

**FACTORS AFFECTING INITIAL ACCEPTANCE OF AND
SUBSEQUENT COMPLIANCE WITH CONTINUOUS POSITIVE
AIRWAY PRESSURE TREATMENT FOR OBSTRUCTIVE SLEEP
APNOEA**

**Submitted in partial fulfilment of the requirements of
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PERSONAL STATEMENT

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ABBREVIATIONS

AASM: American academy of sleep medicine

AHI: Apnoea hypopnoea index

AUC: Area under curve

Auto PAP: Automatic positive airway pressure

Bi-PAP: Bi-level positive airway pressure

BDI: Beck's depression inventory

COPD: Chronic obstructive pulmonary disease.

CPAP: Continuous positive airway pressure

CRF: Case record forms

EPAP: Expiratory positive airway pressure

ER-PAP- Expiratory relief Positive airway pressure

ESS: Epworth sleepiness scale

FOSQ: Functional outcomes of sleep quality

HADS: Hospital anxiety and depression scale

IPAP: Inspiratory positive airway pressure

IQR: Interquartile ratio

KS- Test: Kolmogorov–Smirnov test

MMPI: Minnesota Multiphasic Personality Inventory

MSLT: Mean sleep latency testing

NICE: National institute of clinical excellence

NHS: National health service

NS-SEC: National statistics socio-economic classification

ODI: Overnight desaturation index

OR: Odds ratio

OSA: Obstructive sleep apnoea

OSAHS: Obstructive sleep apnoea hypopnea syndrome

OSLER: Oxford Sleep Resistance test

RDI: Respiratory disturbance index

ROC curve: Receiver operator characteristics curve

RSSC: Respiratory support and sleep centre

SF-36: Short form 36

SAQLI: Sleep apnoea quality of life index

VAS: Visual analogue scale

ABSTRACT

Background: Compliance with CPAP treatment for OSA is not reliably predicted by the severity of symptoms or physiological variables. I conducted a series of studies to examine a range of factors that may affect compliance with CPAP.

Methods: I performed a retrospective study examining association of demographic factors and OSA severity with long-term CPAP compliance. In a prospective study, I looked at the correlation of short and long-term CPAP compliance with socio-economic status, education, type D personality, demographics, disease severity, mood and clinician's prediction. I undertook a prospective, cross-over trial comparing the impact of Bi-level PAP therapy in individuals with low tolerance of CPAP.

Results: In a retrospective analysis, an improvement in subjective daytime somnolence was correlated with optimal compliance. In the prospective study, median compliance with CPAP at 6 months was 5.6 (3.4- 7.1) hours / night with 73% of subjects using CPAP ≥ 4 hours/night. Compliance with CPAP was not found to be associated with socio-economic class for people in work, type D personality, education, sex, age, baseline sleepiness (ESS score) or disease severity (ODI). The clinician's initial impression had no predictive value for individual patients. Subjects who were long-term unemployed or reporting mood disorders (High Beck's Depression Index scores) were likely to have poor compliance and sub-optimal CPAP usage (OR 4.6, $p = 0.011$ and OR 1.4, $p=0.04$ respectively). Subjects experiencing side effects after the first night on treatment showed lower acceptance and subsequent compliance. In the cross-over trial, changing to Bi-level PAP in individuals with

suboptimal compliance due to pressure related intolerance, did not lead to an improvement in CPAP compliance. In post-hoc analysis, compliance and comfort were better in the subgroup that complained of difficulty with exhalation on CPAP.

Conclusion: My research as presented in this thesis, did not find an association between disease severity (ODI), socio-economic status (for people in employment), education or personality type and CPAP compliance. My research demonstrated that subjects with long-term unemployment, mood disorders and those experiencing side effects on the first night of treatment were likely to have sub-optimal compliance. Changing to Bi-level PAP is only likely to be useful for a sub-group of subjects experiencing pressure related intolerance. More research is needed to explore whether intensive support to individuals with OSA and long term unemployment, as well as mood disorders, may improve compliance.

CHAPTER I

INTRODUCTION

CHAPTER I INTRODUCTION

In this chapter, I have presented a summary of the evidence related to compliance with Continuous positive airway pressure (CPAP) therapy in Obstructive sleep apnoea (OSA). Section 1.1 is an overview of the prevalence and impact of OSA. Section 1.2 describes the principles of CPAP therapy, its indications, effectiveness and optimal use. Section 1.3 reviews the factors determining the acceptance and compliance with CPAP.

SECTION 1.1 OBSTRUCTIVE SLEEP APNOEA

1.1.1 Definitions, prevalence and diagnosis

OSA is a condition characterised by repeated episodes of partial or complete collapse of the upper airway during sleep. The airway collapse is associated with reduced or absent airflow despite on-going efforts against the occluded airway. An **obstructive apnoea** is defined as a ≥ 10 second pause in airflow with on-going ventilatory effort. Obstructive hypopnoea is defined as reduction, but not complete cessation of airflow associated fall in arterial oxygen saturation. The American Academy of Sleep Medicine task force proposed that an **obstructive hypopnoea** is either

- (i) A $\geq 30\%$ drop in the nasal flow signal combined with $\geq 4\%$ drop in the oxygen saturation or
- (ii) A $\geq 50\%$ drop in the nasal flow signal for ≥ 10 seconds with $\geq 3\%$ drop in the oxygen saturation (Berry RB, 2007). This definition was modified in

2012 as a $\geq 30\%$ drop in nasal flow signal for ≥ 10 seconds associated with $\geq 3\%$ drop in oxygen saturation or arousal (AASM 2012). The 10-second criterion used to diagnose these events is used by convention (Berry RB, 2007; Quan SF, 1999). The apnoea-hypopnoea index (AHI) is the number of events per hour as recorded during sleep.

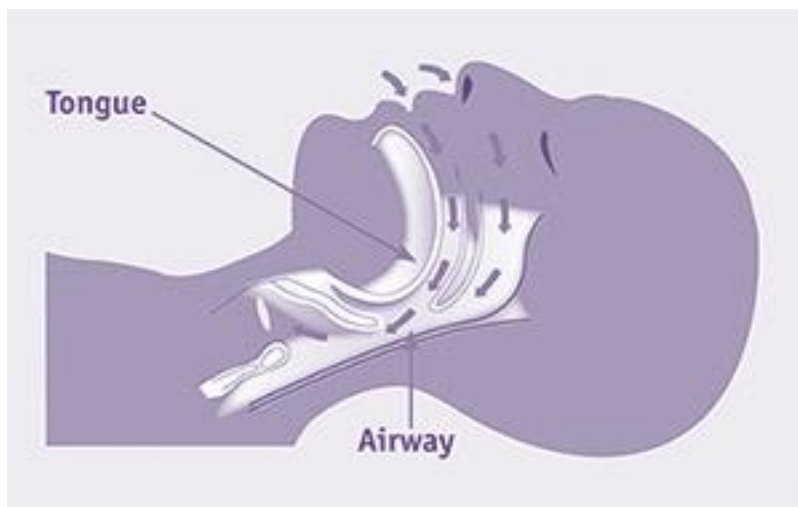
In 1837, Charles Dickens gave what may be the first published description of OSA in "Pickwick papers" (Dickens C, 1837) "Joe", one of the characters was described as, "... and on the box sat a fat and red-faced boy, in a state of somnolency." Sir William Osler, in 1918 wrote of "A remarkable phenomenon associated with excessive fat in young people, is an uncontrollable tendency to sleep-like the fat boy in Pickwick" (Osler, 1918). In 1956, Burwell et al reported several obese, hyper somnolent patients with respiratory and cardiac failure and coined the term "Pickwickian Syndrome" (Burwell CS, 1956).

It wasn't until 1965, that a group of French investigators made the important observation that "Pickwickian" patients had repetitive apnoeic events during sleep (Gastaut H, 1966). A group of German investigators subsequently described a marked improvement in patients treated with tracheostomy (Kuhlo W, 1969). They suggested that a likely reason why apnoeas occur is the collapse and closure of the upper airway during sleep.

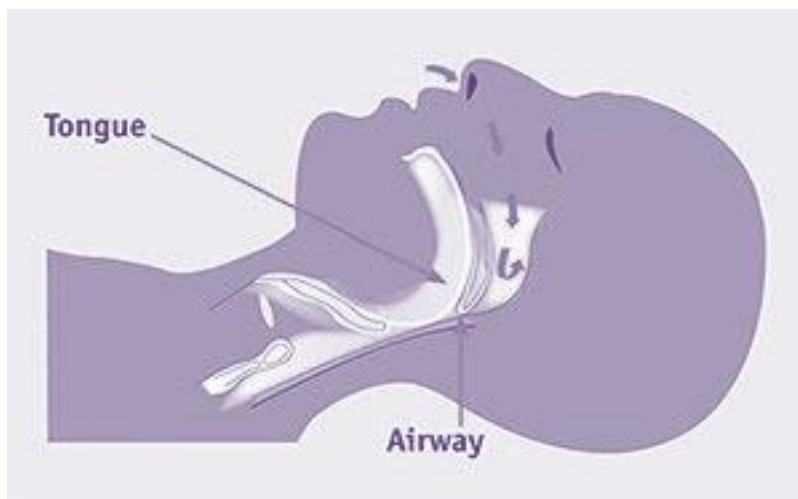
The patency and the tendency of the airway to collapse during sleep is affected by a number of factors. These include the size and shape of the upper airway, the strength and timing of reflex activation of upper airway dilator muscles, surface

forces and the load applied to the airway which is affected by mass loading (usually by adiposity) and position (supine or side lying). Imbalances between the mechanical load and compensatory neuromuscular responses during sleep can result in collapse of the airway (Figure1) (Patil S, 2007).

Figure 1: Anatomy of airway in normal individuals and in OSA



Normal airway



Obstructed airway in OSA

Apnoeas and hypopneas are usually terminated by arousal from sleep. This may lead to interrupted and unrefreshing sleep and excessive daytime sleepiness. Obstructive sleep apnoea hypopnoea syndrome also known as OSAHS, is thus a symptom complex of excessive daytime sleepiness in patients with significant obstructive apnoeas and hypopneas during sleep.

To diagnose OSAHS, individuals must fulfil criteria 1 or 2, plus criterion 3 (Quan SF, 1999).

1. Excessive daytime sleepiness that is not better explained by other factors.
2. Two or more of the following that are not better explained by other factors:
 - Choking or gasping during sleep,
 - Recurrent awakenings from sleep,
 - Unrefreshing sleep,
 - Daytime fatigue,
 - Impaired concentration and/or

3. Overnight monitoring demonstrates five or more obstructed breathing events per hour during sleep. These events may include any combination of obstructive apnoeas/ hypopneas or respiratory effort related arousals (RERA).

RERA is defined as a sequence of breaths characterized by increasing respiratory effort leading to an arousal from sleep, but which does not meet criteria for an apnoea or hypopnoea. These events must fulfil both of the following criteria:

1. Pattern of progressively more negative oesophageal pressure, terminated by a sudden change in pressure to a less negative level and an arousal
2. The event lasts 10 seconds or longer

The justification for using > 5 obstructive events (apnoeas or hypopneas) per hour in diagnosing OSA is based on epidemiological evidence that suggests that clinically significant adverse health effects related to OSA (including sleepiness, hypertension and motor vehicle accidents), may be observed at this threshold (Young T 1997a; Young T 1997b; Young T 1996). Based on the frequency of obstructive breathing events as measured by AHI, OSA severity has been divided into 3 categories (Quan SF 1999):

Mild	5-14 events per hour
Moderate	15-30 events per hour
Severe	> 30 events per hour

However, there is poor correlation between these criteria and the severity of symptoms in individuals with OSA (Yue H, 2009; Johansson P, 2009).

Prevalence

Epidemiological studies have estimated that around 3-7% of adult men and 2-5% of adult women have OSAHS (Lindberg E 2000; Punjabi NM 2008). However, the prevalence of mild OSA ($AHI \geq 5 \text{ hr}^{-1}$) vary from 3 to 28% and moderate OSA range from 1 to 14% in middle aged subjects (Bixler EO 1998; Bixler EO 2001; Young T 1993) (*Table 1*). This variability in reported prevalence is often a function of sample sizes and variance in definition of OSA. In studies with laboratory confirmation of OSA, the

prevalence estimates were in closer agreement (Young T, 1993; Bixler EO, 1998; Duran J, 2001).

Table 1: Prevalence of obstructive sleep apnoea in different population groups

Study Location	N	Age Range (years)	Estimated Prevalence of AHI ≥ 5 events/hour (% [95% CI])		Estimated Prevalence of AHI ≥ 15 events/hour (% [95% CI])	
			Men	Women	Men	Women
Wisconsin	626	30–60	24 (19–28)	9 (6–12)	9 (6–11)	4 (2–7)
India	250	35–65	19.5%	Na	8.4%	Na
Korea	309	40–69	27	16	10.1	4.7
Pennsylvania	1,741	20–99	17 (15–20)	Not given	7 (6–9)	2 (2–3)
Spain	400	30–70	26 (20–32)	28 (20–35)	14 (10–18)	7 (3–11)

(Bearpark H, 1995; Duran J, 2001; Ip MS, 2001; Kim J, 2004; Udwadia ZF, 2004; Peppard PE, 2000).

1.1.2 Risk factors

Age: The prevalence of OSA increases with age. In the elderly, the prevalence of moderate OSA varies from 7- 44% (Duran J, 2001; Bixler EO, 1998, Bixler EO, 2001, Ancoli-Israel S, 1991). Data from “Sleep Heart Health Study” (Sahar E, 2001) and other observational studies have shown that the prevalence of OSA increases steadily during the middle age and plateaus around 65 years.

Excess body weight: Body weight has been shown to be a strong independent predictor for OSA (Bixler EO, 1998; Bearpark H, 1995; Duran J, 2001; Ip MS, 2001; Ip MS, 2004). In the Wisconsin Sleep Cohort study, one standard deviation increase in the body weight was associated with a fourfold increase in disease prevalence (Young T, 1993).

Fat distribution- Central obesity, which has close association with neck circumference, is associated with the severity of OSA, particularly in men (Davidson TM, 2008; Martinez Rivera C, 2008). Postulated links between the two factors include (i) tracheal tug and hence diminished upper airway calibre as a result of central obesity and (ii) leptin deficiency in obese individuals and hence fluid shift with resultant reduced upper airway calibre. (Polotsky M, 2012; White WH, 2013; Degache F, 2013).

Sex: It is recognised that men are at higher risk of developing OSA than women. Clinic based studies show a significant gender gap in OSA prevalence with a ratio of men versus women of 5 to 8:1 (Strohl KP, 1996; Young T, 1993; Bixler EO, 2001; Duran J, 2001; Redline S, 1994). In the general population, this gender difference is less marked. Men outnumber women at 2 to 3: 1 with a further narrowing of gender gap after menopause (Bixler EO, 2001).

Race: Asians have a higher severity than white Caucasians perhaps due to specific cephalometric differences between the two populations (Ong KC, 1998; Li KK, 2000; Lam B, 2005). African – Americans however, have similar disease prevalence as white Caucasians Americans (Young T, 2002; Redline S, 1997).

Smoking and Alcohol: Current smoking is linked with a higher prevalence of snoring and OSA (Stradling JR, 1991; Jennum P, 1992; Wetter DW, 1994). This may be due to

altered neural and mechanical properties of the upper airway secondary to inflammation from smoking resulting in increased airway collapse.

Consumption of alcohol in moderate-severe quantities is also known to influence the severity of OSA (Scanlan MJ, 2000). Possible explanations proposed for its effect on OSA include reduction in arousal response, selective reduction in motor activity of genioglossus and hypoglossus (Krol RC, 1984), increased nasal mucosa oedema and increased resistance (Robinson RW, 1985; Issa FG, 1982).

Familial and genetic: First-degree relatives have a higher risk of the disease (Redline S, 2000; Redline S, 1995). Segregation analysis of the Cleveland Family study showed that up to 35% of the variance in disease severity may be attributable to genetic factors (Buxbaum SG, 2002) and distribution of fat may be a contributory factor in this association.

Craniofacial anatomy: Cephalometric analyses has shown that retrognathia, enlarged tongue/soft palate, inferiorly positioned hyoid bone, retro position of mandible and maxilla, tonsillar hypertrophy, brachycephaly, shorter cranial base and an acute cranial flexure may predispose to apnoea and hypopnoea during sleep (Li KK, 2000; Cistulli PA, 1996). Polycystic ovary syndrome, hypothyroidism, acromegaly and pregnancy may be associated with OSA, due to narrowing of upper airway by increased soft tissue and/ or by macroglossia (Vgontzas AN, 2001; Fogel RB, 2001; Rajgopal KR, 1984; Pien GW, 2005) It should be noted that in each of these conditions there are also endocrine changes, which may affect tone of the muscles in the upper airway.

1.1.3 Clinical presentation

Individuals with OSA commonly present with a history of loud snoring, witnessed apnoeas, interrupted or unrefreshing sleep and excessive daytime sleepiness. They usually have 2 or more of the following symptoms/signs at the time of presentation.

1.1.3.1 Nocturnal symptoms and signs

Snoring is the most common symptom of OSA, present in 70-95% of patients (Whyte KF, 1989). Habitual snorers (snore 3-7 times per week) are more likely to have OSA of mild-moderate severity compared to non-habitual snorers (OR 2.87) (Young T, 1993; Sharma SK, 2006). Snoring is however very common in the general population and therefore not specific to the diagnosis of OSA. Snoring is also significantly associated with male sex, age 25 or more, obesity, daytime sleepiness or naps, night time awakenings, consuming large amounts of caffeine and smoking (Ohayon MM 1993).

Witnessed apnoeas It is usually the bed partner who gives the history of apnoeic episodes (Hoffstein V, 1993) as, most patients are unaware of apnoeas. Witnessed apnoeas are a good predictor of OSA (Deegan PC, 1996; Hoffstein V, 1993) although not specific and can also occur, in association with central sleep apnoea or Cheyne-stokes respiration.

Choking or dyspnoea Choking or dyspnoea that interrupts sleep is reported by 18% to 31% of patients with OSA (Kales A, 1985; Maislin G, 1995). Vigorous inspiratory effort to overcome upper airway obstruction can lead to an enhanced negative intra-thoracic pressure swings, increasing venous return, pulmonary capillary wedge pressure and can contribute to the sensation of dyspnoea (Buda AJ, 1981).

Interrupted or unrefreshing sleep Upper airway collapse is usually terminated by arousal. Arousals are defined as a shift from a state of sleep to a state of wakefulness (Phillipson EA, 1978) and are due to increased respiratory effort against the upper airway obstruction (Berry RB, 1997, Gold AR, 1986). Repeated episodes of apnoeas followed by arousals leads to significantly interrupted and hence unrefreshing sleep.

Nocturia Nocturia is reported by up to 50% of patients with OSA (Guilleminault C, 2004; Barker JC, 1988; Stewart RB, 1992; Middelkoop HA, 1996) and may correlate with severity of disease (Oztura I, 2006; Kiely JL, 2000; Fitzgerald MP, 2006). Proposed mechanisms include increased abdominal pressure and increased atrial natriuretic peptide (Kreiger J, 1989; Umlaut M, 2004).

Erectile dysfunction Erectile dysfunction with impaired nocturnal and early morning penile tumescence (Margel D, 2006; Gonsalves MA, 2005) and a loss of interest in sex is common in men with OSA (Watson R, Sleep Res, 1987). Proposed mechanisms include vascular, endocrine and autonomic neural pathways. (FanfullaF, 2000). There is an association between erectile dysfunction and nocturnal arterial oxygen desaturation (Gonsalves MA, 2005) and endothelial dysfunction (Karacan I 1995; Santamaria JD, 1988; Grunstein RR, 1994).

1.1.3.2 Daytime symptoms

Excessive daytime sleepiness This is the most common complaint of patients with OSA (Kales A 1985; Hofstein V 1993). Attempts to assess subjective sleepiness have

been made using self-reported sleepiness scales (e.g. Epworth sleepiness scale, Berlin questionnaire, Stanford sleepiness scale) (Johns MW, 1991; Herscovitch J, 1981) and by measuring mean sleep latencies or surrogates for sleep in a sleep laboratory.

The Epworth sleepiness scale score (ESS) (*Appendix 1*) is a widely used self-reported scale to assess daytime sleep propensity (Johns MW, 1991). The ESS asks people to rate on a 4-point scale their chance of falling asleep in 8 different situations or activities (0- no chance of falling asleep, 1 is slight chance, 2 is moderate chance and 3 is severe chance). A score of greater than 10 out of a maximum of 24 is considered abnormal and suggests excessive daytime sleepiness (Johns MW, 1991, Johns MW, 1997). It may underestimate the severity of sleepiness in the setting of chronic hypersomnolence and may overestimate the sleepiness in depression or chronic fatigue syndrome (Chervin RD, 1999). Whilst this is still a subjective way of assessing daytime sleepiness and is not a perfect tool, it remains the most widely studied and validated tool for assessing daytime sleepiness. However, only 23% of women and 16% of men with OSA (AHI of 5 or more) reported symptoms of sleepiness, defined by ESS>10. There are however individual differences and lack of correlation between AHI and measures of daytime sleepiness (Gottlieb DJ, 1999, Chervin RD, 1999).

Other daytime symptoms Other symptoms, which are not specific but are commonly associated with OSA, are memory impairment, fatigue, lack of concentration and changes in behaviour/ personality, depression. Untreated OSA is also proven to be associated with matrimonial disharmony (Reishtein JL, 2006).

Road traffic accidents- Individuals with OSA are at increased risk for road traffic accidents (Shiomi T, 2002; George CF, 2001, Horstmann S, 2000, Teran Santos J, 1999,

Young T, 1997a; Tragear V, 2009). The prevalence of OSA is higher amongst commercial drivers with estimates of mild OSA of around 28% and severe OSA around 5% (Pack AI, 2006; Tragear V, 2009).

1.1.4 Diagnosis

The overnight polysomnogram (PSG) has been proposed as the gold standard test for diagnosing OSA. It is a detailed analysis of respiratory events combined with information about the stages of sleep and arousals based on electroencephalogram criteria (Cheeson AL, 1997). PSGs are resource intensive and usually require facilities for overnight stay in a sleep laboratory and trained sleep scientists to analyse the studies. Despite consensus guidelines and attempts at a global standardisation in reporting PSGs, inconsistencies exist in the analysis and interpretation in different sleep laboratories (Redline S, 2000; AASAM, 2007). Moreover, AHI measured by PSG as a marker of OSA lacks a close correlation with excessive daytime somnolence, and with morbidity or mortality (Bennett JA, 1999). There is poor repeatability in the same laboratory and instrumentation may affect the quality of sleep and sleeping position and hence the AHI.

Portable, home based, diagnostic studies including limited (respiratory) sleep studies and nocturnal arterial pulse oximetry monitoring are an alternative to PSG. Limited sleep studies monitor oro-nasal flow, thoracic and abdominal movements, arterial oxygen saturation, snoring, heart rate and body position, whereas nocturnal oximetry records oxygen saturation and heart rate via non-invasive arterial pulse oximeters. Limited sleep studies have clinical correlation with and cost savings compared to PSG

(Golpe R, 2002, Whittle AT, 1997; Verse T, 2000). The primary weakness is the lack of sleep staging, which leads to an uncertainty as to whether respiratory events were occurring during sleep or wakefulness.

An alternative diagnostic strategy in suspected sleep apnoea patients, is to use nocturnal oximetry and if it is inconclusive, then to proceed to respiratory sleep study or PSG. In nocturnal oximetry, a repetitive pattern of 4% or more desaturations followed by a quick return to baseline is typical of OSA. Hypopneas can be present with 3% desaturation and hence are not necessarily picked up on oximetry criteria alone (AASM, 2007, AASM 2012). If the oximetry is non-diagnostic, further investigations including respiratory sleep studies or PSG may be done to confirm the diagnosis. Though nocturnal oximetry is useful in the screening of moderate to severe disease, it is not helpful in mild OSA as it does not distinguish respiratory effort related arousals (RERA) or hypopneas associated with 3% desaturation, which are common in mild disease (Cooper BG, 1991). The sensitivity of nocturnal oximetry in diagnosing OSA is variable from 31-98% with specificity 41-98% (Netzer N 2001) due to differences in equipment with variable signal averaging time and threshold values of desaturation index used in different studies (*Table 2*).

In clinical practice, the diagnostic sensitivity and specificity are likely to improve further if the symptoms of OSA are taken into consideration. Sleep studies including 4% oxygen desaturation index threshold of >10 per hour in symptomatic individuals can reliably be used to diagnose OSA. In a randomised controlled trial involving 246 patients, PSG derived AHI and oximetry derived respiratory disturbance index (RDI calculated as a total number of 4% drop in oxygen saturations from baseline divided

by total monitor probe on time) were highly correlated (R=0.97). The mean difference between AHI and RDI was 2.7. Using a criterion of 10 events every hour for AHI and Respiratory disturbance index (RDI), the sensitivity and specificity were 97% and 80% respectively (Vazquez JC, 2000).

Table 2: Sensitivity and specificity of nocturnal oximetry in diagnosing OSA.

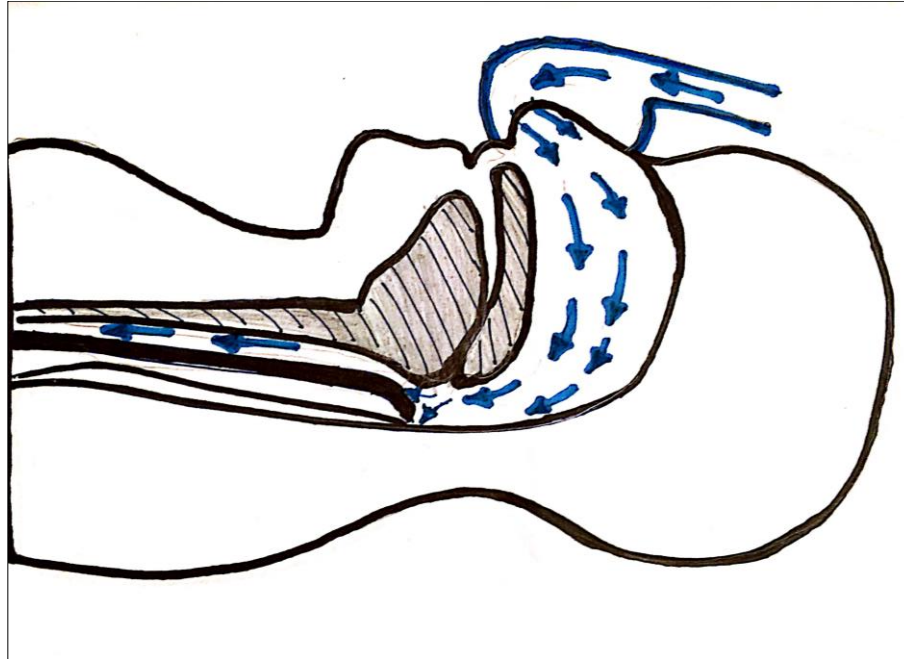
Author	Study Population, No	AHI/ODI Cut-off Point	Screening Specificity, %	Screening Sensitivity, %
Ryan S (1995)	69	≥ 15	100	31
Levy P (1996)	301	≥ 15	94	77
Lacassagne I (1997)	329	≥ 15	57.8	89
Sano K (1998)	40	≥ 15	83.3	73.5
Olson LG (1999)	113	≥ 15	70	88
Golpe R (1999)	116	≥ 10	97	84
Brouillete RT (2000)	349	NA	96	58
Nuber R (2000)	70	NA	77.8	85.2–91.8
Vazquez JC (2000)	246	≥ 10	80	97

1.1.5 CPAP therapy

1.1.5.1 Principles of CPAP therapy – Initially described in 1981 (Sullivan CE, 1981). CPAP IS the primary modality of treatment for OSA. With a mask covering the

nose or nose and mouth with a tight seal attached via a hose to a pressure generator, it works as a pneumatic splint to prevent upper airway collapse during sleep (Figure2).

Figure 2: CPAP with the pneumatic splint



1.1.5.2 Mechanism of upper airway occlusion and its prevention by nasal CPAP

When the patient is awake, muscle tone prevents collapse of the upper airway during inspiration. During sleep, the tongue and soft palate are sucked against the posterior oropharyngeal wall leading to airway narrowing and closure. CPAP provides a pneumatic splint and keeps the upper airway open (Sullivan CE 1981).

Though mechanical pneumatic splinting is thought to be the primary physiological process by which CPAP functions, there are other postulated mechanisms. One proposal is that upper airway stabilization is achieved by an increase in lung volume, which increases the tone of upper airway dilator muscle and prevents collapse (Berry

RB 2003; Hoffstein V 1984). Another is that forces associated with increased lung volume are transmitted to upper airway by the trachea resulting in a “tracheal tug” which stabilizes the airway (Begle RL, 1990; Brown IG, 1985).

1.1.5.3 Effectiveness of CPAP therapy

CPAP is effective in reducing and treating OSA (Ballester E, 1999; Gay P, 2006). There is evidence that CPAP treatment improves daytime sleepiness. In a meta- analysis including 745 patients, treatment with CPAP was associated with an improvement in ESS scores (4.75 vs. 1.10, $p < 0.001$) in severe OSA patients with sleepiness. Control treatment comprised of either no or minimal therapy (lifestyle changes/ weight intervention) OR a true placebo such as Sham CPAP (Patel SR, 2003). Objective measures of sleepiness were also shown to improve (Patel SR, 2003).

Treatment with CPAP has been shown to improve quality of life. Both general (Short Form 36) and disease specific quality of life indices (Sleep apnoea quality of life index, functional outcome of sleep questionnaire) (Smith IE, 1995; D’ambrosia C, 1999; Engleman HM, 1996; Kotterba S, 1998; Redline S, 1998) show an improvement on CPAP treatment in symptomatic individuals.

Improvement in driving simulation performance is seen as early as a few days after starting treatment and (Orth M, 2005; Turkington PM, 2004) some of the improvements appears to be sustained up to 1 week after the withdrawal of CPAP (Kribbs NB, 1993a; Tregear S, 2007; Kohler M, 2011).

A study which compared an OSA cohort using CPAP with population based controls, found the incidence of road traffic accidents is reduced significantly in the group who were treated with CPAP (Karimi M, 2015).

1.1.5.4 Impact of CPAP therapy on cardiovascular risk factors

Extensive research has evaluated the relationship between OSA and hypertension and the impact of CPAP. (Nieto FJ, 2000; Hla KM, 1994; Carlson JT, 1994; Bartel PR, 1995; Young T, 1997b; O'Connor GT, 2009). CPAP treatment leads to a reduction in blood pressure (Dimsdale JE, 2000; Faccenda JF, 2001; Pepperrell JC, 2002; Becker HF, 2003; Norman D, 2006) but the results have not been consistent, in non-sleepy individuals (Robinson GV, 2006; Choi JB 2006, Barbe F, 2001, Monteserrat JM, 2007, Campos-Rodriguez F, 2006). CPAP therapy reduced the risks of future cardiac events including myocardial infarction and atrial tachyarrhythmia (Buchner N J, 2007; Neilan T G, 2013) as well as the risk of future stroke.

In different observational studies, CPAP therapy is associated with reduced mortality, though no randomised controlled studies have been done to prove this association (Campos-Rodriguez F, 2012; Campos-Rodriguez F, 2005; Marti S, 2002).

1.1.5.5 Impact of CPAP therapy on neurocognition and performance

Objectively measured cognitive performances assessed by a battery of neuropsychological tests were impaired in individuals with OSA. (Engleman HM, 2000; Redline S, 1997; Kim HC, 1997; Bedard MA, 1991; Naegele B, 1995; Greenberg GD, 1987). Evidence suggests that this impairment maybe reversible with CPAP (Engleman HM, 1994a).

1.1.5.6 CPAP Prescription

According to the National institute of clinical excellence (NICE) technological appraisal (NICE 2008), CPAP is recommended as a treatment for adults with moderate or severe symptomatic sleep apnoea.

In individuals with mild OSA, CPAP is recommended if:

Symptoms affect their quality of life and ability to go about their daily activities, and lifestyle advice (for example about losing weight, stopping smoking and cutting down on alcohol) and all other possible treatments have not worked or are not appropriate.

In summary, CPAP treatment is known to be an effective treatment in improving daytime sleepiness and quality of life (both generic and sleep apnoea specific) in individuals with OSA. CPAP is also shown to reduce the risk of road traffic accidents, blood pressure and other cardiovascular or cerebrovascular complications.

1.2 CPAP ACCEPTANCE & COMPLIANCE

Though CPAP is an effective treatment in reversing sleep apnoea (McArdle N, 2001) not everyone who is prescribed the treatment, “accepts” it. Also among those who initially accept the treatment, subsequent use may vary from a few nights to all nights every week and from few hours per night to most of the night.

1.2.1 CPAP acceptance

CPAP acceptance is defined as the willingness to consider CPAP treatment and to use it for at least a period of time. There is no consensus on the specific period of time, to

define whether the treatment is accepted or not. It can vary from accepting the idea of having CPAP trial for one week (McArdle N, 1999; Kreiger J, 1996) to a more prolonged period (Rolfe I, 1991).

