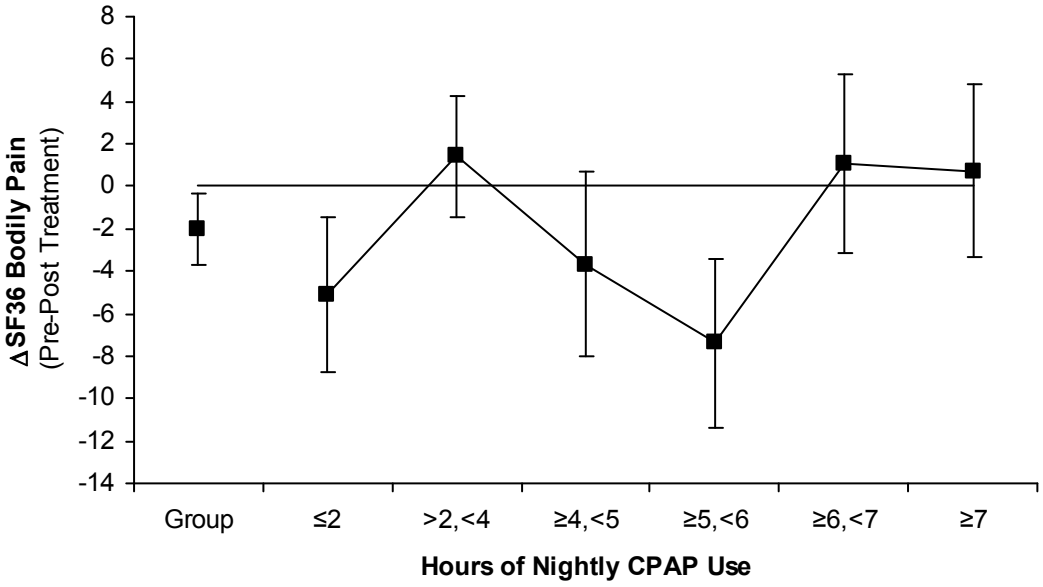
All of the SF36 sub-scales, except bodily pain (p=0.250, the least sensitive SF36 scale to change in OSA [127]. Only vitality showed significantly greater improvements in more adherent patients (treatment by compliance category interaction p=0.006, Figure 4.8), although role-physical and role-emotional approached statistical significance (p=0.051 and p=0.062 respectively).

Figure 4.8. SF36 vitality subscale change across different CPAP adherence levels.



Values are mean ± SEM. Total n=175 (≤2 n=46; >2,<4 n=21; ≥4,<5 n=12; ≥5,<6 n=26, ≥6,<7 n=39; ≥7 n=31). * indicates $p<0.05$ pre- versus post-treatment.

Figure 4.9. SF36 bodily pain subscale change across different CPAP adherence levels.



Values are mean ± SEM. Total n=175 (≤2 n=46; >2,<4 n=21; ≥4,<5 n=12; ≥5,<6 n=26, ≥6,<7 n=39; ≥7 n=31). * Indicates $p<0.05$ pre- versus post-treatment.

4.3.6 Integneuro (Neurocognitive) data

Thirty three of 174 patients eligible for the Chapter 3 study were excluded as a result of the extra exclusion criteria used in this sub-study, with a complete dataset being collected for 141 patients. Representative neurocognitive parameters from each domain of neurocognitive function were chosen as follows: Verbal recall 1 and 7, choice reaction time and executive maze errors and time to completion of the executive maze.