If initial acceptance is defined as individuals willing to undergo CPAP titration and use it for at least one week, 5-50% of individuals appear to reject treatment (McArdle N, 1999; Kreiger J, 1996; Rauscher H, 1991; Fleury B, 1994; Engleman HM, 2003). In one of the early studies, out of 233 patients who were recommended CPAP treatment, 19 (8%) refused treatment and amongst the initial acceptors 181 (78%) were still using the treatment during the follow up period of almost 3 years (Kreiger J, 1992). In a large observational study, 5% of patients with OSA booked for CPAP treatment did not turn up repeatedly. Compared to the individuals who accepted CPAP treatment for the trial 14% of men declined to accept the treatment compared to 31% of women (Engleman HM, 1999).

Sleepiness and severity of disease have not been consistently associated with acceptance. In a prospective observational study, no association was found between poor initial acceptance and daytime sleepiness (measured by ESS) or AHI. Others have shown poor acceptance amongst individuals who are not sleepy or where the severity of sleep apnoea was less profound (Barbe F, 2001, Rauscher H, 1991).

Another study, in a health system where the cost of the treatment (partial or full) is incurred by the patient, showed that out of 162 consecutive patients with OSA of variable severity, only 40% who were recommended treatment accepted it. This was despite the fact that that patients had to pay only 30% of the cost towards CPAP.

Factors associated with the acceptance included older age, higher income, no bed partner and more severe OSA. These were also the patients who would have heard positive experiences from family and friends (Simon-Tuval T, 2009).

Long-term CPAP Compliance

In a study of long-term CPAP use in OSA, independent predictors of long-term CPAP adherence were disease severity (AHI ≥ 15 / hour), daytime somnolence (ESS >10), history of snoring (McArdle N, 1999; Chai-Coetzer CL, 2013). Initial CPAP adherence (one month) was associated with higher CPAP adherence at 12 months.

Amongst patients who accept treatment, 12-25% may be expected to discontinue this in a 3-year follow up (McArdle N, 1999; Kreiger J, 1996; Popescu G, 2001).

In a study where 209 patients were offered a loan of CPAP machine for a home trial and were followed up in the clinic with further usage data available at 1 year follow up (Popescu G, 2000). Following the initial treatment trial 196 (94%) tried a treatment trial at home and 153 (73%) continued. Factors associated with continued use of CPAP at 1 year were disease severity and a greater change in daytime somnolence following initial therapy, while the lack of titration and failure to improve symptoms are likely to lead to poor compliance (Wang Y, 2012).

Compliance is defined as the “degree to which a patient correctly follows medical advice”. Most commonly, it refers to medication or drug compliance, but it can also apply to other situations such as medical device use, self-care, self-directed exercises, or therapy sessions. Compliance with CPAP treatment can be defined as the average use of CPAP every night. Compliance is monitored by inbuilt clock counters (measures the number of hours CPAP is used) or by electronic cards, which

record more accurately the number of hours that the mask was on the face and pressure delivered and thus gives information about night to night variability. There is no accepted definition of “optimal CPAP compliance” though the expert consensus view is to use it more than 4 hours per night and its use more than 70% of the nights (Kribbs NBb, 93). This specific figure of 4 hours per night is arbitrary and is based on minimal criteria for adequate sleep from general sleep duration. It is however accepted that CPAP should be used throughout the duration of the sleep to get the best benefits.

There is a linear dose response relationship between the number of hours CPAP is used and measures of subjective (ESS) and objective sleepiness (Multiple sleep latency testing- MSLT) (Weaver T, 2007). When assessing the impact of CPAP on quality of life (i.e. FOSQ), benefit is seen when used up to 7 hours with no further benefit beyond that period (Weaver T, 2007).

Compliance with CPAP treatment is quite similar to observed adherence rates to other treatment for chronic illnesses. Amongst asthmatics, adherence to medications measured as percentage of prescribed medication taken ranges from 30% to 70% (Bender BG, GINA, Rand CS; Reid D, 2000; Pearson MH, 1999). A similar pattern of adherence has been observed in other chronic illnesses including hypertension, depression, rheumatological illnesses and diabetes and poor adherence to medication is also known to influence the health related outcomes in chronic illnesses (Costa FV, 1996; WHO 2003).

Factors that are known to influence or likely to affect the initial acceptance and

subsequent compliance with the treatment are discussed in the sections 1.2.1- 1.2.5

1.2.2 Sleep apnoea related factors (Severity of OSA)

The severity of underlying OSA (higher AHI, sleepiness and snoring) has been proposed as an important factor, which affects subsequent compliance with CPAP therapy in symptomatic individuals. The relationship is however not very clear with conflicting results from different studies (Lloberes P, 2004; Krieger J, 1992; McArdle N, 1999; Rauscher H, 1993; Somners ML, 2011). However, in a study involving 47 patients with OSA who were followed up closely at 2-8 weeks' intervals, AHI was not found to be associated with optimal compliance (Reeves-Hoche MK, 1994; Engleman HM, 1999; Engleman HM, 1994b). In a randomised multicentre trial in Europe involving 121 patients with OSA who had covert CPAP monitoring, compliance at 3 months was not found to be associated with baseline AHI or severity of OSA. (Pepin JL, 1999)

The level of nocturnal hypoxemia (minimum oxygen desaturation and 4% oxygen desaturation index), another parameter related to the severity of OSA, has not been consistently shown to be associated with adherence and compliance with CPAP (Kribbs NB, 2007; Nosedá A, 2000).

Amongst the factors associated with the severity of OSA a consistent association between adherence and compliance with CPAP has been found with pre-treatment ESS. McArdle and colleagues showed an ESS>10 independently predicted long-term CPAP use (HR 1.98, p<0.001) (McArdle, 1999) (*Table 3.*)

Table 3: Different factors affecting CPAP compliance

Author	Type of study/ duration/ Number of participants	Average CPAP use	Positive associations	Negative associations
Waldhorn RE	Retrospective/3 yr/96	N/A but only 73 (76%) continued CPAP at 14.5 mo	Positive: severe subjective daytime sleepiness; negative: previous palatal surgery	Baseline AHI or sleep staging, AHI or sleep staging on CPAP, CPAP side effects
Krieger J	Prospective/874 d/214	5.6 ± 0.1 (SE) run time	AHI, AI, minimal Sao2, day Pao2, pulmonary artery pressure	
Meurice JC	Prospective/14 mo/44	6.0 ± 2.5 (SD) run time	Initial AHI, % light sleep and % deep sleep, improvement in AHI, mean Sao2 and hypersomnia score	CPAP side effects
Engleman HM	Prospective/3 mo/54	4.7 ± 0.4 (SE) run time, 4.2 effective time	CPAP side effects	AHI, MSLT, ΔMSLT
Kribbs NB	Prospective/3 mo/35	4.9 ± 2.0 (SD) effective time	Satisfaction with CPAP, daily energy level at follow-up	AHI, minimum Sao2, MSLT
Reeves-Hoche MK	Prospective/6 mo/38	4.7 run time, 4.3 effective time	High AHI correlated with effective mask pressure	AHI, age, gender, BMI, weight loss, education level
Engleman HM	Retrospective/632 d/204	5.1 ± 2.5 (SD) run time	Positive: ESS, improvement in nocturnal symptoms and daytime function, negative: CPAP-related awakenings, noise, and sore eyes	AHI, CPAP mask leak, and rubbing, dry throat/nasal stuffiness
Krieger J	Prospective/1,176 d/575	5.7 ± 1.8 (SD) run time	Positive: age, BMI, and AHI, negative: Day Pao2, FEV1, and FVC	Symptoms of OSA and CPAP side effects
Pieters T	Retrospective/784 d/84	5.0 ± 1.8 (SD) run time	Positive: Movement arousal index, negative: age, mean Sao2 during non-REM sleep	
Likar LL	Retrospective/1,151 d/34	5.2 ± 0.5 (SE) (pre-clinic), 6.3 ± 0.6 (SE) (post clinic) run time	Group CPAP clinic education (four sessions)	
Hoy CJ	Prospective RCT/6 mo/intensive support (n = 40) vs standard support (n = 40)	5.4 ± 0.3 (SE) (intensive) vs 3.9 ± 0.4 (SE) (standard) effective time	Intensive support (additional nursing input, 3 nights CPAP titration, and home visits), self-referral	Duration of CPAP therapy
McArdle N	Prospective/median 22 mo/1,155	Median 5.7 run time	Snoring, AHI, ESS, average CPAP use within the first 3 mo	
Pepin JL	Prospective/3 mo/(A) n = 63 CPAP with run time vs (B) n = 58 CPAP with both run time and effective time	5.1 (group A), 5.8 (group B) run time	Improvement of nocturia and subjective sleep disruption	Age, BMI, Pao2, Paco2, FEV1, VC, initial AHI and AHI with CPAP, CPAP level, improvement of snoring and daytime sleepiness, CPAP side effects
Nosedo A	Prospective/4 mo/106	4.9 effective time	Positive: early bedtime, negative: Minimum or mean Sao2, % of slow-	

			wake sleep	
Wolkove N	Retrospective/ 4 years/ 80		Sleep apnoea related symptoms	
Kohler M	Retrospective	6.2	ODI	ESS, Gender, Age, Neck circumference
Chai-Coetzer CL	Prospective / 12 month/ 275	3.3 +_ 2.4	Side effects at 1 month	

1.2.3 Treatment related factors

1.2.3.1 Initiation of CPAP

Initial experiences with CPAP are known to predict the subsequent compliance (Budhiraja R, 2007). In a prospective study, only 26% of patients who used CPAP sub-optimally on day 3, used it more than 4 hours on day 30. Side effects of CPAP were common, being reported by 30-70% of the patients started on the treatment (Hoffstein V, 1992; Engleman HM, 2003; Grunstein RR, 1995). CPAP users reported having a dry mouth (40%), nasal symptoms (31%), poor mask fitting/ leaks (28%) and skin irritation or soreness (17%). Others were inconvenienced by the noise, eye problems and claustrophobia (Chai Coetzer CL, 2013). Conversely, Engleman et al found optimal CPAP usage in individuals who did not report any side effects (Engleman HM, 2003), though this association with reported side effects has not been observed consistently across other groups of patients (Hoffstein V, 1992; Hui DS, 2001; Engleman HM, 1996). Indeed, it is reported that health care personnel may perceive side effects to be more of a problem than patients do (Brostrom A, 2009).

1.2.3.2 Titration

Since the introduction of CPAP to treat OSA was first reported by Sullivan (Sullivan CE, 1983), a range of methods of CPAP titration have been employed with practice varying widely in different centres.

Among the various ways in which CPAP titration can be performed are:

1. Attended in hospital or unattended at home
2. Full night or split night
3. In the daytime or at night
4. Automatic or manual or with the pressure established according to a formula

According to the AASM taskforce, CPAP titration for patients >12 years of age (full or split night) involves the application of CPAP starting at a low pressure (i.e. 5 cm H₂O) and upward titration of pressures at ≥ 1 -cm increments over ≥ 5 -min periods. The titration goal is usually to abolish apnoeas or hypopnoeas, snoring and respiratory effort related arousals by maintaining airway patency, in all the body positions and sleep stages. These are continued until ≥ 30 min without apnoeic events is achieved. Higher starting CPAP may be used in individuals with high BMI or those requiring re-titration studies. Abolishing these sleep related breathing events by optimal CPAP titration should lead to an uninterrupted and refreshing sleep and hence improved daytime / nocturnal symptoms.

Attended polysomnography has been proposed to be the gold standard for PAP titration as it allows sleep stage and determination of arousals and body position (Kushida CA, 2008). However, it is a resource intensive approach as it requires

admission to the sleep laboratory for a night and a trained polysomnographer is needed to institute the titration during the night. Not only is this approach associated with higher financial costs, its effectiveness has been questioned especially due to the availability of effective and good alternative options (Masa JF, 2004).

The alternatives include split night studies or unattended home titration with an auto titrating CPAP. Split night studies involve admitting patients to the sleep laboratory. During the first half of the study, a diagnostic sleep test is performed. This is either a full polysomnography or limited channel respiratory sleep diagnostic test. If it confirms the diagnosis of OSA, then the sleep physiologist starts the patient on CPAP to prevent upper airway collapse, aiming to abolish apnoea/ hypopnoea as well as sleep related arousals. Pressures are gradually titrated till the desired physiological responses are achieved. Patients are then sent home on the fixed nasal CPAP settings achieved during the night of the study. With either of these approaches, the pattern is set on a single night or half night and cannot accommodate night-to-night variability.

Auto CPAP titration is another way to achieve the required therapeutic positive airway pressure. There is significant night-to-night variability in OSA severity with changes due to the patient's position, alcohol consumption and sleep quality among other factors (White LH, 2015). Auto CPAP is designed to detect flow changes and obstruction through the night. The delivered pressure is then adjusted to stop these events. This strategy allows the patient to initiate treatment as an outpatient. Both home studies and split night studies have been found to be cost effective as well as clinically effective alternatives to attended laboratory studies. There is, in addition,

good evidence that auto CPAP is an effective option alternative with short and the long-term compliance which is comparable to that achieved by patients who have had an inpatient titration (Skomro RP, 2010; Nosedá A, 2004; Desai H, 2009).

Full night vs. Split night: A full night titration involves a diagnostic sleep test on one night, which could be home or hospital based, followed by CPAP titration for a full night as an inpatient. Most studies of this approach have shown no difference in compliance or initial acceptance between a full night and split night titration (McArdle N, 2000, Yamashiro Y, 1995). In a cohort study matching patients on split night and full night PSG, no difference was observed in the initial acceptance and adherence rate when patients were followed up for 22 – 27 months (McArdle N, 2000). A case control study found no difference in compliance and acceptance at 4-6 weeks (Strollo PJ 1996), a result reproduced by others (Fleury B 1994; Sanders MH 2000).

Daytime vs. full night: In a cohort study comparing daytime vs. night time titration, no significant difference was observed in the final CPAP level, or the number of failures of treatment. After 12 weeks there was no difference in the number of patients not on CPAP or in those with self-reported CPAP use more than 5 nights per week (Rudkowski JC, 2001). In another smaller study of subjects with severe OSA, no differences were observed in average compliance or objectively measured number of nights CPAP was used, though the two groups were only followed for one week (Rosenthal L, 1998). A prospective study looked at the long-term uptake and compliance when OSA was diagnosed via limited sleep studies followed by daytime titration of the CPAP level (Johnson MK, 2004). At a median follow up of 23 months the median CPAP usage was 5.3 hours per night. Seventy-seven percent of patients

were still using CPAP at 3 years. Another prospective study involving 93 consecutive patients with OSA, CPAP pressure was significantly lower with conventional night-time or daytime manual titration compared to automatic daytime titration (7.5 cm, 7.4 cm and 9.4 cm respectively p 0.001). However, usage and improvement in daytime sleepiness were similar in the three groups (Loberes P, 2004).

Manual vs. Automatic titration (Auto-PAP)/ unattended home titration:

By virtue of their capability of changing pressure to a minimal delivered one to control sleep apnoea it was initially hypothesised that Auto PAP would lead to improved compliance. However experimental studies (discussed in the next section) have failed to show any significant beneficial effects in improving short and long-term compliance. Not only is Auto PAP used as a treatment modality, it is also used as a titration device to establish the best-fixed pressure required to control apnoeas and hypopneas. Masa et al in a randomised study of 315 patients compared Auto PAP with standard manual titration and with a predicted formula titration. No difference was observed between any of the 3 methods in controlling OSA or in the patients' average compliance with CPAP after titration (Masa JF, 2004). Similar observations have been made in other experimental studies (Stradling J, 1997; Berkani M, 1998; Mulgrew AT, 2007).

1.2.3.3 Modes of delivering positive airway pressure

Often the reason cited by patients for their inability to use CPAP is either problem with the interface (mask leaks, mask allergy, skin abrasion, claustrophobia), humidification (air dry or cold), pressure (too much pressure, mask leaks, rhinitis,

rhinorrhoea, aerophagia, difficulty exhaling) or equipment (noise, smell, tubing condensation, spousal intolerance).

In an attempt to improve patient tolerance with positive airway pressure treatment, alternative devices, which deliver pressure to the airway in a different way to conventional fixed pressure CPAP, have been developed. These include Auto PAP, Bi-level PAP, Expiratory relief PAP (C-Flex) and Bi-Flex.

Auto-PAP: delivers variable pressure through the night to control the apnoeic and hypopnoea events. Auto-PAP works with the principle of either detecting changes in “flow” or changes in “impedance”. An algorithm in the device leads it to respond to variation in respiratory flow, flattening of inspiratory flow contour or snoring (Stradling JR, 1997; Lloberes P, 1996; D’Ortho MP, 2000). More recent devices have an algorithm that responds to changes in airway resistance and impedance with the aid of forced oscillation technique (APAP FOT) (Ficker JH, 2003). Once the devices detect the differences in these respiratory parameters, they generate pressures aiming to overcome the obstruction. This dynamic process leads to delivery of variable pressure through the night rather than a fixed pressure as delivered by CPAP. Clinical use can be limited by the inability of Flow devices to discriminate between central and obstructive events, when there is complete cessation of flow. Also, devices based on impedance alone cannot detect leakages or increases of upper airway resistance, resulting in generation of higher pressures than needed (Stamnitz A 2004).

Though the pressure generated during the night to control obstructive events is lower with the Auto-CPAP, this is not translated into an improved effectiveness or compliance on treatment. In a meta-analysis, which looked at 9 available randomised

trials, Auto-PAP was not found to have any advantage over fixed CPAP in reducing AHI (Ayas NT 2004).

Another meta-analysis looked at the impact of pressure modification in improving CPAP usage in OSA patients (Smith IE 2009). Forty-five studies were reviewed including 30 using Auto CPAP (1136 participants). A small but statistically significant improvement in CPAP usage was observed in the Auto CPAP group (0.21 hours per night). However, the clinical significance of this small improvement in hours of use is questionable. Parallel group studies found no differences in the ESS score in different groups though crossover studies showed an improvement in ESS (0.64 units, -0.12- -1.16) in the Auto PAP group. Where measured, participants preferred to take Auto PAP home compared to standard CPAP (Smith IE 2009)

Bi-level-PAP: delivers different but fixed pressures during inhalation and exhalation, and can be used as alternative therapy in OSA patients. There are only a few published studies comparing this mode of PAP delivery with the fixed CPAP. Though it was found to be as effective as CPAP in treating OSA, no differences in efficacy or compliance with the treatment were observed in unselected populations (Reeves-Hoche MK, 1995; Laursen SB, 1998, Gay PC, 2003). Despite of this lack of clear evidence of benefit this mode continues to be used in clinical practice in a selected population of individuals with OSA struggling with CPAP mainly due to pressure intolerance (Smith IE, 2009). Another trial used a modified Bi-level device (Bi-flex), with reduced pressure at the end of inspiration and slightly reduced pressure near the beginning of expiration and compared this with CPAP in a randomised fashion. At 1 month no differences in compliance were observed between the two different modes.

Improvements in ESS and functional outcomes of sleep questionnaire were also similar for the two devices (Gay PC, 2003).

Expiratory relief PAP (C-FLEX): is another way of delivering positive airway pressure where the pressure is reduced at the beginning of expiration on a breath-by-breath basis in proportion to the person's expiratory flow rate. This drop makes exhalation easier compared to CPAP. The maximum pressure drop with this mode is 3.0 cm. Towards the end of expiration, the pressure increases and theoretically the optimal pneumatic splint is maintained so as to prevent airway collapse. It has been hypothesised that by reducing the pressure at the beginning of expiration, it should make it easier for the patient to tolerate PAP and hence improve compliance. However, other studies have yielded conflicting results. In a randomised crossover study, though the expiratory relief mode was found to be as effective as fixed CPAP, compliance was no different (Nillius G, 2006). No significant differences were observed in objective daytime sleepiness and simple response time (psychomotor vigilance test) between the two devices. In a longitudinal study, by Dolan et al, Expiratory Relief-PAP (ER-PAP) was associated with greater mask comfort on visual analogue scales while overall compliance and subjective sleepiness were not superior to CPAP therapy (Dolan DC, 2009). In a small prospective single blind cross over study involving 20 patients with OSA who were followed up for 3 years, ER-PAP was noted to be associated with identical short term compliance compared to CPAP (Wenzel M, 2007).

A-Flex: is a further modification of C-FLEX technology. During the expiratory phase of the respiratory cycle, it works in the same way as ER-PAP. However, it also aims to

soften the pressure transition from inhalation to exhalation by increasing the pressure delivered more gradually to better mirror the normal breathing rhythm of the CPAP user. In a randomised double blind 3 arm study comparing A-Flex with CPAP and Auto CPAP, A-Flex was noted to be equivalent to other devices in terms of efficacy, compliance and functional outcomes measured by FOSQ, ESS and Psychomotor vigilance test. (Kushida CA, 2011).

1.2.3.4 Interface

Approximately two thirds of patients will experience side effects from CPAP including nasal stuffiness/ congestion, skin irritation, eye puffiness, or gastric fullness (Engleman HM, 2003). Yet, side effects of the treatment have not been shown to be predictive of adherence to CPAP (Kribbs NB 1993b; Engleman HM, 2003; Rauscher H, 1993; Waldhorn RE, 1990; Fletcher EC, 1991; Hoffstein V, 1992). Indeed, it has been shown in one study that individuals who reported mask-side effects were in fact those patients who used CPAP regularly (Weaver T, 1997).

There is some evidence that nasal resistance can affect initial acceptance and subsequent compliance with CPAP. Smaller nasal cross-sectional area and reduced volume, measured with acoustic rhinometry, were associated with non-adherence (Hy Li, 2005). Nasal surgery in individuals who were intolerant of CPAP and nasal symptoms with nasal resistance resulted in improved CPAP tolerance post-operatively (Nakata S, 2005)

1.2.3.5 Humidification

Humidification is used to improve patient comfort on CPAP treatment when patients report drying of the airway. However, its effectiveness in improving CPAP compliance is not clearly established. In a randomised crossover trial patients were treated with heated humidification, cold pass-over humidification and had a washout period without humidification. The heated humidifier increased adherence to CPAP compared to either cold pass-over humidifiers or no humidification and specific side effects such as dry mouth or throat and dry nose were reported less frequently when CPAP was used with heated humidity compared to CPAP use without humidity ($p < 0.001$). Interestingly, heated or cold pass-over humidifiers when compared to no humidification equally improved subjective patient satisfaction with treatment (Massie CA, 1999). Another randomised crossover study involving 37 patients demonstrated a small improvement in adherence with CPAP with heated humidification, but no difference in subjective sleepiness or treatment satisfaction (Neil AM, 2003). A trial, involving 125 patients, randomised new CPAP starters to CPAP alone, humidified CPAP or CPAP with topical nasal steroids over a 4-week period. The addition of a humidifier, but not nasal steroids reduced the frequency of nasal symptoms, however no changes were observed in compliance or measures of quality of life (Ryan S, 2009).

Overall, whilst humidifiers are noted to reduce side effects and improve comfort in individuals with OSA. They are not associated with an improvement in adherence and compliance when used unselectively in a population of patients with OSA started on CPAP for the first time.

1.2.4 Socio-demographic factors

1.2.4.1 Sex

In contrast to men, women have different polysomnographic findings for the same degree of symptoms, with lower AHI's and more episodes of airway resistance without complete obstruction. Women diagnosed with OSA are on average older and more obese than the men in the same clinic and can present differently having more symptoms of lack of energy, depression, insomnia and morning headache (Kapsimalis F, 2002; Quintana-Gallego 2004; Vagiakis E, 2006; Smith R, 2002; Tarasiuk A, 2004; Guilleminault C, 1995). Conflicting results have been found when adherence / compliance with CPAP is compared between the sexes. Sin et al in their observational study of new CPAP starters who were followed up for 6 months, found that women on average used CPAP more than men (Sin DD, 2002) While Fleury et al in their study found female sex to be associated with poor compliance with CPAP (OR 2.8, p value 0.02) (Fleury B, 2001). McArdle et al in their prospective observational study looking at long-term compliance of 1255 patients with OSA found that female sex was more often associated with refusal to accept CPAP treatment (32% women refused to use CPAP compared to 14% men), however there were no differences in the subsequent compliance with CPAP (McArdle N, 1999). Another retrospective study found older males to be associated with optimal CPAP compliance at 1 year (Somners ML 2011). Most of the other studies have found no correlation between female sex and compliance with CPAP (McArdle N, 1999; Lewis K, 2004; Lin HS, 2007). Overall no consistent association has been found between sex and CPAP compliance.

1.2.4.2 Socio-economic status

As per the national standard for educational statistics definition “**Socioeconomic status (SES)** is an economic and sociological combined total measure of a person's work experience and of an individual's or family's economic and social position in relation to others, based on income, education, and occupation (National centre for Educational statistics 2008).

The NS-SEC in the UK is another way of defining the socio-economic class. It does not take income into account and is rather constructed to measure the employment relations and conditions of occupations (Goldthorpe, 2007). Conceptually, these are central to showing the structure of socio-economic positions in modern societies and helping to explain variations in social behaviour and other social phenomena. It has also been validated both as a measurement tool and as a good predictor of health, educational and many other outcomes (NS-SEC 2010).

Low socio-economic status (SES), irrespective of whether it is classified on income, education, profession or a combination of these, is linked with an increased risk of mortality and morbidity from cardiovascular illness (Symes SL, 1976; Grafstein O, 1989; Lynch JW, 1998; Salomm V, 2000). It is also associated with higher prevalence of chronic illnesses including COPD, Asthma, Depression and cardiovascular disease (Lorant V, 2003; Clark AM, 2009). Not only is the prevalence of chronic illness high amongst this group, they also have lower health related quality of life. (Kanervisto M2011; Kreiger N, 2001; Cohen BH, 1977; Vieggi G, 2001; Hesselink HE, 2006). Patients with lower SES have been shown to have a greater exposure to risk behaviour, including poor compliance with medications and non-attendance for health checks

ups (Mackenbach JP, 2006). In a cross sectional, population based study involving 13603 men and 18292 women; socioeconomic disadvantage was associated with non-adherence to medications independent of long-term illness (Wamala S, 2007).

There is evidence that low SES could be a risk factor for cardiovascular diseases in adult OSA patients. In a prospective study involving 1019 patients with OSA, low SES judged by income compared to national average income (low income <20% of national average, average income +/- 20% of national average and high income >20% of national average), was found to be an independent risk factor for cardiovascular diseases amongst patients with OSA. For each decrease in income level category there was a 40% increase in the risk of cardiovascular disease (Tarasiuk A, 2006).

To date there are a very few studies looking at the role of SES in acceptance and compliance with CPAP treatment in patients with OSA. One cross sectional study looking at the pattern of acceptance and adherence of CPAP in an Israeli population found the likelihood of CPAP purchase to be determined by income level (OR 2.4, 95%CI 1.3- 4.3) (Simon-Tuval T, 2009). Following a 2-week adaptation period after starting CPAP treatment, 22% of individuals with low income accepted and purchased CPAP compared to 51% and 76% from average and high-income groups respectively. The authors proposed that CPAP acceptance in relation to SES is linked to access and cost of care with individuals with low SES, not being able to afford or access it. Twenty-nine percent of patients in this study, who refused CPAP treatment, reported cost as the reason. However, the association between SES and CPAP acceptance and adherence is not consistent.

In a study in Belgium, socio-economic background as assessed by the educational status did not correlate with CPAP compliance. The same group looked at an association between compliance and status as an employer versus employee. Compliance was found to be similar in the two groups (Verbraecken J, 2007). In a questionnaire based, retrospective study looking at a population of OSA patients in a public and a private hospital, who were commenced on CPAP within the past 6-15 months, no differences in compliance was observed in relation to the income category or the educational status. The limitation of this study was that it was retrospective, with a small number of patients and compliance was the patient's own estimate rather than more accurate objective measurement on the CPAP (Welfare M, 1997). In another retrospective chart review, 42% of patients from an institution serving a minority population (largely lower income, uninsured people) failed to turn up for follow-up of CPAP treatment. In comparison 7% in a voluntary hospital group cohort (mainly middle class and health insured people) failed to turn up (Greenberg H, 2004). A similar study evaluating the relationship between CPAP adherence and race/ other socio-demographic factors in a publicly funded hospital in the US found that African Americans were more likely to be adherent than Caucasians (OR 5.02, 95%CI, 1.59-15.84) (Joo MJ, 2007). One limitation of this study was that the number of Caucasians was relatively small compared to number of the African Americans (18 versus 196).

Co-existence of Mood disorders

Poor socio-economic status may also be associated with chronic depression and anxiety, (Lorant V, 2003; Murphy J, 1991) which have been noted to influence compliance on CPAP therapy (Lewis KE, 2004; Edinger JD, 1994).

A study in New Zealand (looked at the association between CPAP compliance and Socioeconomic / Ethnic status (Bakker JP, 2011). Maori ethnicity was associated with slightly lower CPAP adherence (median CPAP use 5.11 hours' vs. 5.71 hours in non-Maori population). On further multivariate analysis taking into account ethnicity, eligibility for government-subsidised healthcare, individual deprivation scores, income and education; the factors of non-completion of tertiary education and high individual socioeconomic deprivation scores remained significant independent predictors of average CPAP adherence not reaching 4 hours (Bakker JP, 2011).

One limitation in most of these studies looking for an association between SES with CPAP acceptance and compliance is that all (other than the Campbell and Verbraecken study) were done in health care systems where the individuals either purchased their own CPAP machine or needed to be insured (Joo MJ, 2007; Campbell AJ, 2012; Bakker JP, 2011; Greenberg H, 2004). Though Simon-Tuval's study tried to address this issue by giving free access to initial CPAP titration and subsequent 2-week adaptation to all the participants, patients still had to purchase the equipment at the end of the trial period, which may have been the reason for the poor acceptance in the lower income group (Simon-Tuval T, 2009).

Another limitation in most of these studies is that they have used income as the sole factor to determine the SES of an individual. An individual's occupation is likely to be as important a measure of SES as income (National statistics socio-economic classification 2001, office of national statistics). This has formed the basis of socioeconomic classification in many countries including United Kingdom and New Zealand. The National statistics socio-economic classification (NS-SEC), uses an

individual's profession or occupation to derive socio-economic class. There are 5-8 classes, depending on whether the SEC is derived by a self-coded (*Appendix-2*) or by a more structured interviewer coded method. Though the interviewer coded method is more sensitive, it is more time consuming. For purposes of ease and brevity of use the self-coded version is commonly employed. To derive socioeconomic class, four structured questions related to employment, structure of the organisation, supervisory status and occupation are asked. The responses to these questions create an employment and occupation variable, which when fed into a vector helps to derive the socio-economic class (*Table 4*).

Table 4: Five class SEC classification

Class	Label
1	Managerial and professional occupations
2	Intermediate occupations
3	Small employers and own account workers
4	Lower supervisory and technical occupations
5	Semi-routine and routine occupations

So far there is no consensus on the role of socio-economic status in CPAP acceptance and compliance in OSA. Most of the studies done in countries where CPAP treatment is funded privately have shown poor uptake and compliance in individuals with low income. Relationship between the two is however not very clear as there are many confounding factors including higher incidence of anxiety/ depression in low SEC group as well as poor access to treatment.

As highlighted earlier there were likely a few limitations in most of the previous studies. SES was solely derived from income and most were done in privately funded health systems (either partial or full private) meaning that the results cannot be readily extrapolated to the NHS in the UK.

In the National Health Service of the United Kingdom (NHS UK), delivery of most care is free at the point of delivery (prescriptions are an exception) and access to any treatment is not dependent on income or health insurance. This helps to avoid the bias inherent in the previous studies, which have looked at the relationship between the SES and CPAP compliance.

1.2.5 Psychological factors

1.2.5.1 Type D personality

This personality construct was identified while looking at the coping styles in individuals with coronary artery disease (Denollet J, 1995). The type D construct describes individuals who have a tendency to experience high levels of negative emotion (negative affectivity) and inhibit these emotions while avoiding social contact with people (social inhibition). Across time and situations these individuals not only experience negative emotions (anxiety, sadness, anger and hostile feelings), they also inhibit the expression of these emotions in social interaction due to fears of how others may react. They tend to feel inhibited, tense, insecure and uncomfortable when they interact with other people. They not only have significant negative affectivity but also lack the coping mechanism to deal with it. Both negative affectivity and social inhibition are associated with the perception of a socially unsupportive

environment (Pedersen SS, 2004) and they perceive the external world as threatening (Asendorpf JB, 1993).

Type D personality alone, has been associated with poor outcomes in patients with underlying cardiac illness (Denollet J, 2000). Poor self-management, social inhibition and inadequate consultation in individuals with Type D personality could perhaps lead to a lack of adherence with the treatment for chronic medical and surgical illnesses, including the treatment of obstructive sleep apnoea with CPAP.