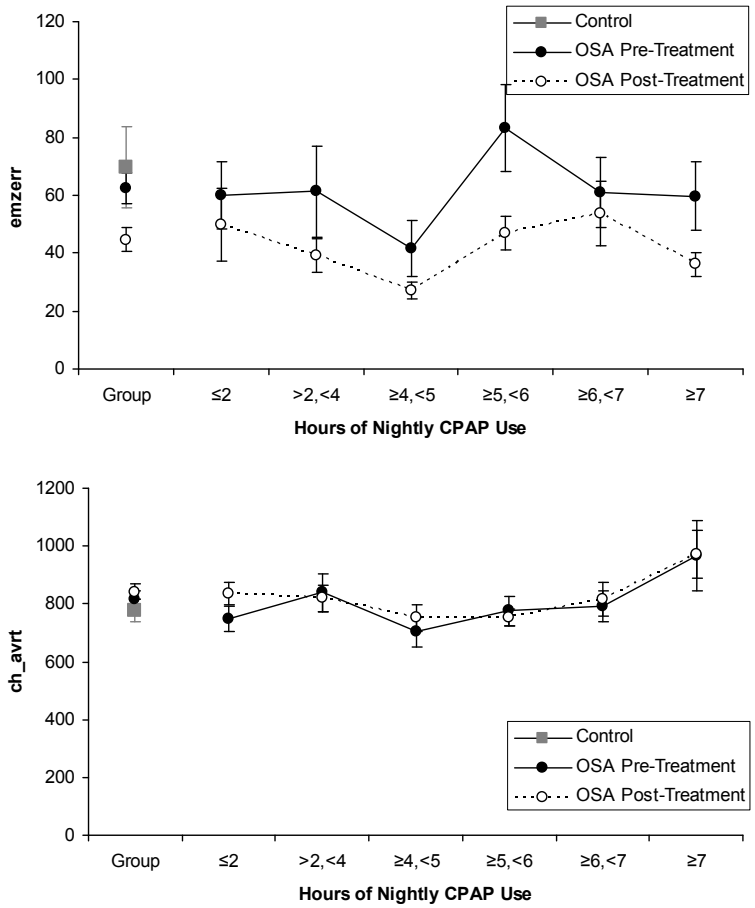
Neurocognitive tests were selected from the test battery of 58 available tests that were representative of the key neurocognitive domains affected by OSA, namely, verbal memory, executive function and vigilance. Overall pre- and post-treatment results were compared to a control group matched for age, sex and years of education (Table 4.3), and pre- vs. post-treatment effects as a function of CPAP compliance category examined for each of the selected tests (e.g. Figure 4.10). Verbal memory and executive function testing showed significant improvement after 3 months of CPAP (all $p<0.001$), but vigilance (as assessed by average reaction time measurement) was not significantly improved after CPAP (Table 4.3). While there were significant overall treatment effects in most of the neurocognitive measures examined, there were no adherence categories or treatment x adherence category interaction effects in any measure

Table 4.3. Selected Neurocognitive parameters before and after CPAP, and compared to a control group

		OSA (n =141)	
	Controls (n=113)	Pre-Treatment	Post-Treatment
Choice Average Reaction Time (msec)	0.78 ± 0.25	0.81 ± 0.38	0.84 ± 0.29
Verbal Recall 1	11.05 ± 1.35	9.62 ± 1.91 *	10.82 ± 1.75 #
Time to complete the executive maze (min)	4.16 ± 2.38	4.87 ± 2.98 *	3.97 ± 2.61 #
Verbal Recall Trial 7 Score	6.78 ± 2.14	5.82 ± 2.37 *	6.52 ± 2.38 #
Executive Maze Total Errors	69.67 ± 92.51	61.05 ± 64.91	43.83 ± 45.48 *#

Values are mean ± SD. * indicates $p<0.05$ versus controls, # indicates $p<0.05$ vs. pre-treatment. Verbal Recall 1 and 7; Ability to correctly recall a set of words given immediately after the words are given (1), and again at a later time (7).

Figure 4.10. Pre- and Post-CPAP treatment Executive maze total errors (top) and reaction time (bottom) as a function of adherence category



Values are mean ± SEM. Total control n=113, OSA n=143 (≤2 n=36; >2,<4 n=17; ≥4,<5 n=8; ≥5,<6 n=20, ≥6,<7 n=32; ≥7 n=30). Emzerr is total executive maze errors and ch_avrt reaction time (msec)

4.4 DISCUSSION

These data illustrate a number of important points. The first is that in clinic patient populations, many treated for OSA with CPAP will not return to a normal level of function after CPAP. The results in Table 3 demonstrate this with only 60% of patients achieved a normal ESS after 3 months of CPAP and

even fewer (35%) achieved a normal FOSQ total score. The lack of normalisation of ESS, for example, might be explained by a number of factors

1. Inadequate CPAP adherence. This is supported by the observation that only 35% using CPAP < 2 hours/night normalised their ESS whereas 81% of patients using CPAP >7 hours/night, did so.