In a cross-sectional study of 247 patients with OSA of variable severity (AHI 30 to 98 /hour), who were on CPAP treatment for 6-182 months there was a significant difference in CPAP compliance patterns between individuals with Type D personality, compared to those without it. People with Type D personality used CPAP on average 1 hour 20 minutes less than those without the trait. Only 50% of individuals used CPAP >4 hours per night, compared to 84% of the non-type D personality (Brostrom A, 2007). One limitation of this study was that it was a retrospective, cross-sectional analysis, with patients included already on CPAP treatment for a variable period of time. Reviewing the literature, there are no prospective studies, which have looked at association between Type D personality and CPAP compliance.

1.2.5.2 Depression

The prevalence of depression is higher in individuals with OSA than the general population. In a prospective study of patients with severe OSA, the prevalence of depression defined as Zung self-rated depression score >50, was 48% (Akashiba T, 2002). Using the Minnesota multiphasic personality inventory, Aikens et al found that

32% of patients with OSA had raised MMPI scores (Aikens JE, 1999a). Another study by the same group found that compared to age and sex matched primary snorers, there were twice as many OSA patients with raised MMPI scores (Aikens JE, 1999b). Using Beck's depression inventory- (BDI) fast score to assess severity of depression, another group found 41% of their patients with OSA had at least mild depression and 12% had moderate to severe depression (Schwartz DJ, 2007). In comparison the prevalence of major depression was 2-4% of in the community, 5-10% in primary care patients and 10-14% in medical inpatients. Although the majority of studies have found an association between depression and OSA, in a longitudinal study over a 5-year period, depressive symptoms were not found to be any different in patients with mild OSA (Phillips BA, 1996; Chervin RD, 2003; Pillar G, 2004).

Some of the symptoms of OSA including excessive daytime sleepiness, fatigue, mood changes, irritability, lack of concentration and poor motivation may be perceived by patients, as well as by the physician's treating them as due to depression rather than OSA (Chervin RD, 2003). These symptoms, overlapping between depression and OSA are more commonly reported by women than men (Pillar G, 2004).

Depression scores, in individuals with OSA, can improve on CPAP treatment. In a prospective study of 50 patients with OSA (RDI 57.4 ± 31.1), the BDI improved significantly after CPAP treatment. This improvement was seen irrespective of whether they were on antidepressants (Schawartz DJ, 2007). Another study of 39 patients with OSA, showed an improvement in somatic and affective/ cognitive symptoms of depression as assessed by BDI 1-3 months after CPAP therapy (Means

MK, 2003). It was suggested that depressive symptoms in these individuals were not due to physical symptoms, but a mood component of OSA.

The improvement was however not seen consistently. In a study involving 80 patients with OSA, no improvement in BDI scores was seen at 3 and 12 months on CPAP treatment (Munoz A, 2000). In another randomised, double-blind, placebo controlled trial using sub-therapeutic CPAP as a control, no improvement in the geriatric depression scale was seen in therapeutic CPAP group compared to the controls (Henke KG, 2001).

Depression can be associated with poor adherence to therapy in other chronic medical disorders (Smith A, 2006; Bosley CM, 1995). In patients with OSA, there is conflicting evidence regarding an association between underlying depression and CPAP use. In a prospective study involving 70 patients, there was no correlation between CPAP compliance and underlying depression measured by the Hospital Anxiety and Depression scores (Lewis KE, 2004). In a study using the Minnesota Multiphasic Personality Inventory to measure depression, individuals who were depressed had poor CPAP compliance compared to those who were not depressed (Edinger JD, 1994).

To summarise, it is not certain whether depression is more common in people with OSA than the general population or if overlapping symptoms lead to an over-diagnosis of depression. Similarly, it is not known whether depression impacts on compliance with CPAP therapy.

1.2.5.3 Anxiety

Anxiety is reported frequently in patients with OSA. Eleven to 28% of OSA patients complain of claustrophobic feelings as well (Edinger JD, 1994, Lewis KE 2004; Stepnowsky CJ, 2002; Lewis KE, 2004). Anxiety is associated with sub-optimal compliance in other chronic medical conditions (Bosley CM, 2004). Anxiety and personal coping strategies have been found to affect CPAP compliance (Budhiraja R, 2015). However, this association has not been found consistently. A prospective cohort study monitoring HADS (Hospital Anxiety and Depression scale) as a measure of anxiety found no association between anxiety and subsequent CPAP usage (Lewis KE, 2004).

1.2.6 Educational and behavioural factors

Information and knowledge about OSA and recognising the importance of adhering to CPAP is associated with improved acceptance and compliance with the treatment. Different studies have reinforced the importance of behavioural and educational interventions in improving health outcomes by recognising the benefits and effectiveness of the treatment. These interventions include:

- Individual educational session delivered by a nurse 2 weeks after commencing CPAP, short (10-20 minutes) educational videotape on OSA (Bosoglu 2011ef)
- Face-to-face education sessions delivered by a trained nurse one and two weeks after initiation (Aloia MS, 2012).
- Group teaching session (Epstein L, 2000; Wang W, 2012).

- Routine Information on diagnosis and treatment of OSA given by a physician, Telephone-linked communications technology (TLC) versus usual care, (DeMolles DA, 2004).
- Given mask to try for 20 minutes, titration of CPAP pressure overnight with following day discharge, nurses telephoned on days two and 21, reviewed in hospital at one, three and six months (Hoy CJ, 1999).
- Locally produced 15-minute videotape, additional nurse led 15-minute educational session, review by physicians at weeks one and two, respiratory nurse telephone call on days one and two, weeks one, two, four, eight and 12 (Hui DS, 2000).
- Initial education at home with partner, two extra nights in hospital, sleep nurses' home visits to participant and partner at seven, 14 and 28 days and four months after starting CPAP. (Hoy CJ, 1999).
- 10-Minute CPAP education programme by respiratory nurse, brochure on OSA and CPAP treatment in Chinese, short trial CPAP therapy with comfortable mask for 30 minutes, CPAP titration on second night of study by Auto Set, nursing support following day, follow-up by nursing staff and physician at 1 and 3 months. (Hui DS, 2000).
- Motivational Enhancement Therapy (MET) sessions delivered by a trained nurse one and two weeks after initiation of treatment. An extra phone call at week three. These sessions consisted of individually tailored counselling (Aloia MS, 2004).

These educational interventions were found to be associated with a small increase in CPAP use of about 35 minutes per night (0.60 hours, 95% CI 0.27 to 0.93 in a meta-analysis (Wozniak DR, 2014). Behavioural interventions increased average CPAP use by 1.44 hours per night (95% CI 0.43 to 2.45). There was a higher likelihood of participants in the educational intervention group using CPAP optimally. Interventions influencing decisional balance in favour of CPAP or those promoting self-efficacy and outcome expectations were associated with an improvement in health behaviour outcomes.

1.3 LONG TERM COMPLIANCE WITH CPAP

In a cost effectiveness model appraised by NICE, it was suggested that the CPAP treatment dominated “non- treatment” after a minimum of 2 years. That is the cost of treatment is more than offset by savings produced by a reduction in the cost that would have accrued due to management of the adverse effects of OSA. CPAP treatment used long-term was also associated with an increase in quality adjusted life years (QALY’s) (NICE technology appraisal, 2008).

There are a few published studies reporting long-term compliance with CPAP. In one of the early studies looking at this question, acceptance of CPAP treatment was greater than 90% at 3 years and greater than 85% at 7 years (Kreiger J, 1996). Hours of use correlated positively with age, body mass index, and AHI, and negatively with daytime partial pressure of oxygen (PaO₂), forced expiratory volume in 1 second (FEV₁), and vital capacity. This study shows that CPAP therapy may be accepted well by OSA patients as well as by non-apnoeic snorers. It was the objective disease severity (as measured by the respiratory event index and daytime and night time hypoxemia), rather than patients' symptoms or complaints, which played a role in the compliance with treatment.

In a retrospective study, which looked at the CPAP use in a private hospital, higher BMI, higher prevalence of witnessed apnoea, higher ESS score at baseline and improvements in daytime activity and improvement in ESS score were associated with successful CPAP use beyond 12 months’ period after initial trial. CPAP induced sleep

disturbance was associated with non-compliance with CPAP therapy (Hussain SF, 2015).

In a single centre experience only 65% of patients with OSA who were recommended to go on CPAP treatment, accepted treatment and of those who initially accepted treatment, only 53% continued with treatment at median 8-year follow-up (Cecila H, 2006). In a study involving 648 patients, who were diagnosed with OSA and accepted CPAP, only 65% used CPAP more than 4 hours per night. Factors associated with optimal use were an improvement in daytime sleepiness and a positive effect of CPAP on sleep (Salepci B, 2013).

A retrospective cohort study from Oxford, UK looked at long-term experiences with CPAP. It showed an adherence rates with CPAP at 5 and 10 years of 81% and 70% respectively (Kohler M, 2010). In their cohort of over 3500 patients with OSA who were commenced on CPAP, the median (IQR) follow-up time on CPAP was 3.9 (1.5-6.9) years. Multivariate analysis suggested that the severity of sleep apnoea measured by overnight desaturation index rather than sleepiness, was the variable best associated with long-term adherence.

In the SAVE study, it was found that CPAP use by patients with coexisting cardiovascular disease and moderate to severe OSA decreased significantly over 12 months. Early patient experiences with CPAP (i.e., adherence and side effects at 1 month) predicted subsequent use at 1 year (Chai-Coetzer CL, 2013).

In a retrospective study of 80 patients who were started on CPAP 4 years earlier, patients with significant daytime sleepiness before they were commenced on the

treatment were more likely to be adherent to the treatment and show an improvement in the symptoms (Wolkove N, 2008).

In summary, whilst initial symptoms (i.e. reports of excessive daytime sleepiness and a high ESS), severity of OSA and lack of initial side effects have been noted to be associated with better CPAP compliance, this association is not consistent and so is similar to the case with initial CPAP acceptance and short-term compliance.

1.4 HYPOTHESIS

Acceptance of and subsequent optimal compliance with CPAP is key to its success in not only improving the symptoms and quality of life of patients with OSAHS, but potentially reducing the future cardiovascular risks. So far there is no consistent association between demographics and disease severity related factors with CPAP compliance and acceptance.

I set out with a series of studies, to look at the factors which may affect compliance with CPAP in those already on CPAP and also new CPAP starters. I hypothesised that underlying mood, personality disorder, socioeconomic status and physician's initial impression whether a person is likely to use the treatment optimally or not can predict subsequent CPAP use. I also hypothesised that amongst the CPAP users, those who are unable to use the treatment optimally and complained of pressure related side effects, a change in device to a Bi-level positive airway pressure device, would improve their subsequent compliance.

1.5 AIMS

The aim of the thesis was:

- To explore the relationship between socio-demographic factors, type D personality and depression in predicting CPAP acceptance and compliance.
- To further study the role of Bi-level PAP in patients sub-optimally compliant with CPAP due to pressure related side effects.

CHAPTER 2

STUDY DESIGN & METHODS

CHAPTER 2 STUDY DESIGN AND METHODS

2.1 Long term compliance with CPAP- A single centre experience

2.1.1 Study design

This was a retrospective study of the long-term compliance with CPAP amongst patients of a single centre. Papworth hospital is a tertiary referral centre for individuals with sleep disorders. The unit opened in 1992, when the staff and patients transferred from Newmarket hospital in Suffolk, UK. CPAP treatment was already established at the centre at the time. From the sleep unit database and health records, we identified all individuals diagnosed with OSA with a nocturnal oxygen desaturation index (ODI) ≥ 5 who had started CPAP at Papworth Hospital between July 1995 and June 1998.

2.1.2 Population

Patients were referred to the sleep centre by both general practitioners and hospital doctors.

2.1.2.1 Exclusions

Patients with a neuromuscular disorder, those who had previously been treated for OSA with CPAP or an alternative device, those who were initiated on Bi-level positive airway pressure (PAP) for associated ventilatory failure, and those who had participated in related pharmaceutical trials were excluded from this study. Individuals where pre-treatment nocturnal oximetry traces were not available or 4% desaturation index was less than 5 per hour were excluded from the study.

2.1.2.2 Diagnosis

Patients were diagnosed with OSA on the basis of characteristic symptoms and overnight arterial pulse oximetry criteria ($> 5, 4\%$ desaturation per hour⁻¹) and Epworth Sleepiness Scale (ESS) score >10 . Overnight oximetry was recorded on Datex Ohmeda 3740 oximeters (*Datex-Ohmeda, Louisville, CO, USA*) and printed using chart recorders.

- (a) The diagnosis of OSA in these cases was established on the basis of overnight oximetry that had a sensitivity of 97% and specificity of 80% in diagnosing sleep apnoea, when RDI of 10 per hour was used as a cut-off.
- (b) When the RDI was changed to 5 per hour, sensitivity and specificity changed to 100% and 43% respectively (Vazquez JC 2000). With the clinical information available at the time of review, there was an improvement in the diagnostic sensitivity. We used 5 per hour desaturation index as cut-off. This was based on the evidence available at that time as well as the standard practice at our centre.
- (c) Patients who were strongly suspected of having OSA but did not demonstrate oxygen desaturations on nocturnal oximetry were re-assessed by polysomnography (PSG).

2.1.2.3 Monitoring

Patients were monitored at least once a year, as per the local treatment policy unless, CPAP treatment was withdrawn, their care was transferred to another hospital, they stopped CPAP or failed to attend appointments. Monitoring comprised an outpatient or inpatient hospital visit where the patient's ESS score and weight were recorded and

average nightly CPAP use calculated from clock readings. Improved compliance was encouraged where necessary. Overnight oximetry whilst using CPAP was recorded at follow-up for at least 2 years and the CPAP level adjusted as required. Oximetry records were printed on chart recorders and analysed visually. Patients who remained excessively sleepy despite optimum CPAP therapy underwent further assessments.

2.1.2.4 Ethics

The study protocol was approved by the Huntingdon Local Research Ethics Committee, Cambridge, UK.

2.1.2.5 Data collection/ Outcome measures

The hospital records were reviewed between August and December 2003. One investigator (EM) re-analysed the overnight oximetry traces to identify mean and minimum oxygen saturation (SpO₂) and calculate the oxygen desaturation index (ODI, ≥4%) per hour. The following were recorded: sex, age, ESS score, nocturnal oximetry data at diagnosis, date when CPAP was started, smoking status, BMI and documented history of cardiovascular disease, lung disease and diabetes. Compliance data were analysed (AG) during the period March-April 2008. Patients still using CPAP at the time their notes were reviewed or when they died were referred to as 'CPAP users'. The latest nocturnal oximetry results, average nightly CPAP use, weight and ESS score whilst using CPAP were recorded for the 'CPAP users' that were still under follow up at Papworth Hospital (Papworth CPAP users).

2.1.2.6 Outcome measures

Primary – Long-term compliance on CPAP (average hours/ night)

Secondary - Association between age, sex, baseline ESS score, improvement in ESS on treatment, severity of OSA measured by desaturation index, anxiety, depression with CPAP compliance.

2.1.3 Statistics

Statistical analyses were performed using SPSS computer software version 15.0 (*SPSS Inc, Chicago, IL, USA*). For 'Papworth CPAP users' the latest treatment follow-up data were compared to the pre-treatment values and relationship with sex. Comparisons were made using Mann Whitney U and Chi-square test as appropriate. Odds ratios were calculated to identify the risk/ association between different variables with sub-optimal compliance.

2.2 A prospective observational study to evaluate the effect of social, demographic factors and personality on CPAP compliance in OSA

2.2.1 Aim

I conducted a prospective study in newly diagnosed OSA patients to determine factors associated with acceptance and long-term compliance with the therapy.

The physician's estimation of the likelihood that the patient would accept CPAP treatment and subsequently comply with the treatment was measured on a visual analogue scale 0-100 at the time of recommending CPAP treatment to an individual.

The staff were the medical team running the sleep clinics. This was a real life assessment and the team had a range of experience in managing patients with sleep disorders.

FACTORS

- Socio-economic status – Derived by national statistics socio-economic classification (NS-SEC), self-coded version (*Appendix 2, 3*).
- Level of education (*Appendix 3*)
- Type D personality – assessed by type D scale-14 (*Appendix 4*). In this pro-forma 2 aspects of personality were assessed including social inhibition and negative affectivity. Individuals completed a DS 14 proforma. Those scoring greater than 10 in either domain were considered to be having a type D personality.
- Depression – assessed by Beck's depression inventory 2 (*Appendix 5*).

Although the gold standard for diagnosing depression is a clinician's assessment at the interview, there are several self-scoring assessment tools available for patients including the updated Beck Depression Inventory (*Appendix 5*). This is frequently used to detect depression and to assess responses to interventions. BDI 2 is a well-validated tool, which is positively correlated with the Hamilton Depression Rating Scale (a tool very closely related to clinical interview for diagnosing depression). There is a Pearson r of 0.71 between the two measures showing good agreement. The BDI 2 has also been shown to have a high one-week test–retest reliability (Pearson $r=0.93$) and high internal consistency ($\alpha = 0.91$). The 21-item survey is self-administered, and each item is scored on a scale of 0-3 against a list of four statements arranged to indicate increasing severity of depression. The BDI 2 is in alignment with DSM–IV criteria. The cut-offs used are: 0–13: minimal depression, 14–19: mild depression, 20–28: moderate depression, and 29–63: severe depression.

- Sex
- Sleep specific quality of life scores (sleep apnoea quality of life index-SAQLI) score (*Appendix 6*).
- Epworth sleepiness scale score (ESS) (*Appendix 1*). A score of >10 is considered to be significant (Johns MW, 1991; Johns MW, 1997).
- Severity of OSA as assessed by 4% oxygen desaturation index (ODI) (Vazquez zJC 2000).

2.2.2 Ethics

The Cambridgeshire 1 research and ethics committee 08/H0304/72 approved this study. The study was conducted during the period Dec 2007 to Jan 2009.

2.2.3 Population

All individuals referred to Respiratory Support and Sleep Centre (RSSC) with a suspected diagnosis of OSA was considered eligible for the study. The diagnosis of OSA was established on the basis of characteristic clinical features assessed at an interview with a sleep specialist and overnight oximetry showing an ODI ≥ 10 hour⁻¹ (Vazquez JC, 2000). Additional multi-channel respiratory sleep studies (*Embletta Portable Diagnostic System, Medcare, Reykjavik, Iceland*) or polysomnography (PSG) were performed if patients with a history strongly suggestive of OSA but with an ODI < 10 per hour.

Inclusion criteria

1. Symptomatic OSA offered CPAP.
2. Objectively confirmed OSA (4% oxygen desaturation Index ≥ 10 /hour or AHI >4 per hour) (Vazquez JC 2000; SIGN 2003).

Exclusion criteria

1. Unable to give consent.
2. Previous use of CPAP or Non-invasive ventilation (NIV).

Before clinic visit -Patients referred with suspected obstructive sleep apnoea (OSA) routinely had nocturnal oximetry test/ sleep study done before their clinic visit and were given information about the study.

First clinic visit- Patients were then assessed in clinics with their sleep study results.

The diagnosis of OSA was established by overnight oximetry showing 4% oxygen desaturation Index (ODI) $\geq 10\text{hour}^{-1}$. Further diagnostic tests i.e. respiratory sleep studies or polysomnography (PSG) were done in patients to confirm the diagnosis of OSA if:

- There was strong suspicion of OSA but 4% ODI $<10\text{ hour}^{-1}$.
- ODI $\geq 10\text{ hour}^{-1}$ but overnight oximetry pattern was not diagnostic.
- Co-morbid cardio-respiratory and neurological conditions which could cause central apnoea or Cheyne - Stokes respiration.

Patients with a confirmed diagnosis of OSA and offered CPAP were consented for participation in the study. Patients were asked to complete a set of questions to assess socio-economic status- derived from the self-coded version of National Statistics – Socio-Economic Classification (NS-SEC) (*Appendix 2*). These questions were related to occupational status of an individual. It specifically took two different domains of socio-economic class into account. The first one was their profession and the second one was their supervisory status. Incorporating this information into an algorithm, we were able to derive the socio-economic class of these individuals. This particular Socio economic classification is a validated and accepted classification used by social scientists. Although there was a detailed version of NS-SEC which classified individuals into 8 socio-economic classes, the self-coded version had a good correlation with the

detailed version (NSSEC 2000), is easier to use and can be completed by untrained individuals. The Self-coded version of NS-SEC divided individuals into 5 socio-economic classes that may be further collapsed to 3 classes. This classification did not include people who were long-term unemployed (unemployed for more than 6 months) or have never worked. For our study we included these individuals as a separate factor.

- Sleep related symptoms- Whether they were excessively sleepy, snored, wake up with unrefreshing feeling, Epworth sleepiness scale score (*Appendix 1*).
- If they have a type D personality (assessed by DS-14 pro-forma) (*Appendix 4*). In this pro-forma 2 aspects of personality were assessed including social inhibition and negative affectivity. Individuals completed DS 14 proforma. Those scoring greater than 10 in either domain were considered to be having a type D personality.
- Depression scores (BDI 2 - Beck's depression inventory 2 (*Appendix 5*)).
- Sleep apnoea quality of life index (SAQLI - self-administered short version) (*Appendix 6*).
- Baseline quality of life scores (Short Form- 36) (*Appendix 7*).
- Nasal symptoms (*Appendix 3*).

Those who agreed to accept CPAP therapy were labelled as "acceptors". Patients who refused an initial trial with CPAP or failed to use CPAP at home during trial period of 6 months were labelled as "non-acceptors".

During initial assessment, before the patients were started on the CPAP treatment,

the physician reviewing the patient documented his/her level of confidence (indicated on a visual analogue scale- 0 to 100) to say the “likelihood of patients complying optimally (using it ≥ 4 hours/night) with CPAP”. Similarly, the physician also documented his/her level of confidence (on visual analogue scale 0- 100) to say, “Whether sleepiness is due to OSA” (*Appendix 8*). Physician's recommending the treatment were either sleep consultants (47 years of cumulative sleep experience) or research registrars (3 years of cumulative sleep experience) who saw the patients for the first time and recommended the CPAP treatment based on their symptoms and sleep study results. There were no set research or clinic parameters, to mark physician's assessment. These individual physicians did not get any specific pre-study training on how to mark these patients with OSA. Their assessment on the visual analogue scale was entirely based on the instinct of a clinician at the time of recommending the initial treatment and assessing patient's response to the recommendation.

Titration with CPAP- CPAP titration was routinely performed against nocturnal oximetry as an in-patient. Patients were admitted to the hospital usually in the evening / afternoon time, when they were familiarised with CPAP, mask fitting and received general education about OSA and CPAP from specialist nursing / technical staff. Titration was performed based on a set protocol in the sleep centre. Patients were monitored for any drops in the oxygen saturations as well as snoring. They were started on a set CPAP pressure to begin with. Once asleep and still showing persistent snoring or drops in oxygen saturations, pressures were increased gradually to optimal ones to stop snoring and desaturating episodes. Following the first night of inpatient

titration, patients recruited in the study were asked questions related to their experiences following initial CPAP titration (*Appendix 9*). They were then seen by a sleep physician or specialist nurses and sent home to be followed up in the clinic. Those recruited in this observational study, received standard care at the sleep centre similar to those who were not involved in the study.

Second clinic visit- Six to ten weeks after initiating CPAP, the patients were routinely reviewed in the clinic or at RSSC with another overnight oximetry on CPAP. Apart from routine evaluation, patients included in the study were asked to complete questionnaires to assess their current health status (SF-36 and SAQLI) as well as depression score (BDI-2). They were also asked questions related to their experiences on CPAP (*Appendix 10*). Compliance data were recorded from an internal clock in the CPAP, which measured the average number of hours CPAP was used per night (*Appendix 11*). Those using CPAP less than 4 hours every night was labelled “poorly compliant”.

Third clinic visit- Patients were followed up at 6 months with repeat overnight oximetry. Other than the routine assessment study subjects completed questionnaires to assess any changes in their health status (SF-36 and SAQLI) or depression scores (BDI-2). Questions similar to ones during their previous visit were asked to assess their experiences on CPAP (*Appendix 12*). Hours of CPAP use were recorded (*Appendix 13*).

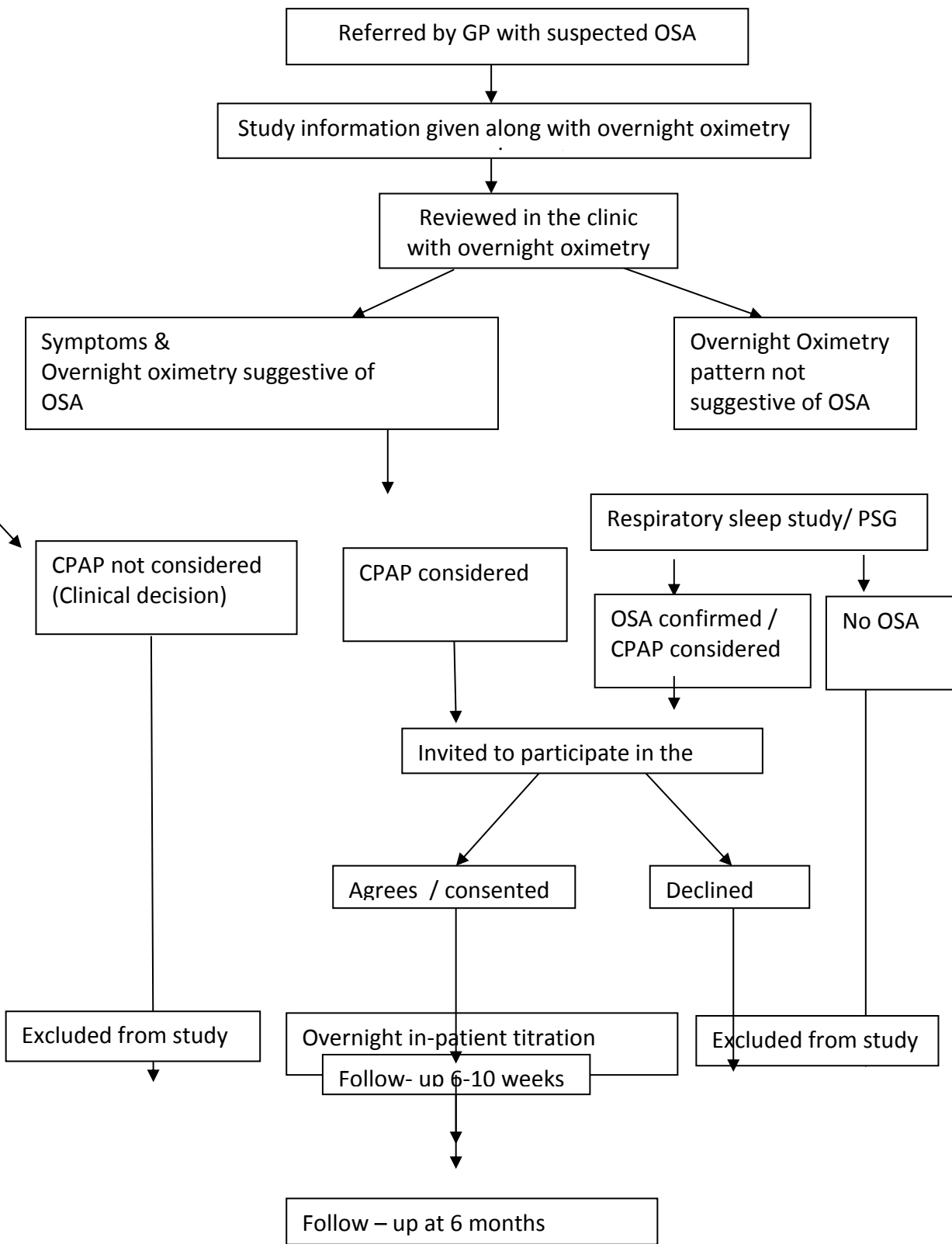
If there was a clinical or CPAP related problem at any stage, which could not be dealt with by advice over 24-hour telephone help line, they were reviewed earlier as per

the standard clinical protocols at our centre. When the patients were unable to attend the follow-up appointments within the expected time period for any reason, we posted the study questionnaires and telephoned them to get information about the CPAP usage and sleep symptoms.

Table 5: Study visits and data collection

	First Visit	6-10-week visit	6-month visit
Sign the study consent form	X		
Medical history	X		
Epworth Sleepiness Scale score	X	X	X
Overnight oximetry	X	X	X
Respiratory channel sleep study (if needed) *	X	X	X
Spirometry	X		
Pro-forma to document socio-demographic Factors	X		
DS -14	X		
BDI-2	X	X	X
SF-36 and SAQLI	X	X	X
CPAP compliance assessment, experiences and side effects		X	X

**Flow chart demonstrating protocol organisation of
Observational CPAP compliance**



Data collection

The following data were collected on case record forms (CRF) and also stored in Microsoft excel spreadsheets which were password protected.

1) Patient characteristics

Hospital and study ID number

Date of Birth

Date of visit

Sex

Height

Weight

BMI

Collar size

Waist circumference

2) Medical, Sleep and socio-demographic history

Cardio respiratory conditions

Other medical problems

Smoking history

Epworth Sleepiness Scale score (ESS): Baseline and follow-up

Socio-economic class- National statistics socio-economic class (NS-SEC), Self-coded versions: Baseline

Physician's prediction of "likelihood of complying optimally on CPAP on a visual analogue scale".

Physician's prediction of "OSA as a likely cause of individual's symptoms".

3) Psychological assessment

Beck's depression Inventory-2 (BDI-2): Baseline and follow-up

D scale- 14 (DS-14): Baseline

4) Quality of life scores

Short form- 36 (SF-36): Baseline and follow-up

Sleep apnoea quality of life index score (SAQLI): Baseline and follow-up

5) Oximetry or Respiratory sleep study

6) Spirometry –

Forced expiratory volume in 1 second (absolute and % predicted): Baseline

Forced vital capacity (absolute and % predicted): Baseline

Forced expiratory volume percentage (FEV %)

7) CPAP start date, acceptance, compliance and side effects.

Statistical Analysis

The primary outcome CPAP compliance as average hours of CPAP use per night was measured on a continuous scale. Main risk factor of interest was socio economic status (SES) variable. This had 5+1 levels.

In order to assess the required sample size, we used the following parameters and made the following assumptions:

- The calculations were based upon the F-test for ANOVA.
- There will be equal numbers of patients in each SES group.
- Four values for the difference in compliance time between the lowest and highest groups were investigated (0.5 hour, 1 hour, 1.5 hours and 2.5 hours).
- Two values for the number of SES levels were investigated (4 and 6 levels).

- Mean hours of CPAP use was 3 hours per night in obstructive sleep apnoea patients in the SES group with the worst compliance. This comes from an estimate from retrospective CPAP compliance data for mean hours CPAP use in non-compliant patients.
- CPAP use will be approximately normally distributed.
- The between-patient standard deviation in sleep apnoea patients is 1.5. This number was obtained from Mortimer et al (Mortimer LL,1998) in patients with sleep apnoea/hypopnoea syndrome or SAHS and Ayalon et al (Aylon L, 2006) in patients with Alzheimer's and OSA. This was also the approximate standard deviation in the <4h and >=4h compliance groups from CPAP data provided by the investigators.
- The significance level used as 0.05/2. The usual significance level was divided by 2 because we have 2 related outcomes, CPAP use at 6 weeks and at 6 months.
- We performed sample size calculations in order to obtain 80% power to detect differences.
- The SAS Proc Power procedure (SAA/ SAT 9.2) was used for all calculations.

To derive the sample size, we reviewed the compliance figures taken from a cohort of patients who were followed up at the sleep centre. Taking information from compliance into account and using above assumptions and with the primary risk factor as the socioeconomic status (SES) variable in its 5-level form, it was postulated

that 240 patients would have given 80% power to detect a 1-hour difference between the groups with the lowest and highest CPAP compliance. We expected that a proportion of patients might not accept treatment. Taking them into account we planned to recruit 260-280 patients in the study to measure any significant difference in the compliance between different socioeconomic groups.

Analytical methods

Statistical analysis was done using SPSS 22[SPSS Inc, IBM]. A non-parametric Kolmogorov–Smirnov test (K–S test or KS test) was used to assess the normality of distribution of continuous variable. Further statistical tests were applied depending upon the distribution of the data. Most of the variables including compliance data were non-normally distributed. Hours of use between different exploratory groups were summarised by median and interquartile range (IQR). Ordinal and categorical variables were correlated using non-parametric Mann-Whitney U test. Compliance between different groups was compared using Chi Square test. Odds ratios were calculated to assess the impact of different factors influencing compliance. Multivariate analysis could not be done due to small number of variables, which were found to be associated with sub-optimal compliance.

Association between different factors affecting acceptance with CPAP was looked at using Chi Square tests.

To assess the significance of the physician's confidence to predict sub-optimal compliance Mann-Whitney U test was used for comparative assessment.

Receiver operator curve (ROC) analysis was done to look for a specific value marked by physician on a visual analogue scale, which may predict sub-optimal compliance.

To assess dependence of early with late compliance on CPAP, Spearman's rank correlation coefficient was used. R-values were calculated using automated analysis on SPSS. Strength of association between the 2 variables was considered strong or weak depending upon how high or low the r-value was (Evans JD, 1996):

0.0 - 0.19 – Very weak

0.2 -0.39 - Weak

0.4 -0.59 - Moderate

0.6 -0.79 - Strong

0.8 -1.0 - Very strong

2.3 The impact of changing the pressure generating device in people with sleep apnoea using CPAP less than 4 hours per night

2.3.1 Introduction

I carried out this study looking at the impact of change to a Bi-level PAP device in patients who are sub-optimally compliant with fixed pressure CPAP and have complained of symptoms suggestive of pressure intolerance. The study was carried out at the Respiratory Support and Sleep Centre at Papworth hospital, Cambridge. The study subjects were recruited from a cohort of 5000 patients with OSA on CPAP followed up at the sleep centre. The protocol was approved by Cambridgeshire research and ethics committee (09/H0308/68).

2.3.2 Study Design

This was a two-period, two-treatment, crossover, randomized, and controlled trial. The treatment arms were 4 weeks long with a 2-week washout period between them.

2.3.3 Population

Subjects were recruited from June 2009 to November 2010 inclusive. Potential subjects were screened from individuals under follow up at RSSC.

Inclusion criteria were:

- A confirmed diagnosis of OSA (apnoea/hypopnoea index [AHI] ≥ 5)
- Being prescribed CPAP for at least 6 weeks

- Compliance with CPAP of <4 hours per night (despite: re-titration to the minimal, effective pressure; review of mask fit and addition of humidification as appropriate)
- Symptoms to suggest pressure intolerance.

Exclusion criteria were:

- Significant airflow obstruction (FEV1/FVC % < 60%)
- Pre- treatment study showing central sleep apnoea (central events more than 50% of AHI)
- Daytime hypercapnoea (PaCO₂ >6.5 kPa) or
- Previous prescription of Bi-level PAP.
- Included in other CPAP compliance study
- Decompensated cardiac failure on clinical examination
- Declined consent
- AHI less than 5 per hour

All subjects meeting the inclusion criteria were invited to join the study and those consenting to participate completed a baseline assessment (vide infra) and were then randomized to either Treatment A or Treatment B. Treatment A was Bi-level PAP (*NIPPY-S, B and D Electromedical Ltd, Stratford upon Avon U.K.*) and Treatment B was a fixed CPAP machine different from the one they had used prior to entering the study (*Phillips/ Respironics, Remstar plus M series with CFLEX disabled*). They were reviewed

and repeated measurements taken at 4 weeks. After 2 weeks' washout, they were issued with the alternative treatment they had not yet used. The diagnosis of OSA was confirmed using respiratory sleep studies (Embletta Portable diagnostic system, Medcare, Reykjavik, Iceland) and repeated in both arms of the intervention to ensure that sleep apnoea was adequately controlled. Sleep studies were scored as per the standard American Academy of Sleep Medicine [AASM 2007]. A trained and accredited sleep physiologist or sleep trainee, as part of the normal clinical practice, reported sleep studies.

Outcome measures

The following measurements were recorded at baseline, 4 and 10 weeks:

Primary

1. *Compliance*- was measured as average number of hours of CPAP use per night measured by inbuilt clock counter in the CPAP or Bi-level PAP machine.

Secondary

2. *Sleepiness*-

(a) Epworth sleepiness scale (ESS) score was used to measure any changes in subjective sleepiness.

(b) Objective changes in daytime sleepiness were assessed by a modified OSLER maintenance of wakefulness test (MWT). The original protocol for the OSLER was for 4 tests through the day. It has been shown that a single test in the morning around 09:00 am (at least 2 hours after waking up) is a reliable substitute for the full protocol (Mazza S, 2002)

3. *Quality of life*- The 'sleep apnoea quality of life index' (SAQLI) was used to measure changes in the sleep related quality of life, following intervention with Bi-level PAP or new CPAP. A change in SAQLI score of 1 is considered to be a significant change (Ward W, 2002).

4. *Comfort level and preference*- The comfort level with each PAP device was measured at each change on a visual analogue scale with measurements from 0-100. Subjects were asked their treatment preference at the end of the trial.

Study type and duration

The study was a two period, two treatments randomised crossover trial design. Patients with average CPAP use less than 4 hours per night who met the inclusion and none of the exclusion criteria were randomized to either receive NIPPY-S first or to receive a brand of fixed CPAP machine different from the one they have used previous to entering the study. They also had a baseline measure of CPAP compliance, daytime sleepiness and quality of life. Patients randomized to receive NIPPY-S in the first period received CPAP in the second period and vice versa. Both groups received a similar level of continuing clinical support by the CPAP practitioners and RSSC nurses (24-hour telephone helpline, early clinic review and advice if there is any problem) as per the standard clinical care at our centre.

Titration on CPAP or Bi-level PAP was done as a day care procedure during the second visit, when patients were randomised to either of the PAP device. Those randomised to new CPAP were started on a fixed CPAP pressure; similar to the ones they were on before being recruited in the study. Those who were randomised to Bi-level PAP were

started on a IPAP similar to the previous CPAP and a fixed EPAP of 4-5. All these individuals have had CPAP titration as an inpatient at some stage during their treatment. Based on their previous inpatient assessments, they were prescribed a fixed pressure. Though there were minor alterations in the pressure setting based on their further assessment as well inability to tolerate pressures, these alterations were minor. For this study, we assumed that the fixed pressure they were using before being recruited in the study was optimal pressure.

During the daytime titration, we used Oximetry and snoring to guide us regarding any changes in the pressure. These titrations were performed in the sleep unit, where individuals reported that they managed to sleep while the pressures were optimised.

Once optimal titration was done, study subjects were reviewed at 4 weeks with repeat measurements of compliance, sleepiness and quality of life. For the second period, those that received CPAP in the first period got NIPPY-S and vice versa. They went home with the advice to start using the new device after 2 weeks. Till that time, they stayed on their initial CPAP. This gave them a washout period of two weeks. They were then followed up for the study at 10 weeks with repeat measures of device compliance, daytime sleepiness and quality of life indices to look for any measurable changes.

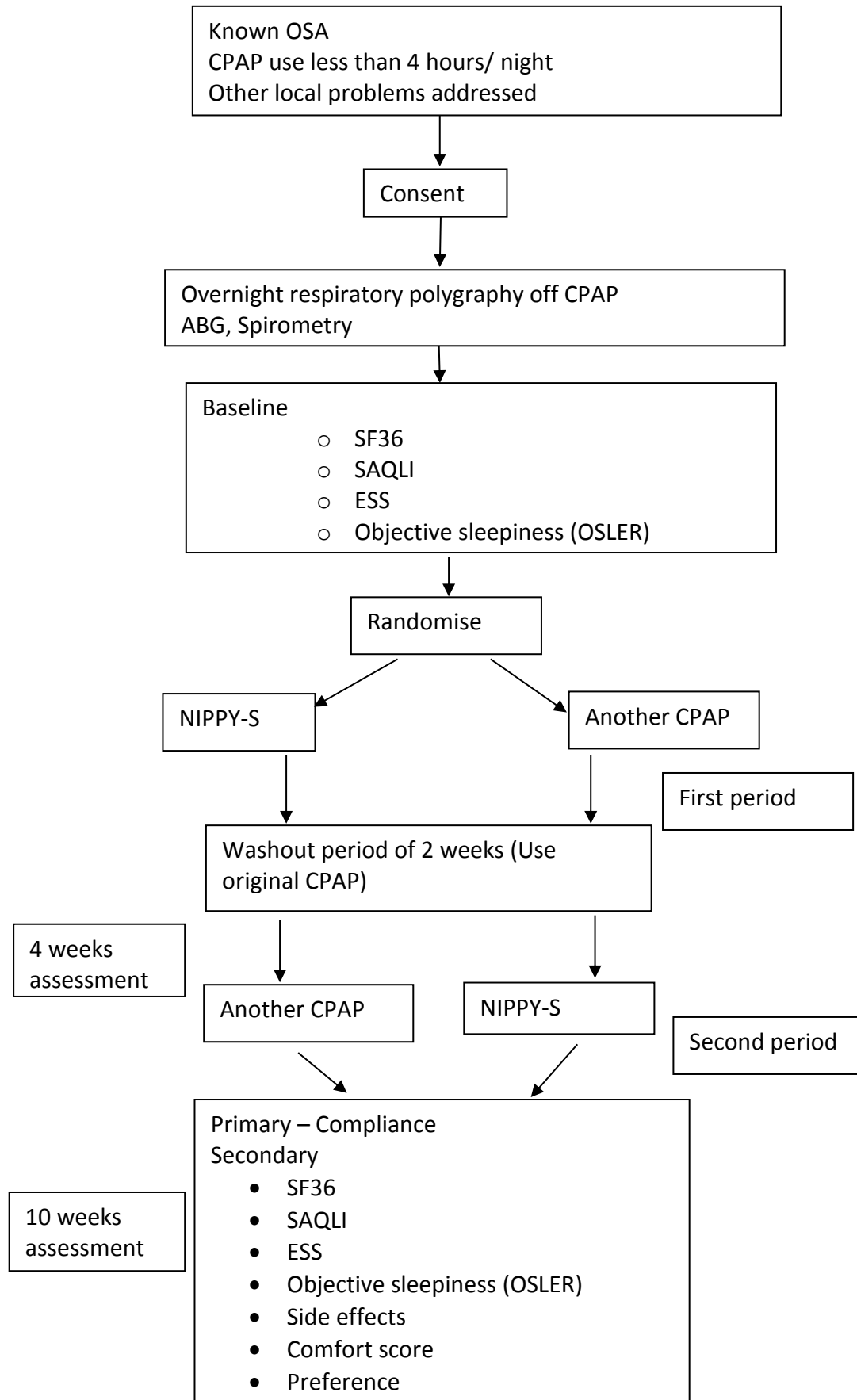
Statistical analysis

Data from a group of CPAP non-compliant patients from Papworth was used to get a mean and standard deviation of CPAP use in hours for use in the sample size calculation. Sample size calculation was performed using S plus power procedure as

well as hand calculations. 29 patients would give 80% power to detect difference of 1 hour between the treatments. Taking 10% drop-out into account from either arm of the crossover design, aim was to recruit 40 patients though with difficulty recruiting and low dropout rate study was stopped after recruiting 28 patients.

Non-parametric Kolmogorov–Smirnov test (KS test) was done to determine the normality of distribution of continuous variable. These variables were found to be normally distributed. Mean hours of CPAP and Bi-level PAP were summarised at 4 weeks and 10 weeks. The number of hours of use of CPAP (the new device) was compared to that on Bi-level PAP using paired t test. The SAQLI, VAS comfort score and Epworth sleepiness scale scores were summarized and analysed using a paired samples t test as well. Side effects and patient preferences were analysed descriptively.

Summary flow chart of Bi-level PAP intervention study



CHAPTER 3

RESULTS

CHAPTER 3 RESULTS

3.1 Long term compliance with CPAP- single tertiary centre experience.

CPAP was offered to 339 patients, of whom 298 (88%) accepted treatment (36 subjects did not tolerate therapy, and 5 reported no benefit and discontinued). Fifty subjects were excluded from the final analysis (treatment was stopped in 19 as their condition improved, 24 moved to a different hospital so that their data were not available and another 7 were switched to Bi-level ventilation). Out of 248 who remained on CPAP at RSSC, 13 patients were lost to follow-up (assumed not to be using CPAP). Eighty-one percent (n=235) of patients continued on long-term CPAP but compliance data was available for 221 (195 males and 26 female).

At baseline, median age was 50 (IQR 15.3) years, ESS score 16 (IQR 6), BMI 32.6 (IQR 10.5) kg/m² and ODI 20 (IQR 27)/hour. The median follow-up was 7 (IQR 1.2) years. Median CPAP use was 6.9 (IQR 2.2) hours / night with 87% using for ≥ 4 hours/ night (*Table 6*).

There was no difference between optimum CPAP use in men and women (*Table 7*). There was no difference in CPAP use in patients with mood disorders (anxiety/ depression) (*Table 8*). There was no difference in optimal CPAP usage in patients with different levels of daytime sleepiness (ESS scores), (*Table 9*). There was no difference in optimal CPAP usage with increasing ODI scores, (*Table 10*).

Table 6: Baseline parameters- Long-term compliance study

Sex (M/F)	196/25
Age in years- Median (IQR)	50.27 (15.3)
Baseline oxygen desaturation index- Median (IQR) hour ⁻¹	20 (27)
Epworth sleepiness scale- Median (IQR)	15.7 (6)
Compliance in hours per night (IQR)	6.9 (2.1)
BMI in Kg.m ⁻²	32.6 (10.5)

Patients (10%) who reported a benefit in daytime sleepiness had sub-optimal compliance on CPAP compared to 35% who did not report any benefit (p= 0.039). Conversely, patients reporting a lack of improvement or worsening in daytime sleepiness symptoms were found to have suboptimal CPAP use (Odds ratio 1.3, p = 0.026) (Table 11,12).

Table 7: Relationship between Sex and sub-optimal compliance

CPAP	< 4 hours/ night	≥ 4 hours / night
Females	4 (16.0%)	21 (84%)
Males	25 (12.8%)	171 (87.2%)

p = NS

Table 8: Relationship between anxiety / depression vs. compliance

Anxiety/ Depression	<i>CPAP < 4 hours/ night</i>	<i>CPAP ≥ 4 hours / night</i>
Present	2 (28.6%)	5 (71.4%)
Absent	27 (12.6%)	187 (87.4%)

p=NS

Table 9: Relationship between ESS vs. compliance

ESS	<i>CPAP < 4 Hr./ night</i>	<i>CPAP ≥4 Hr./ night</i>
<11	5 (19.2%)	21 (80.8%)
11-16	11 (13.4%)	71 (86.6%)
>16	8 (8.2%)	89 (91.8%)

p=NS

Table 10: Relationships between Desaturation Index and compliance

Desaturation Index (/ Hr.)	<i>CPAP <4 Hr./ Night</i>	<i>CPAP ≥ 4 Hr./ Night</i>
< 10	7 (13.0%)	47 (87%)
10- 15	5 (13.5%)	32 (86.5%)

15.1 -30	10(17.5%)	47 (82.5%)
>30	7 (9.6%)	66 (90.4%)

p=NS

Table 11: Relationships between Changes in ESS vs. Compliance

Current ESS	<i>CPAP < 4 Hr./night</i>	<i>CPAP ≥4 Hr./night</i>
Less than baseline	19 (10.1%)	169 (89.9%)
Equals to / worse than baseline	6 (35.3%)	11 (64.7%)

p=0.039

Table 12: Factors associated with long-term compliance

	OR for suboptimal compliance at last visit (p value)
Age >60	4.2 (0.025)
Males vs Females	0.768 (NS)
Most recent ESS> Baseline ESS	1.3 (0.026)
ESS≤ 10 vs. >10 at baseline	2.02 (NS)
DI ≤ 20 (vs. >20) at baseline	1.65 (NS)
Anxiety/ Depression	2.77 (NS)

3.2 A prospective observational study to evaluate the effect of social and personality factors on Continuous positive airway pressure (CPAP) compliance in Obstructive sleep apnoea.

Study Population

The study recruited over a period of 7 months. Screening was performed on 1400 patients with a suspected diagnosis of OSA. During the study period 566 patients were started on CPAP at the centre. Of these, 410 were initially seen by sleep specialists at the Papworth sleep centre and others were admitted to start the therapy, based on sleep studies and assessment by specialists at the referring hospitals. Amongst the patients assessed at the sleep centre, 265 who were recommended CPAP therapy consented to participate in the study. The decision to start them on CPAP treatment was based on the assessment by a sleep disorders specialist. There were 205 men (male to female ratio 3.4:1). Expressed as median (IQR): at baseline the age of participants was 53 (44-61) years, ESS 15 (11-17), BMI 34.8 (31.6- 41.7) kg/m² and ODI 21 (12.3- 41.2) per hour.

One hundred and twenty subjects (45%) were classified as Type D personality. At baseline 32% subjects were taking antidepressant medication or said that they had previously been diagnosed with depression by their general practitioner and 45% of subjects had a BDI-2 score of > 13.

From the cohort of 265 subjects, 9 were switched to a Bi-level device, 5 were excluded (one was diagnosed with an upper airway malignancy, another was cured of OSA by

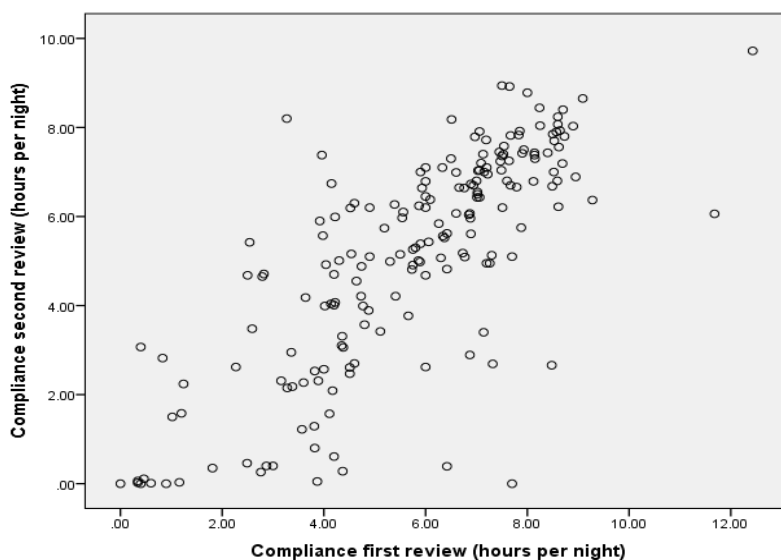
tonsillectomy, 3 did not attend any follow-up visit during the study period), and 5 withdrew consent.

'Acceptance' was calculated as proportion of individuals still using CPAP after 6 months. Non-acceptors were defined as those who either did not take CPAP home after the initial trial on the night of the titration or stopped treatment after a period of time. Individuals who repeatedly failed to attend the follow-up appointments despite reminders represented a challenge. For this study we considered them as non-acceptors, assuming they were not using the CPAP regularly, although this was unknown.

Two hundred and twenty-one subjects (90%) were still using CPAP at 6 months.

There was a strong correlation between early compliance (measured as hours of use at first follow-up 6-10 weeks) and 6 months' compliance ($r = 0.77$) (Figure 3).

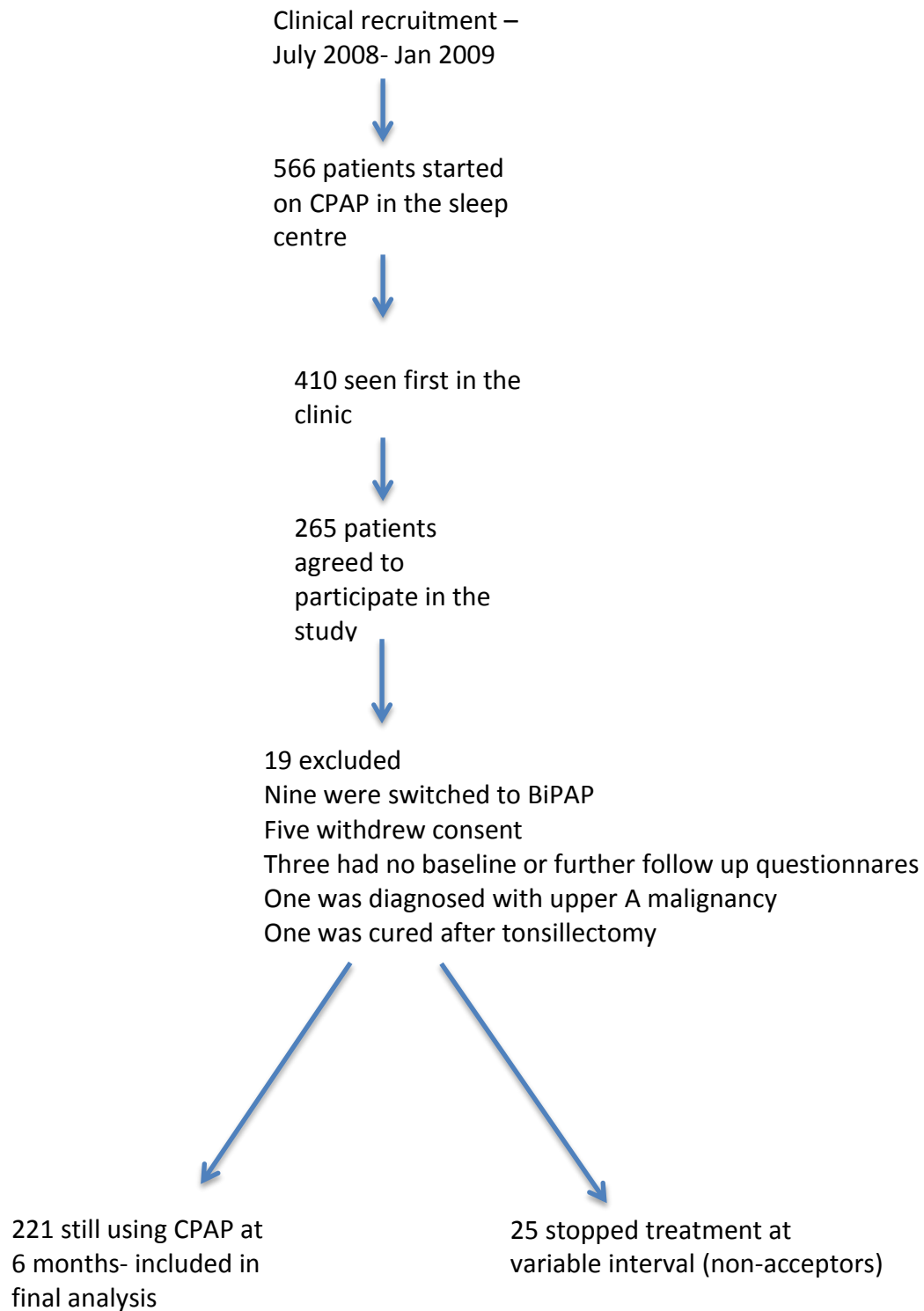
Figure 3: Correlation between early and late compliance with CPAP



Correlation between early (6-10 weeks) and late CPAP compliance (6 months)
 $r = 0.77$ ($p < 0.05$)

The median use at first follow up and 6 months were, 6.0 (4.2-7.5) and 5.6 (3.4- 7.1) hours / night respectively. By definition 19 % were using CPAP sub-optimally at first visit and 27 % at 6 months.

Flow chart of compliance study



The distribution of different SEC categories within the study population is shown in Table 13. The hours of use in each SEC category at first follow up and at 6 months are shown in Figures 4 and 5 respectively. Compared to individuals who were working (or retired from work), those who were long-term unemployed had lower, median hours of CPAP usage at first follow up and at 6 months (*Table 14*). This group was also more likely to use CPAP sub-optimally (< 4 hours / night) at first follow up visit and at 6 months (OR 3.3, and OR 4.59 respectively, see *Table 15, 16 a and 16b*). Patients with high BDI-2 scores indicating underlying depression were more likely to have suboptimal use of CPAP.

Table 13: Distribution of OSA patients in different socio-economic status groups

Socio-economic status	Number	Percentage
1	107	40.4
2	8	3.0
3	45	17.0
4	47	17.7
5	24	9.1
Unemployed- not working	19	7.2
Missing	15	5.7

Figure 4 Socioeconomic class vs. CPAP compliance at first visit

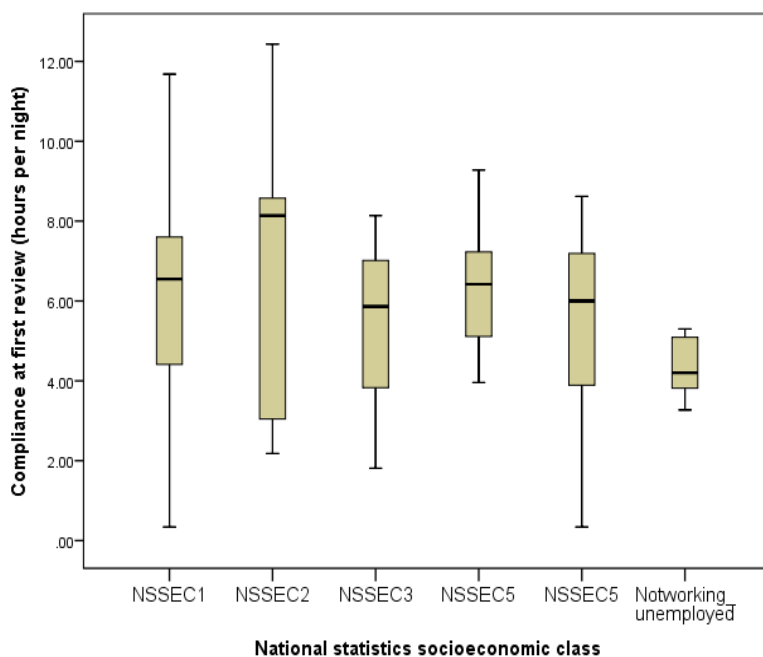
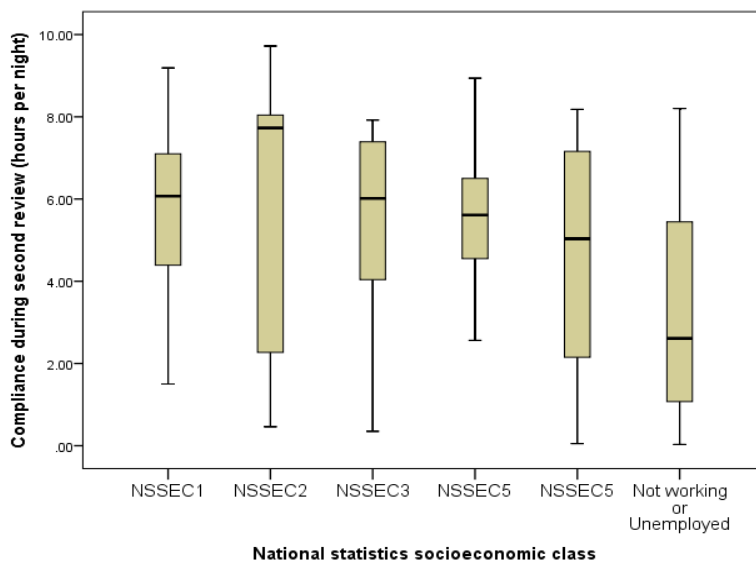


Figure 5: Socioeconomic class vs. CPAP compliance at 6 months



Above figures shows average compliance and its association with socioeconomic groups during first and 6 months followup.

Table 14a: Median hours of use at first follow-up for subjects using CPAP in different sub groups defined by study characteristics.

	First follow-up (6-10 weeks) Median hours of use (IQR) per night	p value
Long-term unemployed vs Employed	4.2 (3.8-5.3) vs. 6.3 (4.3- 7.5)	0.028
Education: Bachelor degree vs Lower educational qualification	6.04 (4.14-7.49) vs. 5.90 (4.53-7.42)	NS
Type D personality vs Non Type D	6.00 (4.2-7.22) vs. 6.07 (4.22-7.49)	NS
Previous diagnosis of depression vs No depression	6.87 (2.92-7.85) vs. 6.00 (4.22- 7.17)	NS
BDI>13 vs ≤ 13	6.00 (4.14-7.65) vs. 6.15 (4.36-7.26)	NS
BDI≥29 vs <29	4.72 (4.30-7.49) vs. 6.20 (3.98-7.19)	NS
Anxiety vs No Anxiety	6.46(3.77-7.87) vs. 6.00 (4.22 -7.22)	NS
Age (greater than 70yr vs ≤ 70)	7.02 (6.6- 7.23) vs. 6.00 (4.1-7.46)	NS
Sex (male vs females)	6.00 (4.2-7.2) vs. 6.36 (4.18-7.19)	NS
ESS>10 vs ≤10	6.02 (4.14-7.45) vs. 6.0 (4.63-7.73)	NS
4% desaturation index >20 vs ≤ 20	6.0 (4.1-7.5) vs. 6.04 (4.16-7.38)	NS

Table 14b: Median hours of use at 6 month follow-up for subjects using CPAP in different sub groups defined by study characteristics.

	6-month follow-up Median hours of use (IQR) per night	p value
Long-term unemployed vs Employed	2.61 (1.0 – 5.7) vs. 5.96 (4.0- 7.2)	0.016
Education: Bachelor degree vs Lower educational qualification	5.75 (3.4-7.13) vs. 6.02 (5.01-7.1)	NS
Type D personality vs Non Type D	5.5 (2.9-7.1) vs. 6.06 (4.14-7.1)	NS
Previous diagnosis of depression vs No depression	5.61(3.00-6.90) vs. 5.74 (3.99-7.10)	NS
BDI>13 vs ≤ 13	5.01(2.62-7.37) vs. 5.99 (4.68-7.00)	NS
BDI≥29 vs <29	4.27 (2.52-6.5) vs. 5.98 (4.01-7.13)	NS
Anxiety vs No anxiety	5.01 (2.56-6.66) vs. 5.84(4.0-7.20)	0.09
Age (greater than 70yr vs ≤70)	6.99 (5.94-7.00) vs. 5.61 (3.4-7.1)	NS
Sex (male vs females)	5.59 (3.4-7.03) vs. 5.97 (4.75-7.6)	NS
ESS>10 vs ≤10	5.6 (3.4-7.1) vs. 6.1 (4.17-7.2)	NS
4% desaturation index >20 vs ≤ 20	6.14 (3.62-7.27) vs. 5.39 (3.2-6.99)	NS

Table 15: Distribution of subjects using CPAP \geq , or less than 4 hours per night by study characteristics.

	First follow-up (6-10 weeks) Percentage with characteristic and compliance \leq 4 hours/night	p value	6-month follow-up Percentage with characteristic and compliance \leq 4 hours/night	p value
Long-term unemployed vs Employed	45% vs. 19%	0.046	64% vs. 26%	0.011
Education: Bachelor degree vs Lower educational qualification	22.2% vs. 12.9%	NS	29.3% vs. 6.3%	0.09
Type D personality vs Non-type D personality	21% vs. 19%	NS	33% vs. 22%	0.056
Previous diagnosis of depression vs No depression	27% vs. 18%	0.088	34% vs. 25%	0.10
BDI>13 vs \leq13	24% vs. 18%	NS	34% vs. 21%	0.03
BDI\geq29 vs <29	29% vs. 19%	NS	50% vs. 25%	0.028
Anxiety vs No anxiety	30% vs. 19%	0.052	40% vs. 25%	0.048
Sex (male vs females)	20.5% vs. 23.8%	NS	30.2% vs. 20.5%	NS
ESS\leq10 vs >10	29% vs. 16%	NS	29.3% vs. 9.2%	NS
4% desaturation index >20 vs \leq20	20% vs. 23%	NS	28% vs. 30%	NS

Table 16a: Different factors affecting compliance at first visit

	OR for suboptimal compliance at first visit (95% confidence interval)	P value
Age >70	1.04 (1.01-1.08)	NS
Type D	1.08 (0.77-1.52)	NS
BDI >13	1.16 (0.8- 1.7)	NS
BDI > 29	1.6 (0.6- 4.4)	NS
Unemployed-not working	3.3 (1.1-10.3)	0.046
Bachelor degrees and above	0.57 (0.21-1.53)	NS
ESS ≤ 10	0.65 (.3- 1.45)	NS
DI ≤ 20	0.90 (0.63-1.30)	NS
Depression	1.44 (0.93-2.22)	0.08

Table 16b: Factors affecting compliance at 6 months

	OR for suboptimal compliance at 6 months (95% confidence interval)	P value
Age >70	1.04 (1.0-1.07)	NS
Type D	1.30 (0.93-1.72)	0.08
BDI >13	1.40 (1.03-1.9)	0.043
BDI > 29	2.65 (1.12-6.3)	0.03
Unemployed-not working	4.59 (1.4-15.0)	0.011
Bachelor degrees and above	1.9 (0.63-5.9)	NS
ESS ≤ 10	1.07 (0.96-1.18)	NS
4% DI <20	1.04 (0.76-1.4)	NS
Anxiety	1.67 (0.99-2.84)	0.06
Depression	1.34 (0.91-1.99)	NS

Physician's prediction

Physicians who recommended the use of CPAP treatment were able to predict compliance with a high degree of accuracy. The group who used CPAP for ≥ 4 hours / night at first visit, were given a likelihood of good compliance of 80%, while those who used CPAP < 4 hours / night were given a likelihood of 72% (Table 17). The difference persisted at 6 months. We looked for a specific cut off point for a physician's initial impression to predict sub-optimal compliance. Though the sensitivity of predicting

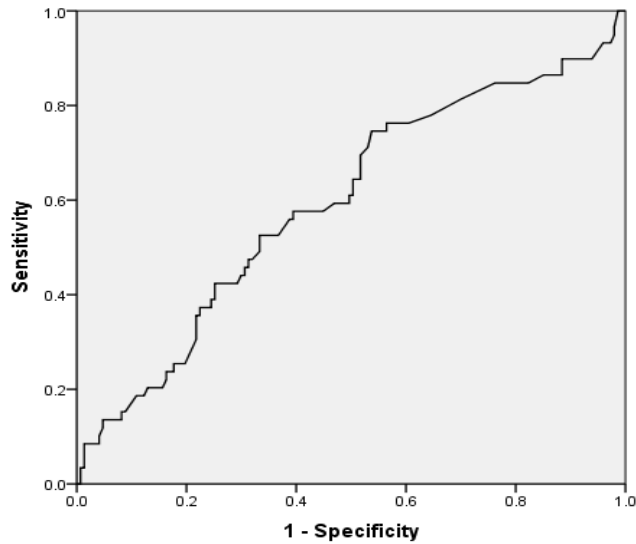
suboptimal compliance was 83 % and specificity 91 %, when a physician marked $\leq 60\%$ on a visual analogue scale, on ROC analysis area under the curve was only 0.59 (Figure 6).