2. The possibility that the ESS normal value used of less than or equal to 10 was not appropriate for the age group of the OSA patients in the study. The commonly used normal-value cut-point for ESS of 10 was derived by Johns in a study in a younger population (mean age 36.4). These healthy subjects ≤had a mean ESS score of 5.9 $\pm$ 2 standard deviations of 2.2 [46]. Bixler's work described excessive daytime sleepiness as being twice as common in 20 year olds as 50 year olds [48]. Thus it is possible that the real normal ESS cut-off in the age-appropriate ESS in the patients we studied should be lower than 10. If true, this would mean that an even higher, rather than lower, proportion of patients would have failed to achieve normal ESS values after CPAP therapy than we have reported.

3. Incomplete control of OSA by CPAP, perhaps as a result of incomplete control of upper airway obstruction, CPAP itself causing sleep disruption through mask leaks or discomfort, or the development of complex sleep apnea on CPAP.

4. Confounding factors contributing to daytime sleepiness other than OSA (sedating medications, depression, obesity itself, chronic sleep restriction etc).

5. The possibility that hypoxic brain injury as a result of untreated OSA might be irreversible. Oxidative neural injury of wake promoting neural groups has been shown in animal models of OSA [125].

6. It may indeed be that post CPAP sleepiness does not exist as a distinct entity at all and the degree of sleepiness seen in patients after CPAP therapy is not different to that seen in the general population. Stradling and colleagues recently reported that the prevalence of post CPAP sleepiness (either measured as ESS >14/24 or ESS >10/24) was not different between a cohort of patients on CPAP and a control group taken randomly from the general population. It should be noted, however, that this control group was not matched for sex and there were significantly more females in the control group than the CPAP group. [126]

We feel that all these issues must be considered after the patient has had a trial of CPAP. It is important that the health professional assessing the patient does not rely simply on the numerical CPAP adherence value, as whether or not daytime sleepiness and quality of life improves or normalises may be depend on a number of other complex and often inter-related factors. Other comorbidities (e.g. depression) and treatments (e.g. sedating medication) should be considered, particularly in the setting of ongoing symptoms.

MWT

The lack of a dose response effect for CPAP on MWT mean sleep latency results was a little surprising, although, caution needs to be exercised in interpreting the results given the lack of a pre-treatment MWT measurements. Given the complexity of our study and the time requests being put on our patients, we felt that to ask them to do another full day test pre-CPAP would have adversely affected recruitment. Whilst it is a limitation that the MWT was only performed at the end of the trial, these results do raise some doubt as to the clinical utility of the MWT in this situation, particularly given that many of the other outcome measures showed a dose-response effect.

In the meta analysis of the effect of CPAP on daytime sleepiness, Patel *et al* [114] pooled the studies that had MSLT or MWT included as part of their testing process and found a mean increase in mean sleep latency of 0.93 minutes across all studies included (MSLT and MWTs). 6 of the 12 studies analysed had an AHI >30 /hr. Given these small changes, use of the MWT as an objective marker of treatment effect on CPAP must be queried. Engelman and colleagues did not find a significant difference between the MWT results in the same group of OSA patients receiving placebo and those with OSA treated with CPAP after 4 weeks of CPAP, although this group had mild OSA and the follow up period was short (4 weeks) [128]. There are several possible explanations for an apparent lack of a treatment effect in the MWT sleep latency in these previous studies and the current one. First, it may be that the test is not sensitive enough to pick up improvements in sleepiness post CPAP. Second, it is known that the MWT result can be affected by

patient motivation [129]. Given that we studied patients referred to a sleep clinic, motivating forces such as fear of loss of drivers licence may have contributed to those with little CPAP usage to try harder to stay awake. The third possible explanation is that the subjective quality of life measures improve after CPAP because of a placebo effect, but more objective measures do not. Whatever the reason, our study findings bring into question the use of the MWT as a test to demonstrate CPAP efficacy in OSA.

It was of interest to note that improvements across all quality of life and sleepiness domains were seen in patients with what might be regarded as suboptimal CPAP compliance. For example, those using CPAP <2 hours per night had a fall in ESS of 3 and a normal mean sleep latency on their MWT. These slightly incongruous results may represent

1. Placebo effect

2. Regression to the mean. Because these were sleep clinic patients referred for assessment of OSA, it is likely that they presented when they were at their worst in terms of symptoms, and over 3 months some improvement might therefore be expected.

3. The possibility that even a small amount of CPAP use can improve daytime sleepiness in some patients.

4. A lower than age-appropriate normal cut-point combined with a ceiling effect within the MWT, where greater resistance to sleepiness in more treatment compliant patients is perhaps clipped by the 40 minute cut-off inherent within the MWT test.

There was some suggestion that there was a threshold of effect when CPAP was used >5 hours per night (Figures 4.4 and 4.5). This is of interest as it is a figure that many clinicians use as a "passmark" for acceptable CPAP compliance. However only 40% of patients had a normal ESS when using CPAP for 5 hours or greater per night.

We don't believe a minimum therapeutic use of CPAP at >5/24 per night would be a positive step. It is known that CPAP use varies widely in the community {62} Given clear treatment benefits demonstrated in the 2-4 and 4-5 hour CPAP usage group, to set a minimum target of >5/24 is not advised and may lead to those using CPAP >5/24 night to have to return machines that are providing symptomatic relief

SF36

In the SF36 subscales, only vitality showed significantly greater improvements in more adherent patients. This is consistent with other published results which showed the therapeutic effect size was greatest for the vitality subscale of the SF36 [118,127]. The bodily pain subscale improved the least, and both in the study by Jenkinson *et al* [127] and this study there was no evidence of any dose response effect.

Neurocognitive function

In terms of neurocognitive function, there were significant improvements after CPAP across most domains of neurocognitive function studied, including executive function and verbal memory. There was, however, no dose-response effect seen for CPAP therapy. This raises the possibility that some (or all) of the improvement seen after CPAP was related to patient learning effects on the BRC neurocognitive test battery. We attempted to minimise learning effects by administering different tests 3 months apart. The absence of a placebo arm nevertheless remains a methodological limitation of the trial.

The potential for practice effects was evaluated in a study by Cooper *et al* using the same test battery and equipment used in the present study [130]. This study assessed dose-dependent effects of methylphenidate. Participants completed the Integneuro test battery 3 times per day, 1 day per week, for 6 weeks. When the first and second administrations were examined, the only test that showed a practice effect was Switching of Attention (t=-2.34, p=.028) [130].

In conclusion, this study in patients with symptomatic (ie ESS >8) moderate to severe OSA (i.e. AHI >30 /h) showed that several key indices of neurobehaviour (e.g. FOSQ, ESS) currently used to assess treatment response failed to normalise in a substantial minority of patients after 3 months of CPAP treatment, even in those who were maximally compliant. In future studies of cohorts of OSA patients, detailed data collection of total sleep time, residual sleep disordered breathing or prevalence of depression should be carefully assessed. It is noted that the patients included in this study were part of a RCT rather than “real world” patients. This raises the

possibility of selection bias, although their mean BMI, age and male/female ration was very similar to our clinic patients so the likelihood of significant selection bias is low.

This Chapter identifies that careful thought and follow up is needed when treating a patient with OSA. Other comorbidities frequently exist and even optimal CPAP compliance may not normalise quality of life and daytime sleepiness measures. The best evidence base for treating OSA patients with CPAP still revolves around quality of life and daytime sleepiness, given the uncertainty around cardiovascular risk reduction with CPAP, but the individual patient can provide treatment challenges and unexpected results.