Physician's also marked their impression on a visual analogue scale as to the likelihood of OSA being the cause of sleepiness (whether ESS likely to improve on CPAP). No significant association was found between the physician's impression and change in ESS (Figure 7). However, a significant correlation was found between a physician's ability to predict OSA as a cause of symptoms and their ability to predict optimal compliance on VAS (Figure 8).

Table 17: Physician's impression (scored between 0 and 100% on a VAS that a patient would use CPAP > 4hours a night) as a predictor of CPAP compliance.

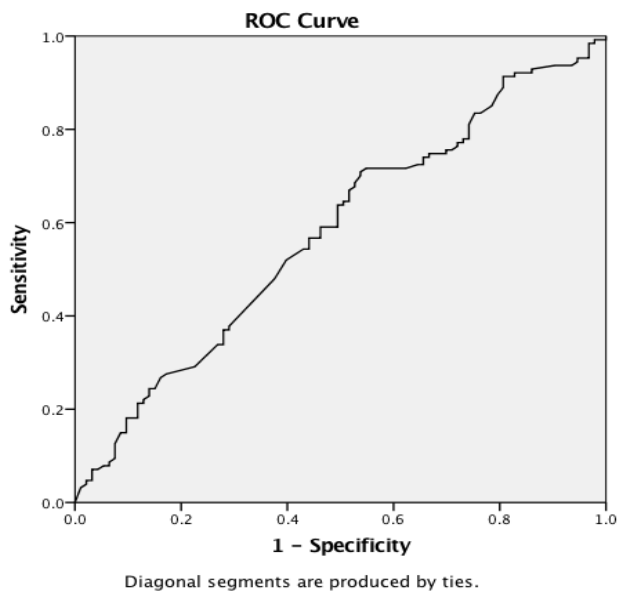
	Impression for those using CPAP <4 hours, Mean (SD) %	Impression for those using CPAP \geq4 hours, Mean (SD) %	
First review	72.4 (18.03)	80.3 (13.29)	P=0.018
6 months	74.8 (17.42)	80.5 (13.90)	P=0.041

Figure 6: ROC analysis of physician's assessment as a predictor of suboptimal compliance at 6months



** In the ROC curve, we looked at the diagnostic value of a physician's assessment to predict optimal compliance on CPAP treatment. Area under Curve (AUC) was 0.59*

Figure 7: ROC analysis of physician's assessment as a predictor of improvement in symptoms (ESS) at 6months



** In the ROC curve, we looked at the diagnostic value of a physician's assessment to predict an improvement in symptoms at 6 months. Area under Curve (AUC) was 0.58*

Figure 8: Correlation between Physician's impression in predicting compliance and impression in predicting OSA as a cause of symptoms

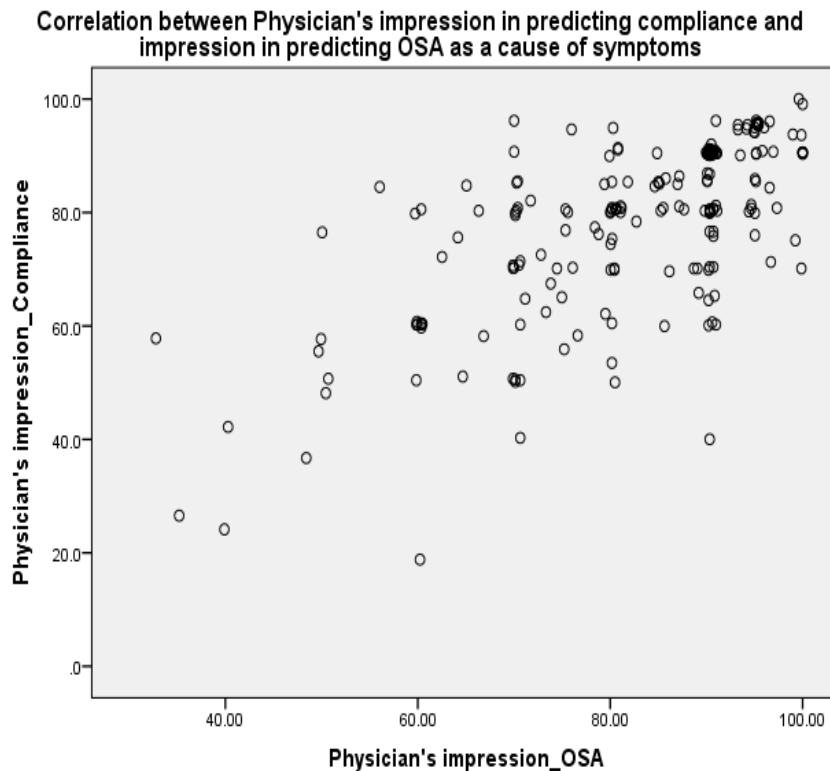


Figure shows correlation between Physician's impression in predicting compliance and impression in predicting OSA as a cause of symptoms (r values = 0.64)

Depression scores

At 6 months, BDI 2 score threshold of 13 was statistically significant in separating the subjects with optimum vs. sub-optimal compliance (*Table 14*). This difference in compliance became more marked for those with BDI score ≥ 29 and was statistically significant ($p=0.03$).

Depression was more common in the subjects who were unemployed. Self-reported anxiety on enrolment to the study also predicted lower hours of use CPAP (*Table 15*).

There was a trend for individuals with type D personality to comply sub-optimally at

6 months, but this did not reach statistical significance. No association was found between hours of use either at first or 6 month follow up with demographic factors (such as sex and age), baseline ESS, or ODI (*Table 15*).

Twenty-five patients declined treatment and were not using CPAP at 6months. Baseline characteristics of these patients were not different from the acceptors (*Table 18*).

Table 18: Distribution of subject's according to non-acceptor status by study characteristics

	CPAP acceptors vs. non-Acceptors	<i>P value</i>
Long-term unemployed	25% vs. 9.2%	<i>NS</i>
Education: Bachelor degree	8.6% vs. 13.6%	<i>NS</i>
Type D personality	6.9% vs. 9.9%	<i>NS</i>
Previous diagnosis of depression	8.6% vs. 11.0%	<i>NS</i>
BDI>13	9.7% vs. 7.3%	<i>NS</i>
BDI≥29	8.4% vs. 7.9%	<i>NS</i>
Anxiety (Self report)	11.8% vs. 9.8%	<i>NS</i>
ESS≥10	14% vs. 9.2%	<i>NS</i>
4% desaturation index >20	8.3% vs. 11.7%	<i>NS</i>

Subjects were asked to complete a questionnaire after the first night of CPAP titration. In this questionnaire, they recorded their experiences of side effects, as well as whether they thought that they were likely to continue with the treatment and whether there was an improvement in their symptoms on treatment. The side effects included local mask related side effects, too much pressure, claustrophobia, nasal stuffiness and leakage, bloating and others (*Table 19*). The patients' initial thoughts about "likelihood of continuing treatment" and experiences after first night of treatment are summarised in Table 20a and 20b.

Eleven percent of individuals ($n = 10$) who complained of side effects after the first night of titration did not accept treatment compared to 5% of those who did not experience or record any side effects ($p = 0.003$) (*Table 21*). Those who accepted CPAP but initially recorded side effects after the first night of treatment were more likely to comply sub-optimally with CPAP at 6 months compared with those with no reported adverse effects of CPAP (*Table 22, $p = 0.002$*). No significant association was however found between experiencing side effects and suboptimal compliance at the first visit (*Table 23*).

Those individuals who after the first night recorded that "they are likely to continue with the treatment" (*Table 24*) or "felt better after using CPAP on the first night" were more likely to accept treatment though no difference in subsequent compliance at 6-10 weeks and 6 months was noted, when compared to the other group (*Table 25*).

Table 19: Side effects on the first night of titration

Side effect	Frequency	Percent
Noise	20	8.1
Uncomfortable with mask	51	20.7
Claustrophobia	14	5.7
Pressure too high	11	4.5
Bloating	9	3.7

Table 20 a: Experiences after the first night on CPAP

Experiences after the first night on CPAP	Frequency	Percent
Did not complete questionnaire	35	15.8
Tremendously better	22	10.0
Moderate better	56	25.3
Slightly better	55	24.9
No improvement	48	21.7
Worse	5	2.3

Table 20 b: Experiences after the first night on CPAP “Likelihood to continue treatment”

Experiences after the first night on CPAP	Frequency	Percent
Missing info	32	14.5
Will not continue	1	.5
Less likely to continue	1	.5
Probably will continue	19	8.6
Most likely	53	24.0
Will definitely	115	52.0

Table 21: Side effects after first night on CPAP vs. Acceptance

	Any problems			Total
	Missing info	Yes	No	
Acceptors	34	82	105	221
Non-acceptors	10	10	5	25

p=0.003

Table 22: Side effects after the titration night vs. suboptimal compliance at second visit

Side effect on the night of CPAP titration	Yes	No
Compliance<4hrs	29 (38.2%)	18 (18.6%)
Compliance≥ 4hrs	47 (61.8%)	79 (81.4%)

p= 0.002

Table 23: Side effects after the titration night vs. suboptimal compliance at first visit

Side effect on the night of CPAP titration	Yes	No
Compliance<4hrs	17 (21%)	17 (18.3%)
Compliance≥ 4hrs	54 (79%)	76 (71.7%)

Table 24: Association between initial experiences on CPAP with acceptance to treatment

	How likely are you to continue with CPAP							Total
	Missing Info	Will not continue	Unlikely to continue	Less likely to continue	Probably will continue	Most likely	Will definitely	
Acceptors	32	1	0	1	19	53	115	221
	14.5%	0.5%	0.0%	0.5%	8.6%	24.0%	52.0%	100.0%
Non-acceptors	11	0	1	0	4	3	7	25
	44%	0.0%	4%	0.0%	12%	12%	28%	100.0%

p value <0.001

Table 25: Association between initial experiences on CPAP with acceptance to treatment

	How did you feel after the first night on CPAP						Total
	Missing Info	Tremendously better	Moderate better	Slightly better	No improvement	Worse	
Acceptors	35	22	56	55	48	5	221
	15.8%	10%	25.3%	24.9%	21.7%	2.3%	100.0%
Non-acceptors	10	0	2	2	10	1	25
	40%	0.0%	8%	8%	40%	4%	100.0%
Total	45	21	57	57	58	6	246

p< 0.05

Unemployment was more likely to be associated with non-acceptance of CPAP (OR 3.29) than the other SEC group members. Other Socio-demographic, psychological or personality factors including, age, sex, ESS, severity of OSA (measured by desaturation index or AHI), Depression, Anxiety and type D personality were not associated with non-acceptance on CPAP treatment (*Table 17*).

3.3 The impact of changing to a Bi-level pressure generating device in people with sleep apnoea using CPAP less than 4 hours per night

In this randomised crossover trial, 31 patients who met the entry criteria and gave consent were recruited to the study. One developed a stroke during the treatment period after initial trial with NIPPY and 2 others did not complete the study (one after initial new CPAP and another one did not complete either limb of the study) and hence were excluded.

There were 23 males and 5 females. At baseline the mean hours of CPAP use were 1.49 hours per night (*Table 26*). When changed from CPAP to Bi-level PAP compliance improved to 2.73 hours per night ($p=0.001$). Reviewing sleep specific symptoms and QOL score (SAQLI) there were significant improvements in SAQLI scores from 3.6 to 4.5 and ESS from 13.2 to 11.2 (*Table 27a*). However, there were similar changes in the control group with a new CPAP brand (*Table 26 b*). The hours of use rose to 2.30 per night ($p=0.06$), ESS fell from 13.2 to 11.5. No changes were seen in the OLSER parameters with either new device.

The key comparison, that is in the number of hours of use with Bi-level PAP and a new brand of CPAP showed no significant difference (*Table 27c*). Patients found Bi-level PAP more comfortable to use compared to new CPAP on a VAS (68 vs. 60mm) but this trend was not statistically significant.

Summary flow chart of Bi-level PAP intervention study

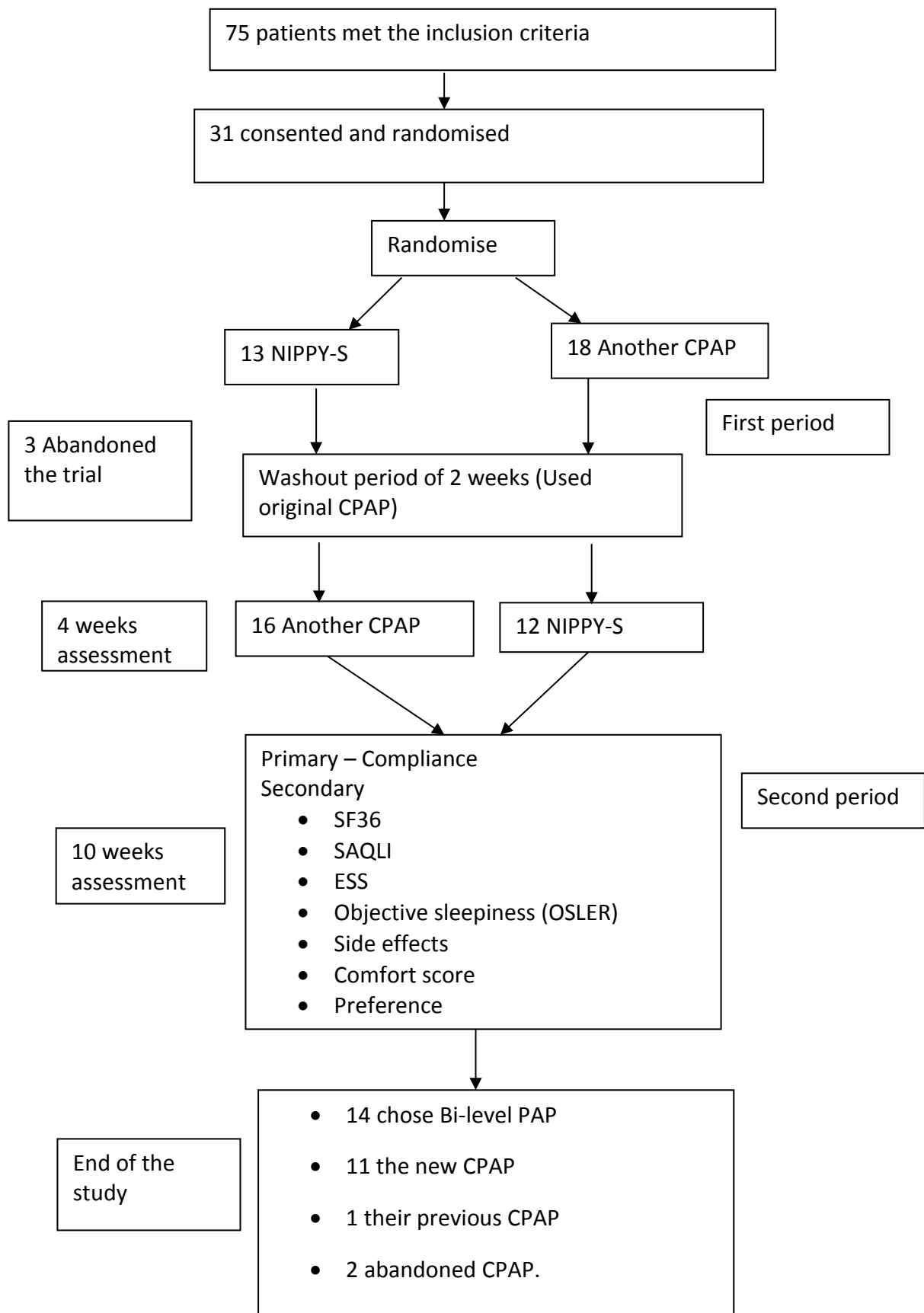


Table 26: Baseline characteristics of Bi-level PAP study

	Mean	Std. Deviation
Compliance on CPAP (hrs. / night)	1.49	0.89
BMI (Kg/ m ²)	35	7
OSLER- Sleep Latency (minutes)	27.5	14.1
OSLER – No of errors per test	30.1	27.7
ESS	13.2	4.7
Sleep study (Off CPAP)		
Mean O2 Sats (%)	92.9	2.5
4% DI (per hour)	32	25.1
AHI (per hour)	35.8	24.9
SAQLI	3.6	1.3

Table 27a: Differences between Old CPAP and Bi-level-PAP

	Baseline (Old CPAP)	Bi-level-PAP	<i>P value</i>
Compliance (hrs. per night)	1.49 (0.89)	2.73 (1.98)	0.001
ESS	13.04 (4.6)	11.2 (4.61)	0.015
Sleep latency (minutes)	27.5 (14.09)	29.4 (13.71)	NS
No of errors	30.07	27.11	NS
SAQLI	3.68 (1.48)	4.5 (1.43)	0.004

Table 27b: Differences between Old CPAP and new CPAP

	Baseline (Old CPAP)	New CPAP	<i>P</i>
Compliance (hrs. per night)	1.49 (0.89)	2.23 (1.56)	0.006
ESS	13.38 (4.65)	11.8(5.45)	0.06
Sleep latency (minutes)	27.5 (14.06)	29.13 (13.00)	NS
No of errors	30.07	32.7	NS
SAQLI	3.6 (1.51)	4.07(1.71)	NS

Table 27c: Differences between New CPAP and Bi-level-PAP

	New CPAP	Bi-level PAP	P value
Compliance (hrs. per night)	2.2 (1.56)	2.7 (1.9)	0.059
ESS	11.5 (5.34)	11.0 (4.75)	NS
OSLER Sleep latency (minutes)	29.4 (13.77)	29.1 (13.00)	NS
No of errors	32.7	27.1	NS
Comfort level with device (0 to 100mm)	60 (23.5)	69 (24.2)	NS
SAQLI	4.5 (1.42)	3.95 (1.78)	NS

Table 28: Subgroup analysis

	N	New CPAP	Bi-level PAP	P value
Compliance (Hours per night)	17	1.94 (1.48)	2.63 (2.1)	0.05
ESS	17	11 (5.0)	10.7 (4.7)	NS
OSLER sleep latency (minutes)	17	31.9 (11.45)	32.8 (11.71)	NS
Comfort level with device (VAS 0 to 100mm)	16	53.4 (25.28)	71.6 (17.7)	0.02
SAQLI	17	3.9 (1.68)	4.6 (1.38)	NS

A post-hoc sub-group analysis was performed on the data for patients who complained specifically of difficulty with exhalation when on their original CPAP device. Bi-level PAP was superior to new CPAP for compliance and comfort.

In post hoc analysis, we looked at a group who specifically complained of difficulty

with exhalation. Compliance was significantly better with Bi-level PAP in this group (2.61 vs. 1.94 hrs., p 0.05). Bi-level PAP was also found to be more comfortable to use in this group (VAS 53 vs. 71, p value 0.02).

At the end of the study, patients marked their preferences for individual interventions, with 15 preferring Bi-level PAP, 11 the new CPAP and 2 finding no difference. When final machines were issued 14 chose Bi-level PAP, 11 the new CPAP, 1 their previous CPAP. Two subjects chose to abandon CPAP treatment. Overall there was no significant difference in the choice of the final PAP device at the end of the study, comparing Bi-level PAP with new CPAP brand.

CHAPTER 4

DISCUSSION

CHAPTER 4 DISCUSSION

Obstructive sleep apnoea is an increasingly common condition (Van Dieren S, 2010). It causes poor health related quality of life and daytime symptoms as well as cardiovascular risk which may be reduced by CPAP therapy in moderate to severe disease (Campos-Rodriguez F, 2005). CPAP is rapidly effective (Filtner AJ, 2012) and symptoms are best controlled in those who use CPAP for the highest number of hours (Weaver T, 2008). Optimal use of CPAP is not only associated with an improvement in symptoms (i.e. less sleepy, improved neurocognitive performance), but is also linked with a reduction in road traffic accidents, better control of blood pressure and a likely reduction in cardiovascular complications.

Several studies have sought association between various factors that impact on both short term and long-term compliance with variable results. So far, apart from an association between disease severity and OSA related symptoms with compliance, no clear and consistent association has been found. Many of the research has been conducted in sleep centres, which would have had different diagnostic criteria and been operating in varied healthcare systems in different countries. This may, in part, explain the considerable heterogeneity among the results. The lack of strong reproducible predictive associations between measures of disease severity and the level of compliance with its treatment raises the question of whether these measures have true biological relevance.

No research has yet explored an association between socioeconomic status derived by occupational and educational status (NS-SEC) with CPAP compliance. There is no

published literature that has examined the physician's competence in predicting CPAP compliance. In individuals who are sub-optimally compliant with CPAP, there is no evidence that a trial with Bi-level PAP makes a difference to their hours of usage.

My thesis sets out to explore these questions through a series of projects. These were to examine the long-term compliance of patients at a single centre, to explore relationships between socio-demographic factors, personality (Type D) and depression with CPAP acceptance and compliance. I also explored the ability of a physician to predict CPAP compliance at the time of initial visit when decision is taken to start CPAP. In a prospective randomised cross-over trial, I reviewed the role of Bi-level PAP in individuals who were sub-optimally compliant with CPAP due to pressure related side effects.

4.1 Long term compliance on CPAP- single centre experience

My retrospective study explored a single centre's experience with long-term compliance with CPAP. Improvement in sleepiness (change in ESS from baseline) was found to be associated with optimal compliance.

McArdle et al in a prospective observational study found a higher baseline ESS to be linked to a better long-term CPAP compliance (McArdle N, 1999). Barbe et al (2001) in their prospective study found no measurable benefit of CPAP in asymptomatic individuals. A meta-analysis of three trials using sham CPAP as control, showed that high usage of CPAP was associated with improved sleepiness (Crawford MR, 2012). Sin et al also demonstrated an association between improvement in ESS and better compliance (Sin D, 2002). It is unclear if patients who are more compliant with CPAP

experience an improvement in daytime sleepiness or those who experience an improvement in their daytime symptoms are more likely to be compliant. None of the current research, including my own work is able to establish a cause and effect association between 'improvement in sleepiness and compliance with CPAP'.

Although a higher ESS score at baseline has been linked with better compliance, the relationship has not been consistent nor predictive. McArdle et al in their multivariate analysis found ESS to be linked to better long-term compliance whereas the others have not shown the same relationship (McArdle N, Waldhorn RE 1990; Wolkove N 2008; Ball EM 2001; Meurice JC 1994; Kreiger j 1996; Pieters T 1996; Likar LL 1997; Engleman HM; Kohler M 2010; Chai-Coetzer 2013).

There was no association between the severity of OSA (measured by 4% oxygen desaturation index) and compliance in my study. Mean compliance between the two groups (those with ODI >30/ hour and < 30/ hour) and proportion of individuals sub-optimally compliant were not different. ODI as a categorical variable demonstrated no relationship with CPAP compliance. Kreiger et al, found no association between the ODI and mean compliance or proportion with sub-optimal compliance (Kreiger J 1992; Kribbs NB 1993b; Budhiraja R 2007; Kohler M 2010). Disease severity as measured with number of apnoeas or desaturations in sleep also had little correlation with daytime sleepiness symptoms in the literature. Therefore, it is perhaps not surprising that CPAP compliance showed a stronger relationship with daytime symptoms rather than physiological parameters of nocturnal apnoeas.

Individuals with a diagnosis of depression and anxiety were less likely to be compliant with CPAP treatment and almost a third were using CPAP <4h/night. Prevalence of anxiety and depression was lower in our retrospective study compared to what has been reported in the literature. Depression is diagnosed in 12-23% of unselected primary care patients (Moussavi S, 2007; Spitzer RL, 1995; Harold G, 1988). The prevalence of depression is higher in OSA patients (21-45 %) (Aikens JE, 1999a; Akashiba T, 2002; Sharafkhaneh A, 2005; Sharafkhaneh A, 2005; Zung WW, 1965; Guilleminault C, 1977; Reynolds CF, 1984; Millman RP, 1989). In my prospective study, a third of patients had a diagnosis of depression.

In my study, demographic parameters such as age, sex and BMI were not associated with compliance. Although there is some evidence in the literature favouring compliance in men, this has not been demonstrated reliably in most trials (Ye L, 2009).

In my study, a high proportion of individuals were still using CPAP and a high proportion were optimally compliant, compared to what usually has been reported in the literature. Eighty-one % of the individuals were still using CPAP at the time of data collection and of them 87 % were complying optimally. It is conceivable that careful selection of patients prior to commencing CPAP treatment may be responsible for this outcome. All our patients had the diagnosis of OSA established on the basis of overnight oximetry supported by clinical features suggestive of symptomatic OSA.

There were limitations to our study. It was a retrospective study with initial data collection in 2003-4 and re-analysed at a later date by a single researcher (AG).

The diagnosis of OSA was established on oximetry rather than a detailed respiratory polygraphy or polysomnography. However routine use of oximetry in conjunction with clinical symptoms suggestive of sleep apnoea is a standard clinical practice in many centres in the UK, including ours. There is evidence that oximetry has good diagnostic specificity to accurately diagnose OSA compared to the other diagnostic tests for sleep apnoea (Whitelaw WA, 2005; Nicholas W 2008)

Another limitation is that a clock counter on the CPAP machine rather than measuring effective mask time or there were no data for night-to-night variation measured compliance. However, a prospective study, which looked at, the same question, found effective mask time was similar to the compliance measured by clock counter device measurement on CPAP (Pepin JL, 1999)

4.2 Social class, education and personality on CPAP compliance

To date there have been few studies looking at the role of socio-economic status in acceptance of and compliance with CPAP treatment in patients with OSA. One cross sectional study looking at the pattern of acceptance of CPAP in an Israeli population found the likelihood of CPAP purchase to be determined by income level (Simon-Tuval T, 2009). Only 22% of individuals with low income accepted and purchased CPAP compared to 51% from average and 76% from higher income groups. Almost a third of patients declined CPAP therapy due to cost.

In my study, there was no correlation between compliance and socio-economic class for those in work. CPAP was provided free of charge. Patients who were long-term

unemployed were 3.6 times more likely to demonstrate sub-optimal compliance at 6 months.

The number of unemployed individuals was small (19 at the start of the study), and this result may not be generalizable. The distributions of patients in different socio-economic classes were similar to the one observed in previous population studies.

Verbracken et al found no difference in the compliance between individuals depending on socio-economic background assessed by educational status (Verbracken J 2007). Bakker et al found non-European ethnicity and low socio-economic status to be associated with poor CPAP compliance (Bakker JP, 2012). On multivariate analysis, factors associated with sub-optimal compliance were primary/secondary education (vs. tertiary education) and high (New Zealand) deprivation index. Poor socio-economic status has been linked with poor adherence to asthma and HIV medications (Bakker JP, 2011; Apter AJ, 1998; Kalichman HC, 1999; Matthews KA, 2011). It is believed that the relationship between socio-economic status and adherence could be due to access to the treatment. In my study done within the NHS and in the above study, access to treatment was not an issue. It was free at the point of delivery. However, for some patients in challenging circumstances, the cost of travel to appointments and anxiety around electricity bills associated with CPAP could be barriers, but we did not specifically enquire about such issues.

Another explanation for the poor compliance in the unemployed group in our study could be a lack of education, awareness about the illness or a greater degree of anxiety and depression in these individuals (Matthews KA 2011; Bakker JP 2011).

Because of the small numbers in the different groups, regression analysis to look at depression and unemployment as independent risks was not feasible.

One of the major differences between my study and other research looking at the role of SES is that we used NS-SEC, which takes occupation and profession into consideration to derive different socioeconomic classes. This did not take income into consideration. Other studies, which took income into consideration, were from health systems, that are not free at the point of delivery, and hence annual income may be a determinant (Greenberg H, 2004a; Greenberg H, 2006b, Joo MJ 2007; Simon-Tuval T, 2009, Campbell AJ, 2012). NS-SEC was the standard accepted classification in the United Kingdom; at the time we designed the study. Subsequently there have been minor modifications to the classifications (NSSEC 2011). It is widely believed that the parameters used in the NS-SEC are a true reflector of socio-economic class of an individual rather than income alone. A similar classification is used in other countries (Rose D, 2006; Milne BJ, 2013).

One of the limitations to the present study is that to derive different socio-economic classes we used a self-coded questionnaire rather than a detailed interview based method, which usually takes around 45 minutes. The concordance between the self-coded and interview based socio economic class is 76% (NS-SEC 2001). It is accepted that for large clinical or population studies, the self-coded version is easier to use, and does not require any formal training for the interviewer (NS-SEC 2001).

A potential limitation is that we did not record SES of the individuals at the end of the study, especially for the ones who were either unemployed or not in work at the beginning of the study. Since we wished to identify factors, which could highlight the

need for extra support at treatment initiation, we did not build in the repeat measure. For completeness, this data, in retrospect would have been useful.

Individuals who have high negative affectivity and social inhibition are classed as Type D personality (Dennolet J, 2005). Negative emotions in these individuals are likely to be associated with self-neglect with possible implications of poor adherence to treatment. Williams et al (Williams L, 2011) looked at the association between type D personality and adherence to medications three months post myocardial infarction. Individuals with type D personality were less likely to comply with medications. It has been argued that type D personality is another measure of depression and hence most of the effects observed within Type D individuals are the likely result of emotional/affect related symptoms. However further studies (Dennelet J, 2005) suggest that it is the interaction between negative affect and social inhibition which adds additional explanatory powers compared to negative emotions or social inhibition alone.

A retrospective study previously described that compliance with CPAP in those with Type D personality was on an average 1 hour 20 minutes less. Also, only 50% of individuals used CPAP >4 hours per night, compared to 84% of the non-type D personality (Brostorm A, 2007). Prospectively, in our study individuals with type D personality showed no difference in the mean compliance. It is not very clear why the results of the previous study were different from ours. One of the arguments is that the Brostorm study was retrospective and type D personality construct was measured retrospectively after the individuals were diagnosed with OSA and already started/established on the treatment. The questions asked to derive the personality trait were based on their current status, which may have been influenced partially by being on

CPAP treatment for a period of time and either succeeding or failing to benefit from it.

The prevalence of depression, when diagnosed by the GP's, in our population of OSA offered CPAP was 33% which is higher than estimates for otherwise unselected primary care patients and hospital inpatients (Moussavi s 2007). Other investigators have found a similar prevalence of depression (32-48%) in OSA population (Aiken JE 1999a). In my study, individuals with a diagnosis of depression were less likely to comply optimally at first review and similarly those with high BDI-2 scores were less likely to comply at 6 months (*Table 13*).

Depression is known to be associated with poor adherence to therapy in other chronic medical disorders (Smith A, 2006). In patients with OSA, there is conflicting evidence regarding any association between underlying depression and CPAP use and this may be partly due to the specificity and sensitivity of the screening questionnaires used. In a prospective study involving 70 patients, there was no correlation between CPAP compliance at 1 month and underlying depression measured by the Hospital Anxiety and Depression scores (Lewis KE 2004). In a prospective study, baseline depressive symptoms measured by BDI were not correlated with CPAP compliance (Wells RD, 2007). In a study using the Minnesota Multiphasic Personality Inventory to measure depression, individuals who were depressed had poor CPAP compliance (Edinger D, 1994).

Depressive symptoms have been shown to improve after CPAP treatment, independent of compliance (Means M, 2003). These results suggest that some of the

depressive symptoms in an OSA population are likely the effect of mood component of OSA and partially reversible.

To the best of our knowledge this is the first study to investigate the confidence of a physician in predicting compliance when they reviewed the patient for the first time. There was a statistically significant association between a physician's confidence that the individual would use CPAP and their hours of use. The differences observed were not large (80.3 vs. 72.5 at 6-10 weeks and 80.4 vs. 73.9 at 6 months), however this favours our hypothesis that a physician can predict CPAP compliance when initiating the treatment. Clinicians with a range of experience made this assessment and we did not separately assess for association between the accuracy of prediction and degree of experience in sleep medicine. It is conceivable that more experienced practitioners might produce better predictions.

In a study where a slightly different model was used, it was found that physician was more optimistic about weight loss after their review; however, they were not very accurate in predicting which patients will or will not change behaviours (K Pollak, 2011). Another prospective study reviewed the role of a Physician in predicting compliance with digoxin, no strong association was found between the two (Gilbert JR, 1980).