Finally, these data are perhaps salutary with respect to the development and implementation of new, simplified management protocols for OSA. If a significant minority or perhaps even a majority of patients in some instances, despite optimal CPAP treatment adherence continue to remain sleepy and have reduced daily functioning, clinicians caring for these patients will need to be skilled in the recognition and treatment of persistent neurobehavioural problems. For example, primary care physicians and nurses as they become more engaged in the management of OSA will need to be alerted to the fact that residual daytime sleepiness could equally be due to lifestyle problems (i.e. insufficient time allotted by patients to sleep), other sleep disorders or medical disorders (e.g. depression) as that of poor adherence to OSA therapy. Careful follow up and clinical review of patients will be an essential component of any new management system. Simplifying the diagnostic and treatment technologies for OSA will likely require an up-skilling of the

professionals caring for patients with OSA so that they are skilled in the management of a wide range of sleep disorders and not simply obstructive sleep apnea and can appreciate the contribution of non-sleep disorders to their patients' symptoms.

CHAPTER 5 SUMMARY AND CONCLUSIONS

5.1 Simplified Diagnosis

This overall aim of this research was to investigate the effectiveness of a simplified model of diagnosis and care for those with obstructive sleep apnea. Given the 2 major barriers to providing health care for OSA are a lack of diagnostic services and a lack of trained health professionals to treat the condition, we set about investigating processes that might contribute to the resolving these current deficiencies.

In Study 1 we showed that amongst patients referred to a Sleep Medicine Service (and thus with a high pre-test probability for OSA) the majority of patients could be accurately identified by overnight oximetry as either having or not having moderate-severe OSA. The primary aim of this study was to find cut-points in oxygen desaturation indices to “rule-in” moderate-severe OSA. Defining moderate-severe OSA as an AHI >30/hr, oximetry could identify OSA very accurately, with a positive likelihood ratio of 15.9. 84% of positive cases were correctly identified, making oximetry a potentially clinically useful test in this patient group.

We presented data to show that oximetry could also be used to “rule out” OSA, with a negative likelihood ratio of 0.11 when defining OSA as an AHI >15/hr. Ruling out OSA at an AHI of <30 has less appeal as many would consider AHIs of between 15-30 as still potentially clinically important.

Home oximetry correlated very well with lab oximetry (r=0.89) despite a small bias towards lab derived oximetry scores being higher than the home measurements. Data collection failures in the home were rare (<2%).

Thus oximetry has considerable appeal as a simplified diagnostic method, and validating its performance gave us confidence to use the portable oximeter as a “rule in” diagnostic tool for our main randomised controlled trial reported in Chapter 3.

The use of the oximeter to diagnose those with OSA could be justified on a wider basis and has particular appeal in rural and remote areas and the developing world, where access to diagnostic services for OSA may be lacking. The pre-test probability for OSA in the group being tested needs to be carefully considered, lower pre-test probabilities of OSA in primary care or occupational settings may lead to less diagnostic certainty unless different (more specific) cut points are used.

We then went on to conduct a RCT that which was the main focus of our research. We set out to answer the question “Can a simplified model of care produce outcomes that are not inferior to current best practice for diagnosis and management of moderate-severe OSA?”

We found that the simplified model of care (nurse-led) was not inferior to current best practice for OSA diagnosis and management for the primary outcome variable, subjective daytime sleepiness. A variety of other outcome measures were also assessed, before and after 3 months of CPAP, including objective daytime sleepiness, CPAP adherence, and quality of life assessments including Short Form 36 and the Functional Outcome of Sleep

Questionnaire. None of these outcome variables was different between the two groups. Neurocognitive function across a range of variables was also not different between the two groups, and patient preference towards either model of care as measured by the VSQ-9 was not different. It must be noted that whilst the overall patient preference scores were not significantly different between the groups, the patient's preferred the simplified nurse-led model of care in terms of the time the health professional spent with them and the adequacy of explanations regarding their health care.

This model could contribute to how patients with moderate-severe OSA are treated in two ways;

1. It has the potential to make the access to health care easier for patients, by expanding health service access and shortening waiting times. It would do this by attacking the two major barriers to routine health care in OSA: viz. limited sleep laboratory facilities and limited availability of sleep physician time.

2. There is the potential for a cost saving of between 10-15% across the Simplified Model of Care. This cost saving could be considerably greater if oximetry was not only used to "rule in" OSA but also to "rule out" OSA. To adopt the latter approach would require some pragmatism. We accept that some patients without moderate-severe OSA might be treated by CPAP (false positives). However it is likely that most of these patients have an AHI >20, thus there is an argument for treatment with a safe therapy such as CPAP. The AHI >30/hr "line" is somewhat arbitrary. However by using oximetry to "rule in" and "rule out" OSA there would be some false negative patient results

and some patients may thus miss out on care for their OSA. Using a cut-point to produce a dip-rate with a high sensitivity will help to minimise these cases. There might be an argument for performing a full PSG on “negative” cases if their ESS is >10 (i.e. they have symptomatic sleepiness).

It is most important to note that the simplified model of care employed in the present study was underpinned by a) knowledge of the pre-test probability of OSA in our referrals, b) the expertise of very experienced CPAP Nursing staff in OSA management, c) tertiary sleep laboratory back up, in terms of interpretation and quality control for oximetry data and APAP data and d) sleep physician input if needed. Any future attempts to roll out similar simplified models of care must be underpinned by similar considerations and facilities. For example screening for OSA in primary care or an occupational setting may require different cut-points and likelihood ratios if the pre-test probability of OSA were lower than in a tertiary referral centre. Many such simplified models of care are emerging in sleep medicine. Many have a strong industry base and some exclude health professionals entirely. We do not believe our model should be used as supportive evidence for such “cut-down” models of care.

5.2 CPAP Effectiveness

In Chapter 4 the CPAP effectiveness over the 3 month trial was described. Many patients did not get back to what would be regarded as normal daytime sleepiness and quality of life measures despite adequate usage of CPAP. The MWT test did not seem to be a very clinically useful test based on our data, with normal results in most and no dose-response effect across a range of

CPAP compliance values. When setting up simplified management strategies for OSA, it is crucial that those evolving the strategies and those providing individual patient care have a clear understanding of the implications of theseee data. Such an understanding will enable careful follow up of all patients with due consideration of the multiple potential interacting factors in those with daytime sleepiness, and thus broader sleep medicine health care than simply the application of CPAP for OSA.

5.3 The Next Step

The studies described in this thesis explored key issues relevant to expanding the capacity of the sleep medicine workforce. Whilst training more sleep physicians is and will continue to be important, there are two groups that could meaningfully add to the workforce, nursing staff and General Practitioners. Thus a logical next step is to roll out some of the simplified models of care into Primary care. The next study constructed and already underway has the following aims;

1. To develop a simple two-stage method (questionnaire followed by home oximetry) for identifying patients in general practice with moderate to severe obstructive sleep apnea (AHI > 30/ h).

2. To conduct a randomised controlled trial of two models of care for moderate to severe OSA. Model A: General practice (sleep specialist nurse assisted); and Model B: Usual care in a specialist sleep centre

Our hypotheses are that;

1. A simple 3-4 item screening questionnaire followed by home oximetry in high risk subjects can identify >85% of cases of moderate to severe OSA in general practice with a high level of confidence (post test probability of disease $\geq$ 90%).

2. Patients with moderate to severe OSA who are managed in general practice will have equivalent outcomes (Epworth Sleepiness Scale, QOL, BP) to those in a specialist sleep centre. Medical costs will be less for general practice care.

With current systems of hospital-based diagnosis and management, many patients with moderate to severe OSA remain undiagnosed and pose a significant and preventable burden to Australia from reduced quality of life and elevated cardiovascular events and motor vehicle accidents. If our hypotheses are supported, the relatively simple screening diagnostic tests and the explicit treatment pathways used in these studies will have a high chance of being translated into routine primary care practice in Australia, and internationally where sleep apnea services are also in short supply. The latter issue will continue to grow in importance in rapidly growing areas such as China and India, where the emerging problem of obesity, the large populations and the lack of Sleep Medicine diagnostic and management services mean that validated simplified care models are likely to be the only option for OSA health care in many areas. These studies have the potential to significantly improve the access and cost effectiveness of care to patients with moderate to severe OSA and reduce

the significant health, and economic burden of OSA, both to the Australian community and also around the world.

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