We also explored associations between the physician's ability to predict how likely the sleepiness was the result of sleep apnoea. Results were very similar to their ability to predict compliance. Interestingly there was a good correlation between the two (r value 0.65). It is likely that in part it is the initial impression about the symptom

correlation with sleep apnoea, which influences the prediction of CPAP compliance. This would add value to the earlier observation that symptomatic patients are more likely to be compliant with CPAP treatment.

We did not find any association between the physiological parameters of severity of OSA, Epworth sleepiness scale score and CPAP compliance. A similar lack of predictive association has been observed by other investigators (Lloberes P, 2004; McArdle N, 1999; Budhiraja R, 2007; Kim JH, 2009).

One possible weakness of the current study is that we used average CPAP compliance measured by the clock counter on a CPAP machine rather than more accurate effective compliance measurement (i.e. time spent at an effective pressure during the night). A prospective study of 121 consecutive patients with sleep apnoea looked at these two modes of measuring compliance (Pepin JL, 1999). This demonstrated that compliance measured by in-built counter is similar to effective CPAP compliance. Though most of the new CPAP machines available have in-built capacity to measure effective compliance; average CPAP compliance measurement using clock counter is still a valid and acceptable practice.

Another weakness is that we could not include consecutive patients, which might have led to selection bias. This was considered at the time of designing the study. In our centre, patients with suspected sleep apnoea are seen in a number of sleep clinics. Many are referred to us from other sleep centres with an established diagnosis of sleep apnoea. Recruiting consecutive patients in the sleep unit was therefore not practical.

Compliance follow-up data were missing in a proportion of patients (13% at first and 7% at 6 months). These patients were repeatedly approached as per the standard accepted clinical practice at and in a proportion, questionnaires were sent to them. In future studies, remote monitoring could allow more complete data sets.

Quality of life (QoL) data were missing during the follow-up visits in a significant proportion of individuals. With large number of missing QoL data it was very difficult to draw any valid conclusions from it; these data have not been analysed/ presented.

In this cohort, initial acceptance of CPAP was 89 %, which compares favourably with published data. Early compliance measured as hours of use was highly correlated with compliance in the long-term (at 6 months). Subjects who were long-term unemployed and those with a high score on BDI-2 were less likely to use CPAP for >4 hours per night. Socio-economic status, education level, ESS and ODI did not predict compliance. Our findings suggest that people who are long-term unemployed or depressed should be identified and offered more intensive support when initiating CPAP therapy to give them the best chance of getting on with the treatment.

4.3 The impact of changing to a Bi-level pressure generating device in people with sleep apnoea using CPAP less than 4 hours per night

My randomised, crossover study examined the effects of Bi-level PAP on patients with poor compliance due to pressure related intolerance. Interventions in both groups led to a statistically significant increase in hours of use. The Bi-level device was not more effective in increasing the hours of use than changing to another CPAP brand.

Six studies comparing CPAP and Bi-level PAP showed no benefit in compliance (Smith IE 2009). Most of the published studies designed to investigate the impact of different ways of delivering PAP have studied unselected subjects, initiating therapy for the first time. In such studies, compliance has been better with standard treatment than in historical series making any treatment or intervention effects harder to demonstrate. To address these issues, I designed study-recruiting patients who had been poorly compliant with standard CPAP despite a range of interventions such as pressure re-titration and the addition of humidification and who reported symptoms of pressure intolerance.

I found an improvement in hours of use with both new CPAP and Bi-level PAP. Mean changes in the compliance from baseline to new CPAP were 44 minutes and 69 minutes when the machines were changed to a Bi-level PAP. Though there were improvements in compliance with each intervention, these are likely to be a placebo effect due to treatment changes. Bi-level PAP device or new CPAP were unlikely to be superior to the existing CPAP.

When comparisons were made between two interventions, there was a non-significant difference in the compliance between the Bi-level PAP and the new PAP (p value= 0.059). The difference became more marked and statistically significant in a sub-group of patients who had complained of difficulty with exhalation (44 minutes, p=0.05).

Studies of CPAP compliance have proposed a range of cut-offs to define adequate use but more than 4 hours is often quoted. (Kribbs NB, 1993b; Rauscher H, 1993; Meurice JC 1994). There is evidence that different measures of benefit have

different sensitivities to hours of use. Weaver and colleagues showed benefit in the ESS up to 4 hours of use, in the objective multiple sleep latency tests up to 6 hours of use and on the Functional Outcomes of Sleep Questionnaire up to 7.5 hours of use. As predicted by Weaver's results, this was associated with a fall in ESS and an improved SAQLI. In my study, there was a trend towards greater use of Bi-level PAP but this was not statistically significant. The extra 30 minutes of use compared to a new CPAP device, was not associated with any difference in the daytime sleepiness or SAQLI. One study of 1 years' duration showed a greater drop out for CPAP than Bi-level PAP (Reeves-Hoche MK, 1995).

In a further subgroup analysis, of patients who complained of difficulty with exhalation, significant differences in compliance and comfort were found between Bi-level PAP and new CPAP group.

There were limitations to the study. Most of the patients had their Bi-level PAP and new CPAP introduced during the daytime. They were titrated as a day care procedure, with starting inspiratory pressure similar to previous CPAP. There is some evidence that PAP can be introduced as a day care procedure (Rabec C, 2010) and this is a routine practice in some UK centres. Since both the interventions were titrated similarly, it is less likely to have affected the comparative results between the two groups.

It is conceivable that the Bi-level device was not optimally setup. Though it seems less likely that it would have influenced the final comparative results; as sleep apnoea control was not different between the Bi-level PAP and CPAP groups. Mean AHI

following titration was not different between the Bi-level PAP group compared to the new CPAP group.

We relied on an inbuilt clock counter in the machines to measure average hours of use over a period of time. The equipment used in the study did not have the algorithms to measure night-to-night variation. Though this measurement may be interesting, it is the mean hours of use that has been best examined as an indicator of effective compliance. Three subjects dropped out after the baseline evaluation but their baseline parameters including compliance / daytime sleepiness were similar to the rest of the subjects that completed the study protocol.

The results of this study do not support routine intervention with Bi-level PAP in individuals who are poorly compliant with CPAP and complain of pressure related side effects. A sub-group of pressure intolerant individuals who specifically reported difficulty with exhalation may do better with bi-level PAP though this was a post hoc analysis and would be more robust if a further trial were performed powered to look at just these individuals. Changing to a different brand of CPAP, with a re-emphasis of the positive benefits of the treatment was as effective in our cohort as a placebo effect including the impact of the added attention offered to the subjects during the trial.

CHAPTER 5

CONCLUSIONS

CHAPTER 5 CONCLUSIONS

In a series of studies, I have explored factors, which may influence compliance with CPAP in OSA.

In the retrospective, observational study (median follow up 7 years), an improvement in ESS from baseline was associated with optimal compliance (≥ 4 hours per night) on CPAP. This suggests that patients with optimal compliance demonstrate a significant improvement in daytime sleepiness. None of the other factors demonstrated any meaningful association with long-term CPAP compliance.

I undertook a prospective, observational study to evaluate relationships between socio-demographic factors or Type D personality and compliance (short term and 6 months' compliance). I did not find any significant association between CPAP compliance with age, gender, symptoms or physiological severity of OSA.

Socio-economic status (assessed by NS-SEC 2001) in a health care model, where care is free at the point of delivery, was not associated with compliance. Subjects who were unemployed long term had sub-optimal compliance.

Subjects with depression showed a trend towards sub-optimal compliance. No association was found with education and Type D personality.

Individuals who experienced side effects after the first night of titration were more likely not to accept the treatment and were poor compliers on CPAP.

In this prospective observational study, I also looked at the question of whether a physician can predict CPAP compliance. The clinicians were able to differentiate the

groups of good and less good compliers but there was no useful cut off on the VAS we employed that would confidently identify the likelihood of individual patients needing extra support.

In a prospective randomised crossover trial, I examined the impact of changes in positive airway pressure device in people who were sub optimally compliant with CPAP with symptoms to suggest pressure intolerance. While the patients found a change in the device gave more comfort, no statistically significant differences in compliance were noted when results were reviewed for the whole group. On further analysis, there were favourable trends to support this practice in a sub-group complaining of difficulty in exhalation.

There are novel results from this series of studies but they generate more questions. Further research in patients who describe difficulty exhaling against CPAP could be helpful in assessing the impact of changing PAP delivery device and compliance with treatment. Exploring a robust diagnosis of mood disorders prevalent in OSA patients and exploring prospectively the impact on compliance would be useful.

The value of CPAP to individual patients and to the economy more generally depends on people with sleep apnoea using their treatment. CPAP acceptance in our current practice is good in the short and long-term. Further support for people who are long-term unemployed and or depressed might lead to even greater uptake. Bi-level PAP should only be issued to people with OSA with the understanding that it may have no impact on compliance and given the cost implications should be discontinued if the patient's compliance does not improve.

Future directions:

Information available from the series of studies that I performed provides the groundwork for possible future research into the factors affecting or associated with optimal compliance with CPAP. More research could be done particularly related to the mood disorders and whether there is a cohort of patients with depression who do not do well on the treatment. Involvement of a psychiatrist to establish firmly the diagnosis of a mood disorder and then examining the impact of therapy perhaps pharmacological or delivered by a clinical psychologist with hopefully an impact on mood / depression. In turn measures of subsequent CPAP usage will help address if there is a benefit over and above that directly on mood through the facilitation of CPAP usage.

With the available information about the impact of different demographic, socio-economic, personality, mood and diseases severity / symptoms related factors in predicting compliance with CPAP, a predictor model can be constructed. By giving different weighting to individual factors in this predictor model, we may be able to test a mathematical model prospectively in an appropriate clinical setting.

APPENDIX 1

EPWORTH SLEEPINESS SCALE FORM

Instructions: Be as truthful as possible. Print the form. Read the situation in the first column; select your response from the second column; enter that number in the third column. Total all of the entries in the third column and enter the total in the last box.

Situation	Responses	Score
Sitting and Reading	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Watching Television	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Sitting inactive in a public place, for example, a theatre or a meeting	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
As a passenger in a car for an hour without a break	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Lying down to rest in the afternoon	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Sitting and talking to someone	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Sitting quietly after lunch when you've had no alcohol	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
In a car while stopped in traffic	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
TOTAL SCORE		

A score of 10 or greater indicates a possible sleep disorder.

APPENDIX 2

THE NS-SEC SELF-CODED METHOD

1. Introduction – When to use the self-coded NS-SEC

This section of the website gives information and instructions on how to administer the five-class self-completion version of NS-SEC. NS-SEC is derived from occupation and employment status information, occupation being ideally coded to the most detailed level of the Standard Occupational Classification 2000 (SOC2000). As there are 353 unit groups within SOC2000, occupational coding is time-consuming and costly. Therefore there is a demand for a simpler and less expensive self-completion version of NS-SEC.

The five-class version of self-coded NS-SEC has the following classes:

Class	Label
1	Managerial and professional occupations
2	Intermediate occupations
3	Small employers and own account workers
4	Lower supervisory and technical occupations
5	Semi-routine and routine occupations

2. Reliability of the self-coded NS-SEC

In comparisons of the self-coded and interviewer-coded five-class NS-SEC there was agreement in classifying 75% of cases. It is apparent that the self-coded five-class NS-

SEC is not as accurate as its interviewer-coded counterpart. Some disagreement between the two classifications may arise from coder error. Despite this, validation exercises show that the self-coded and interviewer-coded five-class NS-SECs display similar patterns and strength in their relationships with other variables (eg with smoking).

3. Questions to include in self-completion questionnaires

The self-coded version of NS-SEC is derived from a combination of information on:

- occupation (self-classified into eight categories), and
- an employment status variable that captures information on employment status and size of organisation.

The latter element of NS-SEC requires knowledge of whether an individual is:

- an employer, self-employed or an employee;
- size of organization, and
- Supervisory status.

The following set of questions should be included in self-completion questionnaires in order to derive NS-SEC. All questions refer to the respondent's last or current main job.

Employment status / size of organisation

The following questions refer to your current main job, or (if you are not working now) to your last main job. Please tick one box only per question.

Question 1 – Employee or self-employed

Do (did) you work as an employee or are (were) you se

Employee

Self-employed with employees

Self-employed / freelance without employees (go to question 4)

Question 2 – Number of employees (Employees)

For employees: *indicate below how many people work (worked) for your employer at the place where you work (worked).*

For self-employed: *indicate below how many people you employ (employed). Go to question 4 when you have completed this question.*

1 to 24

25 or more

Question 3 – Supervisory Status

Do (did) you supervise any other employees?

A supervisor or foreman is responsible for overseeing the work of other employees on a day-to-day basis

Yes

No

Occupation

The following question captures the respondent's last or current main occupation.

Question 4 – occupation

Please tick one box to show which **best** describes the sort of work you do.

(If you are not working now, please tick a box to show what you did in your last job).

Modern professional occupations

 1

such as: teacher - nurse - physiotherapist - social worker - welfare officer
- artist - musician - police officer (sergeant or above) - software designer

Clerical and intermediate occupations

 2

such as: secretary - personal assistant - clerical worker - office clerk -
call centre agent - nursing auxiliary - nursery nurse

Senior managers or administrators

 3

(Usually responsible for planning, organising and co-ordinating work and for finance)

such as: finance manager - chief executive

Technical and craft occupations

 4

Such as: motor mechanic - fitter - inspector - plumber - printer -
tool maker - electrician - gardener - train driver

Semi-routine manual and service occupations

 5

such as: postal worker - machine operative - security guard - caretaker -
farm worker - catering assistant - receptionist - sales assistant

Routine manual and service occupations

 6

such as: HGV driver - van driver - cleaner - porter - packer - sewing machinist -
messenger - labourer - waiter / waitress - bar staff

Middle or junior managers

 7

Such as: office manager - retail manager - bank manager - restaurant manager -
warehouse manager - publican

Traditional professional occupations

 8

such as: accountant - solicitor - medical practitioner - scientist -
civil / mechanical engineer

4. Derivation of five-class NS-SEC from self-coded occupational and employment status variables

There are three steps in deriving the five-class self-coded NS-SEC from the answers to questions 1 to 4.

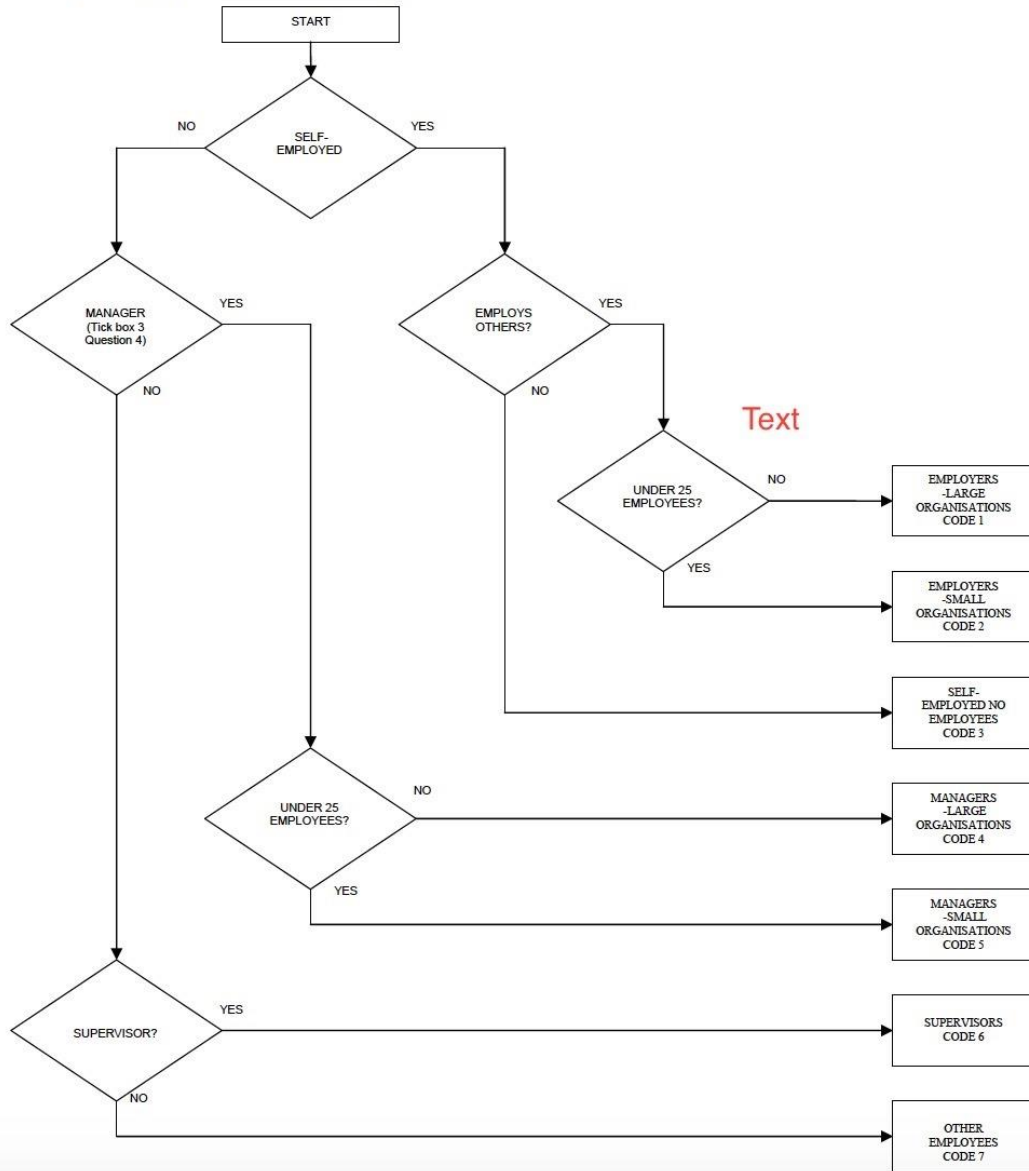
Step 1 Create the employment status variable

The employment status variable has the following codes:

Employment status / size of organisation	
Code	Label
1	Employers - large organisations
2	Employers - small organisations
3	Self-employed, no employees
4	Managers - large organisations
5	Managers - small organisations
6	Supervisors
7	Other employees

The procedure to derive the employment status variable from the answers to questions 1 to 3 is given in the following flow-chart.

Figure 6
Deriving the employment status/size of organisation variable, self-coded method



Step 2 Create the self-coded occupation variable

On the basis of respondents' tick-box responses to question 4 create a variable with the following occupational codes.

Code	Label
1	Modern professional occupations
2	Clerical and intermediate occupations
3	Senior managers or administrators
4	Technical and craft occupations
5	Semi-routine manual and service occupations
6	Routine manual and service occupations
7	Middle or junior managers
8	Traditional professional occupations

Step 3 Derive NS-SEC

Once the employment status variable (step 1) and occupational variable (step 2) have been derived they are combined and an NS-SEC five-class code is assigned for each possible combination. The following matrix table assigns respondents to the appropriate NS-SEC five-class code. In the event of cases with missing information on either employment status or occupation, users may choose to impute missing values or treat these cases as missing data.

A file containing the cross-classification of employment status and occupation with the corresponding NS-SEC code in the form of a vector can be found [here](#)

The resulting five-class NS-SEC classification is as follows:

Class	Label
1	Managerial and professional occupations
2	Intermediate occupations
3	Small employers and own account workers
4	Lower supervisory and technical occupations
5	Semi-routine and routine occupations

NS-SEC SELF-CODED MATRIX DERIVATION TABLE: FIVE CLASSES

Self-coded Occupation	Employment status / size of organisation						
	1 Employers - large organisations	2 Employers - small organisations	3 Self employed - no employees	4 Managers - large organisations	5 Managers - small organisations	6 Supervisors	7 Other employe es
1 Modern professional occupations	1	1	1	1	1	1	1
2 Clerical and intermediate occupation	1	3	3	1	1	1	2
3 Senior managers or administrators	1	3	3	1	1	1	1
4 Technical and craft occupations	1	3	3	1	1	4	4
5 Semi-routine manual and service occupation	1	3	3	1	1	4	5
6 Routine manual and service occupations	1	3	3	1	1	4	5
7 Middle or junior managers	1	3	3	1	1	1	1
8 Traditional professional occupation	1	1	1	1	1	1	1

1. Employee –
2. Self-employed with employees -
3. Self-employed / freelance without employees –
4. Not applicable / unemployed

b. Number of employees -

For employees: indicate below how many people **work (worked)** for your employer at the place where you work (worked).

For self-employed: indicate **below how many people do (did)** you employ.

1. 1 to 24 -
2. 25 or more –
3. Not applicable

c. Supervisory Status Do (did) you supervise any other employees?

(A supervisor or foreman is responsible for overseeing the work of other employees on a day-to-day basis).

Yes / No

d. Occupation- Please tick **one box** which describes the sort of work you do

Modern professional occupations

Such as: teacher - nurse - physiotherapist - social worker - welfare officer - artist - musician - police officer (sergeant or above) - software designer

1

Clerical and intermediate occupations

Such as: secretary - personal assistant - clerical worker - office clerk - Call centre agent - nursing auxiliary - nursery nurse

2

Senior managers or administrators

(Usually responsible for planning, organising and co-ordinating work and for finance) *Such as:* finance manager - chief executive

3

Technical and craft occupations

Such as: motor mechanic - fitter - inspector - plumber - printer - Tool maker - electrician - gardener - train driver

4

Semi-routine manual and service occupations

Such as: postal worker - machine operative - security guard - caretaker - farm worker - catering assistant - receptionist - sales assistant

5

Routine manual and service occupations

Such as: HGV driver - van driver - cleaner - porter - packer - sewing

6

machinist - messenger - Labourer - waiter / waitress - bar staff

Middle or junior managers

 7

Such as: office manager - retail manager - bank manager - restaurant manager - warehouse manager - publican

Traditional professional occupations

 8

Such as: accountant - solicitor - medical practitioner - scientist - Civil / mechanical engineer

e. Never worked / long term unemployed- Yes / No / Not applicable
(not working for more than 6 months)

House-wife / House-husband - Yes / No

Student - Yes / No

Retired - Yes / No

Current symptoms (Please circle yes or no)		Of these symptoms please rank the most important 1-3 (1 = most important)
1. Excessive daytime sleepiness	yes / no	<input type="checkbox"/>
2. Physical fatigue	yes / no	<input type="checkbox"/>
3. Snoring	yes / no	<input type="checkbox"/>
4. Witnessed apnoeas (Stop breathing during sleep)	yes / no	<input type="checkbox"/>
5. Doesn't wake up refreshed	yes / no	<input type="checkbox"/>
6. Low mood	yes / no	<input type="checkbox"/>
7. Choking	yes / no	<input type="checkbox"/>
8. Insomnia (Difficulty initiating or maintaining sleep)	yes / no	<input type="checkbox"/>
9. Poor quality sleep for the partner	yes / no	<input type="checkbox"/>
10. Nocturia (Wake up to pass urine during night)	yes / no	<input type="checkbox"/>
11. Any other symptom		<input type="checkbox"/>

Duration of most important symptom ____ months ____ years

Currently on treatment for depression Yes / no

Do you think you suffer from claustrophobia Yes / No

Previous nasal surgery Yes / No

Upper airway symptoms (Please mark on a scale of 0-10 how troublesome following symptoms are)

	None		Severe
Dry nose	0	-----Δ-----	10
Runny nose	0	-----Δ-----	10
Nasal congestion	0	-----Δ-----	10
Dry throat-	0	-----Δ-----	10
Nasal bleeding	0	-----Δ-----	10
Dripping feeling at the Back of the throat	0	-----Δ-----	10
Reduced sense of smell	0	-----Δ-----	10

If female – Pre-menopausal/ Peri-menopausal / Post-menopausal

If postmenopausal whether on HRT- Yes

APPENDIX 4

DS-14 Personality assessment Pro-forma	Study no. -	Date:
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Below are a number of statements that people often use to describe themselves. Please read each statement and then circle the appropriate number next to the statement to indicate your answer. Your own impression is the only thing that matters.

0 = False 1= Rather false 2= Neutral 3= Rather true 4= True

- | | | | |
|--|-----------|---|-----------|
| 1. I make contact easily when I meet people | 0 1 2 3 4 | 8. I find it hard to start conversation | 0 1 2 3 4 |
| 2. I often make a fuss about unimportant things | 0 1 2 3 4 | 9. I am often in bad mood | 0 1 2 3 4 |
| 3. I often talk to strangers | 0 1 2 3 4 | 10. I am closed kind of person | 0 1 2 3 4 |
| 4. I often feel unhappy | 0 1 2 3 4 | 11. I would rather keep other people at a distance | 0 1 2 3 4 |
| 5. I am often irritated | 0 1 2 3 4 | 12. I often find myself worrying about something | 0 1 2 3 4 |
| 6. I often feel inhibited in social interactions | 0 1 2 3 4 | 13. I am often down in the dumps | 0 1 2 3 4 |
| 7. I take a gloomy view of things | 0 1 2 3 4 | 14. When socializing, I don't find the right things to talk about | 0 1 2 3 4 |

"Negative affectivity" scale: Add scores for questions 2, 4, 5, 7, 9, 12, and 13

"Social inhibition" scale: Add scores for questions 1*, 3*, 6, 8, 10, 11, and 14

A person is qualified as a type D personality if they score 10 or higher on both negative affectivity and social inhibition scales.

APPENDIX 5

Beck's Depression Inventory 2 (BDI-2)

Study no. -

Date:

This questionnaire consists of 21 groups of statements aiming to assess mood status. Please read each group of statements carefully, and then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including item 16 (changes in sleeping pattern) or item 18 (changes in appetite).

1. Sadness

- 0 I do not feel sad
- 1 I feel sad all the time
- 2 I am sad all the time
- 3 I am so sad or unhappy that I can't stand it

2. Pessimism

- 1 I am not discouraged about my future
- 2 I feel more discouraged about my future than I used to be
- 3 I do not expect things to work out for me
- 4 I feel my future is hopeless and will get only worse

3. Past failure

- 1 I do not feel like a failure
- 2 I have failed more than I should have
- 3 As I look back I see a lot of failures
- 4 I feel I am total failure as a person

4. Loss of pleasure

- 1 I get as much pleasure as I ever did from the things I enjoy
- 2 I don't enjoy things as I used to be
- 3 I get very little pleasure from the things I used to enjoy
- 4 I can't get any pleasure from the things I used to enjoy

5. Guilty feelings

- 1 I don't feel particularly guilty
- 2 I feel guilty over many things I have done or should have done
- 3 I feel guilty most of the time
- 4 I feel guilty all the time

6. Punishment feelings

- 1 I don't feel I am being punished
- 2 I feel I may be punished
- 3 I expect to be punished
- 4 I feel I am being punished

7. Self dislike

- 1 I feel the same about myself as ever
- 2 I have lost confidence in myself
- 3 I am disappointed in myself
- 4 I dislike myself

8. Self- Criticalness

1. I don't criticize or blame myself more than usual
2. I am more critical of myself than I used to be
3. I criticize myself for all my faults
4. I blame myself for everything bad that happens

9. Suicide thoughts or wishes

1. I don't have any thoughts of killing myself
2. I have thought of killing myself but will not carry them out
3. I would like to kill myself
4. I would kill myself if I have the chance

10. Crying

- 0 I don't cry anymore than I used to
- 1 I cry more than I used to
- 2 I cry over every little thing
- 3 I feel like crying but I can't

11. Agitation

- 0 I am no more restless or wound up than usual
- 1 I feel more restless or wound up than usual
- 2 I am so restless or agitated that it is so hard to stay still
- 3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of interest

1. I have not lost interest in other people or activities
2. I am less interested in other people or activities
3. I have lost most of my interest in other people or things
4. It's hard to get interested in anything

13. Indecisiveness

1. I make decisions about as well as ever
2. I find it more difficult to make decisions than usual
3. I have much greater difficulty in making decisions that I used to
4. I have trouble making my decisions

14. Worthlessness

1. I do not feel I am worthless
2. I don't consider myself as worthwhile
3. I feel more worthless as compared to other people
4. I feel utterly worthless

15. Loss of energy

1. I have as much energy as ever
2. I have less energy than I used to have
3. I don't have enough energy to do very much
4. I don't have enough energy to do anything.

16. Changes in sleeping pattern

- 0 I haven't experienced any changes in my sleeping pattern
- 1a I sleep somewhat more than usual 1b I sleep somewhat less than usual
- 2a I sleep a lot more than usual 2b I sleep a lot less than usual
- 3a I sleep most of the day 3b I wake up 1-2 hour early and can't go back to the sleep

17. Irritability

- 0 I am no more irritable than usual
- 1 I am more irritable than usual
- 2 I am much more irritable than usual
- 3 I am irritable all the time

18. Changes in appetite

- 0 I have not experienced any changes in my appetite
- 1a My appetite is somewhat less than usual 1b My appetite is somewhat more than usual
- 2a My appetite is much less than usual 2b My appetite is much greater than before
- 3a I have no appetite at all 3b I crave food all the time

19. Concentration difficulty

- 0 I can concentrate as well as ever
- 1 I can't concentrate as well as usual
- 2 It's hard to keep my mind on anything for long
- 3 I find it hard to concentrate on anything

20. Tiredness or fatigue

- 0 I am no more tired or fatigued than usual
- 1 I get more tired or fatigued more easily than usual
- 2 I am too tired or fatigued to do a lot of things I used to do
- 3 I am too tired or fatigued to do most of the things I used to

21. Loss of interest in sex

- 0 I have not noticed any recent change in my interest in sex
- 1 I am less interested in sex than I used to be
- 2 I am much less interested in sex now
- 3 I have lost interest in sex completely

Higher total scores indicate more severe depressive symptoms. The standardized cutoffs used are:

0–13: minimal depression

14–19: mild depression

20–28: moderate depression

29–63: severe depression.

APPENDIX 6

SAQLI (Sleep apnoea quality of life Index) -	Study no. -	Date:
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This questionnaire assesses the health status related to sleep apnoea and is designed to find out how you have been doing and feeling in the last 4 weeks. Please answer each question and mark it 1-7 according to the following:

A very large = 1 A large = 2 A moderate to large = 3 A moderate = 4
A small to moderate = 5 A small = 6 No or none = 7

OVER THE PAST 4 WEEKS:

1. How much (amount) have you had to push yourself to remain alert during a typical day (e.g. work, school, childcare, housework)?

1 2 3 4 5 6 7

2. How have (amount of time) you had to use all your energy to accomplish your most important activity (e.g. work, school, childcare, housework)?

1 2 3 4 5 6 7

3. How much difficulty (amount) have you had finding the energy to do other activities (e.g. exercise, relaxing)?

1 2 3 4 5 6 7

4. How much difficulty (amount) have you had fighting to stay awake?

1 2 3 4 5 6 7

5. How much of a problem has it been to be told that your snoring is irritating?

1 2 3 4 5 6 7

6. How much of a problem have frequent conflicts or arguments been?

1 2 3 4 5 6 7

7. How often (amount of time) have you looked for excuses for being tired?

1 2 3 4 5 6 7

8. How often (amount of time) have you not wanted to do things with your family and/or friends?

1 2 3 4 5 6 7

9. How often (amount of time) have you felt depressed, down, or hopeless?

1 2 3 4 5 6 7

10. How often (amount of time) have you been impatient?

1 2 3 4 5 6 7

11. How much of a problem has it been to cope with everyday issues?

1 2 3 4 5 6 7

12. How much of a problem have you had with decreased energy?

1 2 3 4 5 6 7

13. How much of a problem have you had with fatigue?

1 2 3 4 5 6 7

14. How much of a problem have you had waking up feeling unrefreshed?

1 2 3 4 5 6 7

APPENDIX 7

SF- 36 (Short form 36)	Study no. -	Date:
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The following questions ask for your views about your health and how you feel about life in general. If you are unsure about how to answer any question, try and think about your overall health and give the best answer you can. Do not spend too much time answering, as your immediate response is likely to be the most accurate.

1. In general, would you say your health is:
- | | | | | |
|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Excellent | Very good | Good | Fair | Poor |
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
2. **Compared to one year ago**, how would you rate your health in general **now?**
- | | | | | |
|---|--|--------------------------------------|---|--|
| Much better
now than one
year ago | Somewhat
better
now than one
year ago | About the
same as one
year ago | Somewhat
worse
now than one
year ago | Much worse
now than one
year ago |
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
3. The following questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?
- | | Yes,
limited
a lot | Yes,
limited
a little | No, not
limited
at all |
|---|--------------------------|-----------------------------|------------------------------|
| A <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| B <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| C Lifting or carrying groceries | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| D Climbing <u>several</u> flights of stairs | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| e Climbing <u>one</u> flight of stairs | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| f Bending, kneeling, or stooping | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| g Walking <u>more than a mile</u> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| h Walking <u>several blocks</u> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| i Walking <u>one block</u> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| j Bathing or dressing yourself | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

4. **During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

- | | Yes | No |
|---|-----------------------|-----------------------|
| a Cut down on the <u>amount of time</u> you spent on work or other activities | <input type="radio"/> | <input type="radio"/> |
| b <u>Accomplished less</u> than you would like | <input type="radio"/> | <input type="radio"/> |
| c Were limited in the <u>kind</u> of work or other activities | <input type="radio"/> | <input type="radio"/> |
| d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort) | <input type="radio"/> | <input type="radio"/> |

5. **During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

- | | Yes | No |
|---|-----------------------|-----------------------|
| a Cut down on the <u>amount of time</u> you spent on work or other activities | <input type="radio"/> | <input type="radio"/> |
| b <u>Accomplished less</u> than you would like | <input type="radio"/> | <input type="radio"/> |
| c Did work or other activities <u>less carefully than usual</u> | <input type="radio"/> | <input type="radio"/> |

6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?**

- | Not at all | Slightly | Moderately | Quite a bit | Extremely |
|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

7. **How much bodily pain have you had during the past 4 weeks?**

- | None | Very mild | Mild | Moderate | Severe | Very severe |
|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

- | Not at all | A little bit | Moderately | Quite a bit | Extremely |
|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

9. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.**

How much of the time during the past 4 weeks...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a Did you feel full of pep?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b Have you been a very nervous person?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c Have you felt so down in the dumps that nothing could cheer you up?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d Have you felt calm and peaceful?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
e Did you have a lot of energy?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
f Have you felt downhearted and blue?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
g Did you feel worn out?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
h Have you been a happy person?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
i Did you feel tired?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

10. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

11. **How TRUE or FALSE is each of the following statements for you?**

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b I am as healthy as anybody I know	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c I expect my health to get worse	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d My health is excellent	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

APPENDIX 8

CPAP study Pro-forma - first visit (To be completed by physician)	Study no-	Date
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BMI (Body Mass Index) - Neck size - cm

Waist circumference - cm

Blood pressure - mmHg

Epworth sleepiness scale - / 24

FEV1 - Litres (% predicted)

FVC - Litres (% predicted)

Overnight sleep study

Mean Oxygen Saturation %
 Minimum Oxygen Saturation %
 Desaturation Index / hour
 Apnoeic Hypopneic Index / hour

Co-morbidities - Hypertension / Ischemic Heart Disease (IHD) / Congestive cardiac failure/ previous cardiac surgery / AF / TIA / Stroke / Diabetes / Asthma/ Gout / Anxiety / Depression / Hypothyroid / Other

Smoking- Current smoker / Ex Smoker / Never smoked

If current smoker or smoked in the past ___ pack years

Alcohol - Units/ week

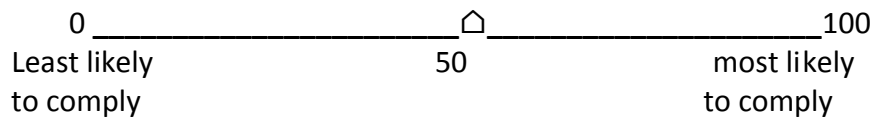
Compliance with other medications (Own assessment)

1. Very good
2. Miss it sometime
3. Miss it frequently
4. Not on any regular medications (pills/ Inhalers)

Physician's impression regarding OSA as a cause of sleepiness (ESS likely to improve on CPAP)

0 _____ 100 Not
 at all confident Very confident

Physician's confidence regarding patients likely to use CPAP more than 4 hour/ night



Patient's perception

- How much sleep did they take when well hrs/ night
 (Before sleep apnoea symptoms developed)
- How much do they sleep now hrs/ night
- How much sleep do the patients think they need to feel refreshed hrs/night

CPAP accepted

Yes / no

APPENDIX 9

CPAP study Pro-forma – following titration (To be completed by patient)	Study no	Date
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Could you please fill-in this pro-forma, which has a number of questions to assess any side effects you may have experienced during first night on CPAP and your own assessment regarding long term usage of CPAP.

1. Did you experience any problems on CPAP Yes* / No

***If the answer** to above question is “yes” then which side effect(s) did you have on the first night

1. The air pressure was too high
2. Uncomfortable feeling/ pain with the mask
3. Claustrophobia
4. Noise
5. Nasal stuffiness / leaky nose
6. Bloating / swallowing too much air
7. Any other –

2. Do you feel any better following the first night of CPAP?

Tremendously / moderately / slightly / no improvement / Worse
better better better

3. In your own assessment how likely is it that you will continue with CPAP long term?

Will not / Unlikely / less likely / probably / most likely / will definitely
Continue to continue to continue will continue to continue continue

4. How strongly do you agree with this statement?

“I will definitely continue to use CPAP in the long term”

Absolutely agree / Mostly agree / neither agree nor disagree /

Mostly disagree / definitely disagree

APPENDIX 10

CPAP study Pro-forma - 2nd visit (To be completed by patient)	Study no	Date
---	-----------------	-------------

Could you kindly complete this booklet of questions which aims to assess the impact of CPAP treatment and any changes in health status or mood scores. This will help us establish a link between different factors affecting CPAP usage. Please circle the appropriate answers. If there are any doubts completing it please ask the doctor or a specialist nurse.

Still using CPAP

Yes / No

Any problems/ side effects on CPAP. Please mark them from 1-7,

(1. Very big problem, 2. Big problem, 3. Moderate to big problem, 4. Moderate problem, 5. Small to moderate problem, 6. Small problem, 7. No problem)

or

Cite the reason(s) for stopping CPAP if you are not using it anymore

Problems with CPAP or mask	If you are still using CPAP then please mark the problems associated with its use according to severity (from 1-7)	If you have stopped using CPAP then mark the reason for stopping it (you can mark more than 1 reason in the order of importance).
Pain from mask / head gear		
Unsightly mask / cosmetic reasons		
Cold air from expiratory valve		
Mask leaks		
Claustrophobic with mask		
Too much air pressure		
Erosion / ulcer on nose		
Noise from CPAP disturbing sleep		
Local nasal side effects		
Partner doesn't like it		
Lack of improvement in symptoms		
Any other reason -		

How much impact has the treatment had on your life

Tremendous / Moderate / Slight **improvement** / No improvement / Worse
Improvement improvement

Upper airway symptoms -Please mark on a scale of 0-10, how troublesome following symptoms are

	None		Severe
Dry nose	0-----	Δ	-----10
Runny nose	0-----	Δ	-----10
Nasal congestion-	0-----	Δ	-----10
Dry throat-	0-----	Δ	-----10
Nasal bleeding-	0-----	Δ	-----10
Dripping feeling at the Back of the throat	0-----	Δ	-----10
Reduced sense of smell-	0-----	Δ	-----10

APPENDIX 11

CPAP study Pro-forma - 2 nd visit (To be completed by physician/ CPAP practitioner)	Study no	Date
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BMI

Date CPAP started

CPAP pressure cm of Water

Type of mask Nasal / Full face / Total face

Any changes in mask Yes / No

Humidifier Yes / No

Patient's perception

- How much do they sleep now on CPAP hrs/ night
- How much CPAP do they think they are using hrs/ night?

CPAP Hours of use- Hours / Night

ESS /24

ONSS results

Mean Oxygen Saturation %
Minimum Oxygen Saturation %
Desaturation Index / Hour
Apnoeic Hypopneic Index / Hour

Any other changes / events since previous review -

APPENDIX 12

CPAP study Pro-forma - 3 rd Visit (To be completed up by patient)	Study no	Date
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Could you kindly complete this booklet of questions which aims to assess the impact of CPAP treatment and any changes in health status or mood scores. This will help us establish a link between different factors affecting CPAP usage. Please circle the appropriate answers. If there are any doubts filling it up please ask the doctor or a specialist nurse.

Still using CPAP

Yes / No

Any problems/ side effects on CPAP. Please mark them from 1-7 ;

(1. Very big problem, 2. Big problem, 3. Moderate to big problem, 4. Moderate problem, 5. Small to moderate problem, 6. Small problem, 7. No problem)

or

Cite the reason(s) for stopping CPAP if you are not using it anymore

Problems with CPAP or mask	If you are still using CPAP then please mark the problems associated with its use according to severity (from 1-7)	If you have stopped using CPAP then mark the reason for stopping it (you can mark more than 1 reason in the order of importance).
Pain from mask / head gear		
Unsightly mask / cosmetic reasons		
Cold air from expiratory valve		
Mask leaks		
Claustrophobic with mask		
Too much air pressure		
Erosion / ulcer on nose		
Noise from CPAP disturbing sleep		
Local nasal side effects		
Partner doesn't like it		
Lack of improvement in symptoms		
Any other reason -		

How much impact treatment has had on your life -

Tremendous Improvement / Moderate improvement / Slight improvement / No improvement / Worse

Upper airway symptoms - Please mark on a scale of 0-10 how troublesome following symptoms are (0 is no problems and 10 is severe problems).

	None		Severe
Dry nose	0	-----Δ-----	10
Runny nose	0	-----Δ-----	10
Nasal congestion-	0	-----Δ-----	10
Dry throat-	0	-----Δ-----	10
Nasal bleeding-	0	-----Δ-----	10
Dripping feeling at the Back of the throat	0	-----Δ-----	10
Reduced sense of smell-	0	-----Δ-----	10

APPENDIX 13

CPAP study Pro-forma - 3 rd Visit (To be completed up by physician / CPAP practitioner)	Study no	Date
---	----------	------

BMI

CPAP pressure cm of Water

Type of mask Nasal / Full face / Total face

Any changes in mask Yes / No

Humidifier Yes / No

Patient's perception

- How much do they sleep now on CPAP hrs/ night
- How much CPAP do they think they are using / night?

CPAP Hours of use- Hours / Night

ESS /24

ONSS results

Mean Oxygen Saturation %
Minimum Oxygen Saturation %
Desaturation Index / Hour
Apnoeic Hypopneic Index / Hour

Any other changes / events since previous review -

APPENDIX 14

CONTRIBUTION OF INDIVIDUAL RESEARCHERS IN DIFERENT STUDIES:

The initial research ideas and protocol development for each of the studies arose from discussions and subsequent planning meetings between AG and IES.

Study 1- Retrospective cohort study: Long term compliance with CPAP- single centre experience-

Initial data were collected by one researcher EM as part of another research project looking at possible associations between different factors predicting mortality in patients who are using CPAP long term. CPAP compliance related data was subsequently reviewed and analysed by AG.

Study 2- Prospective cohort study: The impact of social and personality factors on CPAP compliance in OSA

Screening, first and subsequent visit data collection was done by AG.

Other sleep specialists at the centre, IES, MD, TQ, JMS and MA, helped with the recruitment and also with the first visit data collection. Subsequent review and analysis of data was done by AG with help from RC.

Study 3- Prospective interventional study: The impact of changing the pressure-generating device in people who are suboptimally compliant on CPAP treatment.

Screening, first and subsequent visit data collection was done by AG.

Other sleep specialists at the centre, IES, MD, TQ, JMS, NO and MA, helped with the recruitment and also with the first visit data collection. Subsequent review and analysis of data was done by AG with help from RC.

AG = Atul Gulati

EM = Emma Morrish

IES = Ian Smith

JMS= John Shneerson

MA= Masood Ali

MD = Michael Davis

NO = Nick Oscroft

RC = Rebecca Chadwick

REFERENCES

- Aikens, J.E., Caruana-Montaldo, B., Vanable, P.A., Tadimeti, L. and Mendelson, W.B., 1999. MMPI correlates of sleep and respiratory disturbance in obstructive sleep apnea. *Sleep*, 22(3), pp.362-369.
- Aikens, J.E. and Mendelson, W.B., 1999. A matched comparison of MMPI responses in patients with primary snoring or obstructive sleep apnea. *Sleep*, 22(3), pp.355-359.
- Akashiba, T., Kawahara, S., Akahoshi, T., Omori, C., Saito, O., Majima, T. and Horie, T., 2002. Relationship between quality of life and mood or depression in patients with severe obstructive sleep apnea syndrome. *CHEST Journal*, 122(3), pp.861-865.
- Aloia MS, Arnedt JT, Riggs RL, Hecht J, Borrelli B. Clinical management of poor adherence to CPAP: motivational enhancement. *Behavioral sleep medicine*. 2004 Nov 1;2(4):205-22.
- American Academy of Sleep Medicine and Iber, C., 2007. *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications*. American Academy of Sleep Medicine.
- Berry, R.B., Budhiraja, R., Gottlieb, D.J., Gozal, D., Iber, C., Kapur, V.K., Marcus, C.L., Mehra, R., Parthasarathy, S., Quan, S.F. and Redline, S., 2012. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. *J Clin Sleep Med*, 8(5), pp.597-619.
- Ancoli-Israel, S., Kripke, D.F., Klauber, M.R., Mason, W.J., Fell, R. and Kaplan, O., 1991. Sleep-disordered breathing in community-dwelling elderly. *Sleep*, 14(6), p.486.
- Apter, A.J., Reisine, S.T., Affleck, G., Barrows, E. and ZuWallack, R.L., 1998. Adherence with twice-daily dosing of inhaled steroids: socioeconomic and health-belief differences. *American Journal of Respiratory and Critical Care Medicine*, 157(6), pp.1810-1817.
- Koenig, H.G., Meador, K.G., Cohen, H.J. and Blazer, D.G., 1988. Depression in elderly hospitalized patients with medical illness. *Archives of internal medicine*, 148(9), pp.1929-1936.
- Asendorpf, J.B. and Baudonnière, P.M., 1993. Self-awareness and other-awareness: Mirror self-recognition and synchronic imitation among unfamiliar peers. *Developmental Psychology*, 29(1), p.88.
- Ayalon, L., Ancoli-Israel, S., Stepnowsky, C., Marler, M., Palmer, B.W., Liu, L., Loreda, J.S., Corey-Bloom, J., Greenfield, D. and Cooke, J., 2006. Adherence to continuous positive airway pressure treatment in patients with Alzheimer disease and obstructive sleep apnea. *The American journal of geriatric psychiatry*, 14(2), pp.176-180.
- Ayas, N.T., Patel, S.R., Malhotra, A., Schulzer, M., Malhotra, M., Jung, D., Fleetham, J. and White, D.P., 2004. Auto-titrating versus standard continuous positive airway

pressure for the treatment of obstructive sleep apnea: results of a meta-analysis. *Sleep*, 27(2), pp.249-253.

Bakker, J.P., O'Keeffe, K.M., Neill, A.M. and Campbell, A.J., 2011. Ethnic disparities in CPAP adherence in New Zealand: effects of socioeconomic status, health literacy and self-efficacy. *Sleep*, 34(11), p.1595.

Ball, E.M. and Banks, M.B., 2001. Determinants of compliance with nasal continuous positive airway pressure treatment applied in a community setting. *Sleep medicine*, 2(3), pp.195-205.

Ballester, E., Badia, J.R., Hernandez, L., Carrasco, E., de PABLO, J.U.A.N., Fornas, C., Rodriguez-Roisin, R. and Montserrat, J.M., 1999. Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. *American Journal of Respiratory and Critical Care Medicine*, 159(2), pp.495-501.

Barbé, F., Mayoralas, L.R., Duran, J., Masa, J.F., Maimó, A., Montserrat, J.M., Monasterio, C., Bosch, M., Ladaria, A., Rubio, M. and Rubio, R., 2001. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness: a randomized, controlled trial. *Annals of Internal Medicine*, 134(11), pp.1015-1023.

Barker, J.C. and Mitteness, L.S., 1988. Nocturia in the elderly. *The Gerontologist*, 28(1), pp.99-104.

Bartel, P.R., Looock, M., van der Meyden, C., Robinson, E. and Becker, P., 1995. Hypertension and sleep apnea in black South Africans a case control study. *American journal of hypertension*, 8(12), pp.1200-1205.

Basoglu, O.K., Midilli, M., Midilli, R. and Bilgen, C., 2012. Adherence to continuous positive airway pressure therapy in obstructive sleep apnea syndrome: effect of visual education. *Sleep and Breathing*, 16(4), pp.1193-1200.

Bearpark, H., Elliott, L., Grunstein, R., Cullen, S., Schneider, H., Althaus, W. and Sullivan, C., 1995. Snoring and sleep apnea. A population study in Australian men. *American journal of respiratory and critical care medicine*, 151(5), pp.1459-1465.

Bédard, M.A., Montplaisir, J., Richer, F., Rouleau, I. and Malo, J., 1991. Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. *Journal of clinical and experimental neuropsychology*, 13(6), pp.950-964.

Bender BG, Bender SE. Patient-identified barriers to asthma treatment adherence: responses to interviews, focus groups, and questionnaires. *Immunol Allergy Clin North Am* 2005; 25:107.

Bender, B., Milgrom, H. and Rand, C., 1997. Nonadherence in asthmatic patients: is there a solution to the problem?. *Annals of Allergy, Asthma & Immunology*, 79(3), pp.177-187.

Bennett, J.A. and Kinnear, W.J.M., 1999. Sleep on the cheap: the role of overnight oximetry in the diagnosis of sleep apnoea hypopnoea syndrome. *Thorax*, 54(11), pp.958-959.

Berkani, M., Lofaso, F., Chouaid, C., d'Ortho, M.P., Theret, D., Grillier-Lanoir, V., Harf, A. and Housset, B., 1998. CPAP titration by an auto-CPAP device based on snoring detection: a clinical trial and economic considerations. *European Respiratory Journal*, 12(4), pp.759-763.

Berry, R.B., Budhiraja, R., Gottlieb, D.J., Gozal, D., Iber, C., Kapur, V.K., Marcus, C.L., Mehra, R., Parthasarathy, S., Quan, S.F. and Redline, S., 2012. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. *J Clin Sleep Med*, 8(5), pp.597-619.

Berry, R.B. and Gleeson, K., 1997. Respiratory arousal from sleep: mechanisms and significance. *Sleep*, 20(8), pp.654-675.

Berry, R.B., White, D.P., Roper, J., Pillar, G., Fogel, R.B., Stanchina, M. and Malhotra, A., 2003. Awake negative pressure reflex response of the genioglossus in OSA patients and normal subjects. *Journal of Applied Physiology*, 94(5), pp.1875-1882.

Beulens, J.W., Grobbee, D.E. and Nealb, B., 2010. The global burden of diabetes and its complications: an emerging pandemic. *European Journal of Cardiovascular Prevention & Rehabilitation*, 17(1 suppl), pp.s3-s8.

Bixler, E.O., Vgontzas, A.N., Lin, H.M., Ten Have, T., Rein, J., Vela-Bueno, A. and Kales, A., 2001. Prevalence of sleep-disordered breathing in women: effects of gender. *American journal of respiratory and critical care medicine*, 163(3), pp.608-613.

Bixler, E.O., Vgontzas, A.N., Ten Have, T., Tyson, K. and Kales, A., 1998. Effects of age on sleep apnea in men: I. Prevalence and severity. *American Journal of Respiratory and Critical Care Medicine*, 157(1), pp.144-148.

Bosley, C.M., Fosbury, J.A. and Cochrane, G.M., 1995. The psychological factors associated with poor compliance with treatment in asthma. *European Respiratory Journal*, 8(6), pp.899-904.

Bratton, D.J., Stradling, J.R., Barbé, F. and Kohler, M., 2014. Effect of CPAP on blood pressure in patients with minimally symptomatic obstructive sleep apnoea: a meta-analysis using individual patient data from four randomised controlled trials. *Thorax*, 69(12), pp.1128-1135.

- Broström, A., Strömberg, A., Mårtensson, J., Ulander, M., Harder, L. and Svanborg, E., 2007. Association of Type D personality to perceived side effects and adherence in CPAP-treated patients with OSAS. *Journal of sleep research*, 16(4), pp.439-447.
- Broström, A., Strömberg, A., Ulander, M., Fridlund, B., Mårtensson, J. and Svanborg, E., 2009. Perceived informational needs, side-effects and their consequences on adherence—a comparison between CPAP treated patients with OSAS and healthcare personnel. *Patient education and counseling*, 74(2), pp.228-235.
- Brouillette, R.T., Morielli, A., Leimanis, A., Waters, K.A., Luciano, R. and Ducharme, F.M., 2000. Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. *Pediatrics*, 105(2), pp.405-412.
- Buchner, N.J., Sanner, B.M., Borgel, J. and Rump, L.C., 2007. Continuous positive airway pressure treatment of mild to moderate obstructive sleep apnea reduces cardiovascular risk. *American journal of respiratory and critical care medicine*, 176(12), pp.1274-1280.
- Buda, A.J., Schroeder, J.S. and Guilleminault, C., 1981. Abnormalities of pulmonary artery wedge pressures in sleep-induced apnea. *International journal of cardiology*, 1(1), pp.67-74.
- Budhiraja, R., Kushida, C.A., Nichols, D.A., Walsh, J.K., Simon, R.D., Gottlieb, D.J. and Quan, S.F., 2015. Impact of Randomization, Clinic Visits, and Medical and Psychiatric Comorbidities on Continuous Positive Airway Pressure Adherence in Obstructive Sleep Apnea. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*.
- Budhiraja, R., Parthasarathy, S. and Drake, C.L., 2007. Early CPAP use identifies subsequent adherence to CPAP therapy. *SLEEP*, 30(3), pp.320-324.
- Burwell, C.S., Robin, E.D., Whaley, R.D. and Bickelmann, A.G., 1956. Extreme obesity associated with alveolar hypoventilation—a Pickwickian syndrome. *The American journal of medicine*, 21(5), pp.811-818.
- Buxbaum, S.G., Elston, R.C., Tishler, P.V. and Redline, S., 2002. Genetics of the apnea hypopnea index in Caucasians and African Americans: I. Segregation analysis. *Genetic epidemiology*, 22(3), pp.243-253.
- C. Dickens; *The Posthumous Papers of the Pickwick Club*. Chapman & Hall, London (1837).
- Campbell, A., Neill, A. and Lory, R., 2012. Ethnicity and socioeconomic status predict initial continuous positive airway pressure compliance in New Zealand adults with obstructive sleep apnoea. *Internal medicine journal*, 42(6), pp.e95-e101.

- Campos-Rodriguez, F., Grilo-Reina, A., Perez-Ronchel, J., Merino-Sanchez, M., Gonzalez-Benitez, M.A., Beltran-Robles, M. and Almeida-Gonzalez, C., 2006. Effect of continuous positive airway pressure on ambulatory BP in patients with sleep apnea and hypertension: a placebo-controlled trial. *CHEST Journal*, 129(6), pp.1459-1467.
- Campos-Rodriguez, F., Martinez-Garcia, M.A., de la Cruz-Moron, I., Almeida-Gonzalez, C., Catalan-Serra, P. and Montserrat, J.M., 2012. Cardiovascular mortality in women with obstructive sleep apnea with or without continuous positive airway pressure treatment: a cohort study. *Annals of internal medicine*, 156(2), pp.115-122.
- Campos-Rodriguez, F., Pena-Grinan, N., Reyes-Nunez, N., De la Cruz-Moron, I., Perez-Ronchel, J., De la Vega-Gallardo, F. and Fernandez-Palacin, A., 2005. Mortality in obstructive sleep apnea-hypopnea patients treated with positive airway pressure. *CHEST Journal*, 128(2), pp.624-633.
- Catcheside, P.G., 2010. Predictors of continuous positive airway pressure adherence. *F1000 Med Rep*, 2, p.70.
- Cecilia, H. and Haraldsson, P.O., 2006. 134 CPAP—an 8-year follow-up on acceptance, dropout and compliance on OSAS patients. *Sleep Medicine*, 7, pp.S15-S16.
- Chai-Coetzer, C., Luo, Y.M., Antic, N., Xi-Long, Z., Chen, B.Y., He, Q.Y., Heeley, E., Huang, S.G., Anderson, C., Zhong, N.S. and McEvoy, R., 2013. Predictors of long-Term adherence to Continuous Positive Airway Pressure Therapy in Patients with obstructive sleep apnea and cardiovascular disease in the SAVE Study. *Sleep*, 36(12), pp.1929-1937.
- Chervin, R.D. and Aldrich, M.S., 1999. The Epworth Sleepiness Scale may not reflect objective measures of sleepiness or sleep apnea. *Neurology*, 52(1), pp.125-125.
- Chervin, R.D., 2000. Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. *CHEST Journal*, 118(2), pp.372-379.
- Cheshire, K., Engleman, H., Deary, I., Shapiro, C. and Douglas, N.J., 1992. Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. *Archives of Internal Medicine*, 152(3), p.538.
- Chesson, A.L., Ferber, R.A., Fry, J.M., Grigg-Damberger, M., Hartse, K.M., Hurwitz, T.D., Johnson, S., Littner, M., Kader, G.A., Rosen, G. and Sangal, R.B., 1997. Practice parameters for the indications for polysomnography and related procedures. *Sleep*, 20(6), pp.406-422.
- Choi, J.B., Nelesen, R. and Loreda, J.S., 2006. Sleepiness in obstructive sleep apnea: a harbinger of impaired cardiac function. *SLEEP*, 29(12), pp.1531-1536.
- Cistulli, P.A., 1996. Craniofacial abnormalities in obstructive sleep apnoea: implications for treatment. *Respirology*, 1(3), pp.167-174.

- Clark, A.M., DesMeules, M., Luo, W., Duncan, A.S. and Wielgosz, A., 2009. Socioeconomic status and cardiovascular disease: risks and implications for care. *Nature Reviews Cardiology*, 6(11), pp.712-722.
- Cohen, B.H., Ball, W.C., Brashears, S., Diamond, E.L., Kreiss, P., Levy, D.A., Menkes, H.A., Permutt, S. and Tockman, M.S., 1977. Risk factors in chronic obstructive pulmonary disease (COPD). *American journal of epidemiology*, 105(3), pp.223-232.
- Collop, N.A., Adkins, D. and Phillips, B.A., 2004. Gender differences in sleep and sleep-disordered breathing. *Clinics in chest medicine*, 25(2), pp.257-268.
- Cooper, B.G., Veale, D., Griffiths, C.J. and Gibson, G.J., 1991. Value of nocturnal oxygen saturation as a screening test for sleep apnoea. *Thorax*, 46(8), pp.586-588.
- Costa, F.V., 1996. Compliance with antihypertensive treatment. *Clinical and experimental hypertension*, 18(3-4), pp.463-472.
- Crawford, M.R., Bartlett, D.J., Coughlin, S.R., Phillips, C.L., Neill, A.M., Espie, C.A., Dungan, G.C., Wilding, J.P., Calverley, P.M., Grunstein, R.R. and Marshall, N.S., 2012. The effect of continuous positive airway pressure usage on sleepiness in obstructive sleep apnoea: real effects or expectation of benefit?. *Thorax*, 67(10), pp.920-924.
- D'Ambrosio, C., Bowman, T. and Mohsenin, V., 1999. Quality of life in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure—a prospective study. *CHEST Journal*, 115(1), pp.123-129.
- D'Ortho, M.P., Grillier-Lanoir, V., Levy, P., Goldenberg, F., Corriger, E., Harf, A. and Lofaso, F., 2000. Constant vs automatic continuous positive airway pressure therapy: home evaluation. *CHEST Journal*, 118(4), pp.1010-1017.
- Davidson, T.M. and Patel, M.R., 2008. Waist circumference and sleep disordered breathing. *The Laryngoscope*, 118(2), pp.339-347.
- Deegan, P.C. and McNicholas, W.T., 1996. Predictive value of clinical features for the obstructive sleep apnoea syndrome. *European Respiratory Journal*, 9(1), pp.117-124.
- Degache, F., Sforza, E., Dauphinot, V., Celle, S., Garcin, A., Collet, P., Pichot, V., Barthélémy, J.C., Roche, F. and PROOF Study Group, 2013. Relation of central fat mass to obstructive sleep apnea in the elderly. *Sleep*, 36(4), pp.501-507.
- DeMolles, D.A., Sparrow, D., Gottlieb, D.J. and Friedman, R., 2004. A pilot trial of a telecommunications system in sleep apnea management. *Medical Care*, 42(8), pp.764-769.
- Denollet J, Pedersen SS, Ong AT, Erdman RA, Serruys PW, van Domburg RT. Social inhibition modulates the effect of negative emotions on cardiac prognosis following

percutaneous coronary intervention in the drug-eluting stent era. *Eur Heart J* 2006;27:171–7.

Denollet, J., Sys, S.U. and Brutsaert, D.L., 1995. Personality and mortality after myocardial infarction. *Psychosomatic Medicine*, 57(6), pp.582-591.

Denollet J, Vaes J, Brutsaert DL. Inadequate response to treatment in coronary heart disease: Adverse effects of type D personality and younger age on 5-year prognosis and quality of life. *Circulation* 2000;102:630–5

Denollet, J., 2005. DS14: standard assessment of negative affectivity, social inhibition, and Type D personality. *Psychosomatic medicine*, 67(1), pp.89-97.

Denollet, J., Vaes, J. and Brutsaert, D.L., 2000. Inadequate Response to Treatment in Coronary Heart Disease Adverse Effects of Type D Personality and Younger Age on 5-Year Prognosis and Quality of Life. *Circulation*,102(6), pp.630-635.

Desai, H., Patel, A., Patel, P., Grant, B.J. and Mador, M.J., 2009. Accuracy of autotitrating CPAP to estimate the residual apnea–hypopnea index in patients with obstructive sleep apnea on treatment with autotitrating CPAP. *Sleep and Breathing*, 13(4), pp.383-390.

Dimsdale, J.E., Lored, J.S. and Profant, J., 2000. Effect of continuous positive airway pressure on blood pressure A placebo trial. *Hypertension*,35(1), pp.144-147.

Dolan, D.C., Okonkwo, R., Gfullner, F., Hansbrough, J.R., Strobel, R.J. and Rosenthal, L., 2009. Longitudinal comparison study of pressure relief (C-Flex™) vs. CPAP in OSA patients. *Sleep and Breathing*, 13(1), pp.73-77.

Duran, J., Esnaola, S., Rubio, R. and Iztueta, Á., 2001. Obstructive sleep apnea–hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *American journal of respiratory and critical care medicine*, 163(3), pp.685-689.

Edinger, J.D., Carwile, S., Miller, P., Mayti C. and Hope, V., 1994. Psychological status, syndromic measures, and compliance with nasal CPAP therapy for sleep apnea. *Perceptual and motor skills*, 78(3c), pp.1116-1118.

Engleman, H.M. and Wild, M.R., 2003. Improving CPAP use by patients with the sleep apnoea/hypopnoea syndrome (SAHS). *Sleep medicine reviews*, 7(1), pp.81-99.

Engleman, H.M., Asgari-Jirhandeh, N., McLeod, A.L., Ramsay, C.F., Deary, I.J. and Douglas, N.J., 1996. Self-reported use of CPAP and benefits of CPAP therapy: a patient survey. *CHEST Journal*, 109(6), pp.1470-1476.

- Engleman, H.M., Martin, S.E., Douglas, N.J. and Deary, I.J., 1994. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. *The Lancet*, 343(8897), pp.572-575.
- Engleman, H.M., Martin, S.E. and Douglas, N.J., 1994. Compliance with CPAP therapy in patients with the sleep apnoea/hypopnoea syndrome. *Thorax*, 49(3), pp.263-266.
- Epstein L, Graham L Turner A, Larkin E, Garshick E, Ayas N 2000. Comparison of two methods for achieving CPAP compliance. *American Journal of Respiratory and Critical Care Medicine* 2000;161(3 Suppl):A358.
- Evans JD. Straightforward statistics for the behavioral sciences. Pacific Grove, CA:Brooks/Cole Publishing Co., 1996.
- Faccenda, J.F., Mackay, T.W., Boon, N.A. and Douglas, N.J., 2001. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. *American Journal of Respiratory and Critical Care Medicine*, 163(2), pp.344-348.
- Fanfulla, F., Malaguti, S., Montagna, T., Salvini, S., Bruschi, C., Crotti, P., Casale, R. and Rampulla, C., 2000. Erectile dysfunction in men with obstructive sleep apnea: an early sign of nerve involvement. *Sleep*, 23(6), pp.775-781.
- Ficker, J.H., Clarenbach, C.F., Neukirchner, C., Fuchs, F.S., Wiest, G.H., Pour Schahin, S., Harsch, I.A. and Hahn, E.G., 2003. Auto-CPAP therapy based on the forced oscillation technique. Auto-CPAP-Therapie auf der Basis der Oszilloresistometrie. *Biomedizinische Technik/Biomedical Engineering*, 48(3), pp.68-72.
- Filtner, A.J., Reyner, L.A. and Horne, J.A., 2012. One night's CPAP withdrawal in otherwise compliant OSA patients: marked driving impairment but good awareness of increased sleepiness. *Sleep and Breathing*, 16(3), pp.865-871.
- FitzGerald, M.P., Mulligan, M. and Parthasarathy, S., 2006. Nocturic frequency is related to severity of obstructive sleep apnea, improves with continuous positive airways treatment. *American journal of obstetrics and gynecology*, 194(5), pp.1399-1403.
- Fletcher, E.C. and Lockett, R.A., 1991. The effect of positive reinforcement on hourly compliance in nasal continuous positive airway pressure users with obstructive sleep apnea. *American Review of Respiratory Disease*, 143(5_pt_1), pp.936-941.
- Fleury, B., Rakotonanahary, D., Tehindrazanarivelo, A.D., Hausser-Hauw, C. and Lebeau, B., 1994. Long-term compliance to continuous positive airway pressure therapy (nCPAP) set up during a split-night polysomnography. *Sleep*, 17(6), pp.512-515.

Fogel, R.B., Malhotra, A., Pillar, G., Pittman, S.D., Dunaif, A. and White, D.P., 2001. Increased Prevalence of Obstructive Sleep Apnea Syndrome in Obese Women with Polycystic Ovary Syndrome 1. *The Journal of Clinical Endocrinology & Metabolism*, 86(3), pp.1175-1180.

Gastaut, H., Tassinari, C.A. and Duron, B., 1966. Polygraphic study of the episodic diurnal and nocturnal (hypnic and respiratory) manifestations of the Pickwick syndrome. *Brain research*, 1(2), pp.167-186.

Gay, P., Weaver, T., Loubé, D., Iber, C., Standards of Practice Committee and American Academy of Sleep Medicine, 2006. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. *Sleep*, 29(3), p.381.

Gay, P.C., Herold, D.L. and Olson, E.J., 2003. A randomized, double-blind clinical trial comparing continuous positive airway pressure with a novel bilevel pressure system for treatment of obstructive sleep apnea syndrome. *Sleep*, 26(7), pp.864-869.

George, C.F.P., 2001. Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. *Thorax*, 56(7), pp.508-512.

Gilbert, J.R., Evans, C.E., Haynes, R.B. and Tugwell, P., 1980. Predicting compliance with a regimen of digoxin therapy in family practice. *Canadian Medical Association Journal*, 123(2), p.119.

Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). Full text available online at: www.ginasthma.org (Accessed on January 30, 2015).

Gold, A.R., Schwartz, A.R., Bleecker, E.R. and Smith, P.L., 1986. The Effect of Chronic Nocturnal Oxygen Administration upon Sleep Apnea 1–3. *American Review of Respiratory Disease*, 134(5), pp.925-929.

Goldthorpe, J.H. (2007) 'Social class and the differentiation of employment contracts' in J.H. Goldthorpe *On Sociology (Second Edition)*, Vol. 2: Illustration and Retrospect. Stanford CA: Stanford University Press: Ch. 5 101-24.

Golpe, R., Jiménez, A. and Carpizo, R., 2002. Home sleep studies in the assessment of sleep apnea/hypopnea syndrome. *CHEST Journal*, 122(4), pp.1156-1161.

Golpe, R., Jimenez, A., Carpizo, R. and Cifrian, J.M., 1999. Utility of home oximetry as a screening test for patients with moderate to severe symptoms of obstructive sleep apnea. *Sleep*, 22(7), pp.932-937.

Goncalves, M.A., Guilleminault, C., Ramos, E., Palha, A. and Paiva, T., 2005. Erectile dysfunction, obstructive sleep apnea syndrome and nasal CPAP treatment. *Sleep medicine*, 6(4), pp.333-339.

- Gottlieb, D.J., Whitney, C.W., Bonekat, W.H., Iber, C., James, G.D., Lebowitz, M., Nieto, F.J. and Rosenberg, C.E., 1999. Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study. *American Journal of Respiratory and Critical Care Medicine*, 159(2), pp.502-507.
- Grafstein, O. and Ellenweig, A.Y., 1989. Primary care utilization in Israel--analysis of national data. *Israel journal of medical sciences*, 25(1), pp.32-37.
- Greenberg, G.D., Watson, R.K. and Deptula, D., 1987. Neuropsychological dysfunction in sleep apnea. *Sleep: Journal of Sleep Research & Sleep Medicine*.
- Greenberg, H., Fleischman, J., Gouda, H.E., Angel, E., Lopez, R., Mrejen, K., Web, A. and Feinsilver, S., 2004. Disparities in obstructive sleep apnea and its management between a minority-serving institution and a voluntary hospital. *Sleep and Breathing*, 8(4), pp.185-192.
- Grunstein, R., 1994. Endocrine and metabolic disturbances in obstructive sleep apnea. *Lung biology in health and disease*, 71, pp.449-491.
- Grunstein, R.R., 1995. Sleep-related breathing disorders. 5. Nasal continuous positive airway pressure treatment for obstructive sleep apnoea. *Thorax*, 50(10), pp.1106-1113.
- Guilleminault C, Eldridge FL, Tilkian A, et al. Sleep apnea syndrome due to upper airway obstruction: a review of 25 cases. *Arch Intern Med*. 1977;137:296–300.
- Guilleminault, C and Lee, JH (2004) Does benign 'primary snoring' ever exist in children? ... *J. Psychosom. Res.*, 53: 617–623
- Habra ME, J Psychosomatic Res 2004 Habra, M.E., Linden, W., Anderson, J.C. and Weinberg, J., 2003. Type D personality is related to cardiovascular and neuroendocrine reactivity to acute stress. *Journal of psychosomatic research*, 55(3), pp.235-245.
- Harold G. Henke, K.G., Grady, J.J. and Kuna, S.T., 2001. Effect of nasal continuous positive airway pressure on neuropsychological function in sleep apnea–hypopnea syndrome: a randomized, placebo-controlled trial. *American journal of respiratory and critical care medicine*, 163(4), pp.911-917.
- Herscovitch, J. and Broughton, R., 1980. Sensitivity of the stanford sleepiness scale to the effects of cumulative partial sleep deprivation and recovery oversleeping. *Sleep*, 4(1), pp.83-91.
- Hesselink, A.E., Van Der Windt, D.A.W.M., Penninx, B.W.J.H., Wijnhoven, H.A.H., Twisk, J.W.R., Bouter, L.M. and van Eijk, J.T.M., 2006. What predicts change in pulmonary function and quality of life in asthma or COPD?. *Journal of Asthma*, 43(7), pp.513-519.

Hla, K.M., Young, T.B., Bidwell, T., Palta, M., Skatrud, J.B. and Dempsey, J., 1994. Sleep apnea and hypertension: a population-based study. *Annals of Internal Medicine*, 120(5), pp.382-388.

Hoffstein, V. and Szalai, J.P., 1993. Predictive value of clinical features in diagnosing obstructive sleep apnea. *Sleep*, 16(2), pp.118-122.

Hoffstein, V., Zamel, N. and Phillipson, E.A., 1984. Lung Volume Dependence of Pharyngeal Cross-Sectional Area in Patients with Obstructive Sleep Apnea 1–3. *American Review of Respiratory Disease*, 130(2), pp.175-178.

Hoffstein, V., Viner, S., Mateika, S. and Conway, J., 1992. Treatment of obstructive sleep apnea with nasal continuous positive airway pressure. *Am Rev Respir Dis*, 145(841), p.e5.

Horstmann, S., Hess, C.W., Bassetti, C., Gugger, M. and Mathis, J., 2000. Sleepiness-related accidents in sleep apnea patients. *Sleep*, 23(3), pp.383-389.

Hoy, Carol J., Marjorie Vennelle, Ruth N. Kingshott, Heather M. Engleman, and Neil J. Douglas. "Can intensive support improve continuous positive airway pressure use in patients with the sleep apnea/hypopnea syndrome?." *American Journal of Respiratory and Critical Care Medicine* 159, no. 4 (1999): 1096-1100.

Hui DS, Chan JK, Choy DK, Ko FW, Li TS, Leung RC, et al. Effects of augmented continuous positive airway pressure education and support on compliance and outcome in a Chinese population. *Chest*. 2000;117(5):1410–6

Hui, D.S., Choy, D.K., Li, T.S., Ko, F.W., Wong, K.K., Chan, J.K. and Lai, C.K., 2001. Determinants of continuous positive airway pressure compliance in a group of Chinese patients with obstructive sleep apnea. *CHEST Journal*, 120(1), pp.170-176.

Hussain, S.F., Irfan, M., Waheed, Z., Alam, N., Mansoor, S. and Islam, M., 2014. Compliance with continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea among privately paying patients—a cross sectional study. *BMC pulmonary medicine*, 14(1), p.188.

Ip, M.S., Lam, B., Lauder, I.J., Tsang, K.W., Chung, K.F., Mok, Y.W. and Lam, W.K., 2001. A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. *CHEST Journal*, 119(1), pp.62-69.

Ip, M.S., Lam, B., Tang, L.C., Lauder, I.J., Ip, T.Y. and Lam, W.K., 2004. A community study of sleep-disordered breathing in middle-aged Chinese women in Hong Kong: prevalence and gender differences. *CHEST Journal*, 125(1), pp.127-134.

Issa, F.G. and Sullivan, C.E., 1982. Alcohol, snoring and sleep apnea. *Journal of Neurology, Neurosurgery & Psychiatry*, 45(4), pp.353-359.

Jennum P. and Søl, A., 1992. Epidemiology of snoring and obstructive sleep apnoea in a Danish population, age 30–60. *Journal of sleep research*, 1(4), pp.240-244.

Johansson P, Alehagen U, Svanborg E, Dahlstrom U, Brostrom A. Sleep disordered breathing in an elderly community-living population: Relationship to cardiac function, insomnia symptoms and daytime sleepiness. *Sleep Med.* 2009;10:1005–1011

Johns, M.W., 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *sleep*, 14(6), pp.540-545.

Johns, M. and Hocking, B., 1997. Excessive Daytime Sleepiness Daytime Sleepiness and Sleep Habits of Australian Workers. *Sleep*, 20(10), pp.844-849.

Joo, M.J. and Herdegen, J.J., 2007. Sleep apnea in an urban public hospital: assessment of severity and treatment adherence. *J Clin Sleep Med*, 3(3), pp.285-8.

Kales, A., Caldwell, A.B., Cadieux, R.J., Vela-Bueno, A., Ruch, L.G. and Mayes, S.D., 1985. Severe obstructive sleep apnea—II: Associated psychopathology and psychosocial consequences. *Journal of chronic diseases*, 38(5), pp.427-434.

Kalichman, S.C., Catz, S. and Ramachandran, B., 1999. Barriers to HIV/AIDS treatment and treatment adherence among African-American adults with disadvantaged education. *Journal of the National Medical Association*, 91(8), pp.439-446.

Kanervisto, M., Vasankari, T., Laitinen, T., Heliövaara, M., Jousilahti, P. and Saarelainen, S., 2011. Low socioeconomic status is associated with chronic obstructive airway diseases. *Respiratory medicine*, 105(8), pp.1140-1146.

Kapsimalis, F. and Kryger, M.H., 2002. Gender and obstructive sleep apnea syndrome, part 1: Clinical features. *Sleep*, 25(4), pp.412-419.

Karacan, I. and Karatas, M., 1995. Erectile dysfunction in sleep apnea and response to CPAP. *Journal of sex & marital therapy*, 21(4), pp.239-247.

Karimi, M., Hedner, J., Häbel, H., Nerman, O. and Grote, L., 2014. A Sleep Apnea-Related Risk of Motor Vehicle Accidents is Reduced by Continuous Positive Airway Pressure: Swedish Traffic Accident Registry Data. *Sleep*, 38(3), pp.341-349.

Kiely, J.L. and McNicholas, W.T., 2000. Cardiovascular risk factors in patients with obstructive sleep apnoea syndrome. *European Respiratory Journal*, 16(1), pp.128-133.

Kim, H.C., Young, T., Matthews, C.G., Weber, S.M., Woodard, A.R. and Palta, M., 1997. Sleep-disordered breathing and neuropsychological deficits: a population-based study. *American journal of respiratory and critical care medicine*, 156(6), pp.1813-1819.

Kim, J., In, K., Kim, J., You, S., Kang, K., Shim, J., Lee, S., Lee, J., Lee, S., Park, C. and Shin, C., 2004. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. *American journal of respiratory and critical care medicine*, 170(10), pp.1108-1113.

Kim, J.H., Kwon, M.S., Song, H.M., Lee, B.J., Jang, Y.J. and Chung, Y.S., 2009. Compliance with positive airway pressure treatment for obstructive sleep apnea. *Clinical and experimental otorhinolaryngology*, 2(2), pp.90-96.

Kohler, M., Smith, D., Tippet, V. and Stradling, J.R., 2010. Predictors of long-term compliance with continuous positive airway pressure. *Thorax*, 65(9), pp.829-832.

Kohler, M., Stoewhas, A.C., Ayers, L., Senn, O., Bloch, K.E., Russi, E.W. and Stradling, J.R., 2011. Effects of continuous positive airway pressure therapy withdrawal in patients with obstructive sleep apnea: a randomized controlled trial. *American journal of respiratory and critical care medicine*, 184(10), pp.1192-1199.

Koenig, H.G., Meador, K.G., Cohen, H.J. and Blazer, D.G., 1988. Depression in elderly hospitalized patients with medical illness. *Archives of internal medicine*, 148(9), pp.1929-1936.

Kotterba, S., Widdig, W., Duscha, C. and Rasche, K., 1997. [Event related potentials and neuropsychological studies in sleep apnea patients]. *Pneumologie (Stuttgart, Germany)*, 51, pp.712-715.

Kribbs, N.B., Pack, A.I., Kline, L.R., Getsy, J.E., Schuett, J.S., Henry, J.N., Maislin, G. and Dinges, D.F., 1993. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. *American Review of Respiratory Disease*, 147(5), pp.1162-1168.

Kribbs, N.B., Pack, A.I., Kline, L.R., Smith, P.L., Schwartz, A.R., Schubert, N.M., Redline, S., Henry, J.N., Getsy, J.E. and Dinges, D.F., 1993. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *American Review of Respiratory Disease*, 147(4), pp.887-895.

Krieger, J., 1992. Long-term compliance with nasal continuous positive airway pressure (CPAP) in obstructive sleep apnea patients and nonapneic snorers. *Sleep: Journal of Sleep Research & Sleep Medicine*.

Krieger, J., Kurtz, D., Petiau, C., Sforza, E. and Trautmann, D., 1996. Long-term compliance with CPAP therapy in obstructive sleep apnea patients and in snorers. *Sleep*, 19(9 Suppl), pp.S136-43.

Krieger, J., Laks, L., Wilcox, I., Grunstein, R.R., Costas, L.J., McDougall, J.G. and Sullivan, C.E., 1989. Atrial natriuretic peptide release during sleep in patients with obstructive sleep apnoea before and during treatment with nasal continuous positive airway pressure. *Clin Sci*, 77(4), pp.407-411.

- Krieger, N., 2001. A glossary for social epidemiology. *Journal of epidemiology and community health*, 55(10), pp.693-700.
- Krol RC, Knuth SL, Bartlett D Jr. 1984 Selective reduction of genioglossal muscle activity by alcohol in normal human subjects *Am Rev Respir Dis*. Feb;129(2):247-50
- Kuhlo, W., Doll, E. and Franck, M.C., 1969. [Successful management of Pickwickian syndrome using long-term tracheostomy]. *Deutsche medizinische Wochenschrift (1969)*, 94(24), pp.1286-1290.
- Kushida, C.A., Berry, R.B., Blau, A., Crabtree, T., Fietze, I., Kryger, M.H., Kuna, S.T., Pegram, G.V. and Penzel, T., 2011. Positive airway pressure initiation: a randomized controlled trial to assess the impact of therapy mode and titration process on efficacy, adherence, and outcomes. *Sleep*, 34(8), pp.1083-92.
- Lacassagne, L., Didier, A., Murriss-Espin, M., Charlet, J.P., Chollet, P., Leophonte-Domairon, M.L., Tiberge, M., Pessey, J.J. and Leophonte, P., 1997. [Role of nocturnal oximetry in screening for sleep apnea syndrome in pulmonary medicine. Study of 329 patients]. *Revue des maladies respiratoires*, 14(3), pp.201-207.
- Lacasse, Y., Godbout, C. and Series, F., 2002. Independent validation of the sleep apnoea quality of life index. *Thorax*, 57(6), pp.483-488.
- Lam, B., Ip, M.S.M., Tench, E. and Ryan, C.F., 2005. Craniofacial profile in Asian and white subjects with obstructive sleep apnoea. *Thorax*, 60(6), pp.504-510.
- Laursen, S.O.R.B.O.R., Dreijer, B.O.R., Hemmingsen, C. and Jacobsen, E., 1998. Bi-level positive airway pressure treatment of obstructive sleep apnoea syndrome. *Respiration*, 65(2), pp.114-119.
- Levy, P., Pepin, J.L., Deschaux-Blanc, C., Paramelle, B. and Brambilla, C., 1996. Accuracy of oximetry for detection of respiratory disturbances in sleep apnea syndrome. *Chest Journal*, 109(2), pp.395-399.
- Lewis, K.E., Seale, L. and Bartle, I.E., 2004. Early predictors of CPAP use for the treatment of obstructive sleep apnea. *SLEEP*, 27(1), pp.134-8.
- Li, H.Y., Engleman, H., Hsu, C.Y., Izci, B., Vennelle, M., Cross, M. and Douglas, N.J., 2005. Acoustic reflection for nasal airway measurement in patients with obstructive sleep apnea-hypopnea syndrome. *Sleep*, 28(12), p.1554.
- Li, K.K., Kushida, C., Powell, N.B., Riley, R.W. and Guilleminault, C., 2000. Obstructive Sleep Apnea Syndrome: A Comparison Between Far-East Asian and White Men. *The Laryngoscope*, 110(10), pp.1689-1693.
- Likar, L.L. and Erickson, M.D., 1997. Compliance With Nasal CPAP Therapy. *Chest*, 111, pp.1273-77.

- Lin, H.S., Prasad, A.S., Pan, C.J.G. and Rowley, J.A., 2007. Factors associated with noncompliance to treatment with positive airway pressure. *Archives of Otolaryngology–Head & Neck Surgery*, 133(1), pp.69-72.
- Lindberg, E. and Gislason, T., 2000. Clinical review article: epidemiology of sleep-related obstructive breathing. *Sleep medicine reviews*, 4(5), pp.411-433.
- Lloberes, P., Ballester, E., Montserrat, J.M., Botifoll, E., Ramirez, A., Reolid, A., Gistau, C. and Rodriguez-Roisin, R., 1996. Comparison of manual and automatic CPAP titration in patients with sleep apnea/hypopnea syndrome. *American journal of respiratory and critical care medicine*, 154(6), pp.1755-1758.
- Lloberes, P., Rodríguez, B., Roca, A., Sagales, M.T., de la Calzada, M.D., Giménez, S., Romero, O. and Sampol, G., 2004. Comparison of conventional nighttime with automatic or manual daytime CPAP titration in unselected sleep apnea patients: study of the usefulness of daytime titration studies. *Respiratory medicine*, 98(7), pp.619-625.
- Lorant, V., Deliège, D., Eaton, W., Robert, A., Philippot, P. and Anseau, M., 2003. Socioeconomic inequalities in depression: a meta-analysis. *American journal of epidemiology*, 157(2), pp.98-112.
- Lynch, J.W., Kaplan, G.A., Pamuk, E.R., Cohen, R.D., Heck, K.E., Balfour, J.L. and Yen, I.H., 1998. Income inequality and mortality in metropolitan areas of the United States. *American Journal of Public Health*, 88(7), pp.1074-1080.
- Mackenbach, J.P., 2006. *Health inequalities: Europe in profile*. Produced by COI for the Department of Health.
- Maislin, G., Pack, A.I., Kribbs, N.B., Smith, P.L., Schwartz, A.R., Kline, L.R., Schwab, R.J. and Dinges, D.F., 1995. A survey screen for prediction of apnea. *Sleep*, 18(3), p.158.
- Margel, D., Shochat, T., Getzler, O., Livne, P.M. and Pillar, G., 2006. Continuous positive airway pressure reduces nocturia in patients with obstructive sleep apnea. *Urology*, 67(5), pp.974-977.
- Marin, J.M., Carrizo, S.J., Vicente, E. and Agustí, A.G., 2005. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *The Lancet*, 365(9464), pp.1046-1053.
- Marshall, N.S., Neill, A.M. and Campbell, A.J., 2008. Randomised trial of compliance with flexible (C-Flex) and standard continuous positive airway pressure for severe obstructive sleep apnea. *Sleep and Breathing*, 12(4), pp.393-396.
- Marti, S., Sampol, G., Munoz, X., Torres, F., Roca, A., Lloberes, P., Sagales, T., Quesada, P. and Morell, F., 2002. Mortality in severe sleep apnoea/hypopnoea syndrome patients: impact of treatment. *European Respiratory Journal*, 20(6), pp.1511-1518.

- Martinez-Rivera, C., Abad, J., Fiz, J.A., Rios, J. and Morera, J., 2008. Usefulness of truncal obesity indices as predictive factors for obstructive sleep apnea syndrome. *Obesity*, 16(1), pp.113-118.
- Masa, J.F., Jiménez, A., Durán, J., Capote, F., Monasterio, C., Mayos, M., Terán, J., Hernández, L., Barbé, F., Maimó, A. and Rubio, M., 2004. Alternative methods of titrating continuous positive airway pressure: a large multicenter study. *American journal of respiratory and critical care medicine*, 170(11), pp.1218-1224.
- Masa, J.F., Corral, J., Pereira, R., Duran-Cantolla, J., Cabello, M., Hernández-Blasco, L., Monasterio, C., Alonso, A., Chiner, E., Rubio, M. and Garcia-Ledesma, E., 2011. Effectiveness of home respiratory polygraphy for the diagnosis of sleep apnoea and hypopnoea syndrome. *Thorax*, pp.thx-2010.
- Massie, C.A., Hart, R.W., Peralez, K. and Richards, G.N., 1999. Effects of humidification on nasal symptoms and compliance in sleep apnea patients using continuous positive airway pressure. *CHEST Journal*, 116(2), pp.403-408.
- Matthews, K. and Gallo, L.C., 2011. Psychological Perspectives on Pathways Linking Socioeconomic Status and Physical Health. *Psychological Perspectives on Pathways Linking Socioeconomic Status and Physical Health (January 2011). Annual Review of Psychology*, 62, pp.501-530.
- McArdle, N., Devereux, G., Heidarnjad, H., Engleman, H.M., Mackay, T.W. and Douglas, N.J., 1999. Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. *American Journal of Respiratory and Critical Care Medicine*, 159(4), pp.1108-1114.
- McArdle N, Grove A, Devereux G, Mackay-Brown L, Mackay T, Douglas NJ. Split-night versus full-night studies for sleep apnoea/hypopnoea syndrome. *Eur Respir J*. 2000;15:670-5.
- McNicholas, W.T., 2008. Diagnosis of obstructive sleep apnea in adults. *Proceedings of the American thoracic society*, 5(2), pp.154-160.
- Means, M.K., Lichstein, K.L., Edinger, J.D., Taylor, D.J., Durrence, H.H., Husain, A.M., Aguillard, R.N. and Radtke, R.A., 2003. Changes in depressive symptoms after continuous positive airway pressure treatment for obstructive sleep apnea. *Sleep and Breathing*, 7(1), pp.31-42.
- Meurice, J.C., Dore, P., Paquereau, J., Neau, J.P., Ingrand, P., Chavagnat, J.J. and Patte, F., 1994. Predictive factors of long-term compliance with nasal continuous positive airway pressure treatment in sleep apnea syndrome. *CHEST Journal*, 105(2), pp.429-433.
- Middelkoop, H.A., Smilde-van den Doel, D.A., Neven, A.K., Kamphuisen, H.A. and Springer, C.P., 1996. Subjective sleep characteristics of 1,485 males and females aged

50–93: effects of sex and age, and factors related to self-evaluated quality of sleep. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 51(3), pp.M108-M115.

Millman, R.P., Fogel, B.S., McNamara, M.E. and Carlisle, C.C., 1989. Depression as a manifestation of obstructive sleep apnea: reversal with nasal continuous positive airway pressure. *Journal of Clinical Psychiatry*.

Milne, B.J., Byun, U., & Lee, A. (2013). *New Zealand socio-economic index 2006*. Wellington: Statistics New Zealand.

Montserrat, J.M., Garcia-Rio, F. and Barbe, F., 2007. Diagnostic and therapeutic approach to nonsleepy apnea. *American journal of respiratory and critical care medicine*, 176(1), pp.6-9.

Mortimore, I.L., Whittle, A.T. and Douglas, N.J., 1998. Comparison of nose and face mask CPAP therapy for sleep apnoea. *Thorax*, 53(4), pp.290-292.

Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V. and Ustun, B., 2007. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *The Lancet*, 370(9590), pp.851-858.

Mulgrew, A.T., Fox, N., Ayas, N.T. and Ryan, C.F., 2007. Diagnosis and initial management of obstructive sleep apnea without polysomnography: a randomized validation study. *Annals of Internal Medicine*, 146(3), pp.157-166.

Naëgelé, B., Thouvard, V., Pépin, J.L., Lévy, P., Bonnet, C., Perret, J.E., Pellat, J. and Feuerstein, C., 1995. Deficits of cognitive executive functions in patients with sleep apnea syndrome. *Sleep: Journal of Sleep Research & Sleep Medicine*.

Nakata, S., Noda, A., Yagi, H., Yanagi, E., Mimura, T., Okada, T., Misawa, H. and Nakashima, T., 2005. Nasal resistance for determinant factor of nasal surgery in CPAP failure patients with obstructive sleep apnea syndrome. *Rhinology*, 43(4), p.296.

National Center for Educational Statistics. 31 March 2008.

<http://nces.ed.gov/programs/coe/glossary/s.asp>

Neilan, T.G., Farhad, H., Dodson, J.A., Shah, R.V., Abbasi, S.A., Bakker, J.P., Michaud, G.F., van der Geest, R., Blankstein, R., Steigner, M. and John, R.M., 2013. Effect of sleep apnea and continuous positive airway pressure on cardiac structure and recurrence of atrial fibrillation. *Journal of the American Heart Association*, 2(6), p.e000421.

Neill, A.M., Wai, H.S., Bannan, S.P.T., Beasley, C.R., Weatherall, M. and Campbell, A.J., 2003. Humidified nasal continuous positive airway pressure in obstructive sleep apnoea. *European Respiratory Journal*, 22(2), pp.258-262.

Netzer, N., Eliasson, A.H., Netzer, C. and Kristo, D.A., 2001. Overnight pulse oximetry for sleep-disordered breathing in adults: a review. *CHEST Journal*, 120(2), pp.625-633.

Nieto, F.J., Young, T.B., Lind, B.K., Shahar, E., Samet, J.M., Redline, S., D'Agostino, R.B., Newman, A.B., Lebowitz, M.D. and Pickering, T.G., 2000. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *Jama*, 283(14), pp.1829-1836.

Nilius, G., Happel, A., Domanski, U. and Ruhle, K.H., 2006. Pressure-relief continuous positive airway pressure vs constant continuous positive airway pressure: a comparison of efficacy and compliance. *CHEST Journal*, 130(4), pp.1018-1024.

Nosedá, A., Jann, E., Hoffmann, G., Linkowski, P. and Kerkhofs, M., 2000. Compliance with nasal continuous positive airway pressure assessed with a pressure monitor: pattern of use and influence of sleep habits. *Respiratory medicine*, 94(1), pp.76-81.

Nosedá, A., Kempnaers, C., Kerkhofs, M., Braun, S., Linkowski, P. and Jann, E., 2004. Constant vs auto-continuous positive airway pressure in patients with sleep apnea hypopnea syndrome and a high variability in pressure requirement. *CHEST Journal*, 126(1), pp.31-37.

Nuber, R., Vavrina, J. and Karrer, W., 1999. [Predictive value of nocturnal pulse oximetry in sleep apnea screening]. *Schweizerische medizinische Wochenschrift. Supplementum*, 116, pp.120S-122S.

O'Connor, G.T., Caffo, B., Newman, A.B., Quan, S.F., Rapoport, D.M., Redline, S., Resnick, H.E., Samet, J. and Shahar, E., 2009. Prospective study of sleep-disordered breathing and hypertension: the Sleep Heart Health Study. *American journal of respiratory and critical care medicine*, 179(12), pp.1159-1164.

Ohayon, M.M., Guilleminault, C., Priest, R.G. and Caulet, M., 1997. Snoring and breathing pauses during sleep: telephone interview survey of a United Kingdom population sample. *Bmj*, 314(7084), p.860.

Olson, L.G., Ambrogetti, A. and Gyulay, S.G., 1999. Prediction of sleep-disordered breathing by unattended overnight oximetry. *Journal of sleep research*, 8(1), pp.51-55.

Ong, K.C. and Clerk, A.A., 1998. Comparison of the severity of sleep-disordered breathing in Asian and Caucasian patients seen at a sleep disorders center. *Respiratory medicine*, 92(6), pp.843-848.

Orth, M., Duchna, H.W., Leidag, M., Widdig, W., Rasche, K., Bauer, T.T., Walther, J.W., De Zeeuw, J., Malin, J.P., Schultze-Werninghaus, G. and Kotterba, S., 2005. Driving simulator and neuropsychological testing in OSAS before and under CPAP therapy. *European Respiratory Journal*, 26(5), pp.898-903.

- Osler, W., 1905. *The Principles and Practice of Medicine: For the Use of Students and Practitioners*. Appleton.
- Oztura, I., Kaynak, D. and Kaynak, H.C., 2006. Nocturia in sleep-disordered breathing. *Sleep medicine*, 7(4), pp.362-367.
- Pack, A.I., Maislin, G., Staley, B., Pack, F.M., Rogers, W.C., George, C.F. and Dinges, D.F., 2006. Impaired performance in commercial drivers: role of sleep apnea and short sleep duration. *American journal of respiratory and critical care medicine*, 174(4), pp.446-454.
- Patel, S.R., White, D.P., Malhotra, A., Stanchina, M.L. and Ayas, N.T., 2003. Continuous positive airway pressure therapy for treating gess in a diverse population with obstructive sleep apnea: results of a meta-analysis. *Archives of Internal Medicine*, 163(5), pp.565-571.
- Patil, S.P., Schneider, H., Schwartz, A.R. and Smith, P.L., 2007. Adult obstructive sleep apnea: pathophysiology and diagnosis. *Chest Journal*, 132(1), pp.325-337.
- Pedersen, S.S. and Denollet, J., 2004. Validity of the Type D personality construct in Danish post-MI patients and healthy controls. *Journal of psychosomatic research*, 57(3), pp.265-272.
- Pederson SS, Eur J Cardiovasc Pre Rehabil 2003- Pedersen, S.S. and Denollet, J., 2003. Type D personality, cardiac events, and impaired quality of life: a review. *European journal of cardiovascular prevention & rehabilitation*, 10(4), pp.241-248.
- Pelletier-Fleury, N., Rakotonanahary, D. and Fleury, B., 2001. The age and other factors in the evaluation of compliance with nasal continuous positive airway pressure for obstructive sleep apnea syndrome. A Cox's proportional hazard analysis. *Sleep medicine*, 2(3), pp.225-232.
- Pepin, J.L., Krieger, J., Rodenstein, D., Cornette, A., Sforza, E., Delguste, P., Deschaux, C., Grillier, V. and Levy, P., 1999. Effective compliance during the first 3 months of continuous positive airway pressure: a European prospective study of 121 patients. *American journal of respiratory and critical care medicine*, 160(4), pp.1124-1129.
- Peppard, P.E., Young, T., Palta, M. and Skatrud, J., 2000. Prospective study of the association between sleep-disordered breathing and hypertension. *New England Journal of Medicine*, 342(19), pp.1378-1384.
- Peppard, P.E., Young, T., Palta, M., Dempsey, J. and Skatrud, J., 2000. Longitudinal study of moderate weight change and sleep-disordered breathing. *Jama*, 284(23), pp.3015-3021.

Pepperell, J.C., Ramdassingh-Dow, S., Crosthwaite, N., Mullins, R., Jenkinson, C., Stradling, J.R. and Davies, R.J., 2002. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *The Lancet*, 359(9302), pp.204-210.

Phillipson, E.A., 1978. Control of Breathing during Sleep 1, 2. *American Review of Respiratory Disease*, 118(5), pp.909-939.

Phillips, B.A., Berry, D.T. and Lipke-Molby, T.C., 1996. Sleep-disordered breathing in healthy, aged persons: fifth and final year follow-up. *CHEST Journal*, 110(3), pp.654-658.

Pien, G.W., Fife, D., Pack, A.I., Nkwuo, J.E. and Schwab, R.J., 2005. Changes in symptoms of sleep-disordered breathing during pregnancy. *Sleep*, 28(10), pp.1299-1305.

Pieters, T., Collard, P., Aubert, G., Dury, M., Delguste, P. and Rodenstein, D.O., 1996. Acceptance and long-term compliance with nCPAP in patients with obstructive sleep apnoea syndrome. *European Respiratory Journal*, 9(5), pp.939-944.

Pillar, G. and Lavie, P., 1998. Psychiatric symptoms in sleep apnea syndrome: effects of gender and respiratory disturbance index. *CHEST Journal*, 114(3), pp.697-703.

Pollak, K.I., Coffman, C.J., Alexander, S.C., Tulskey, J.A., Lyna, P., Dolor, R.J., Cox, M.E., Brouwer, R.J.N., Bodner, M.E. and Østbye, T., 2012. Can physicians accurately predict which patients will lose weight, improve nutrition and increase physical activity?. *Family practice*, p.cms004.

Polotsky, M., Elsayed-Ahmed, A.S., Pichard, L., Harris, C.C., Smith, P.L., Schneider, H., Kirkness, J.P., Polotsky, V. and Schwartz, A.R., 2012. Effects of leptin and obesity on the upper airway function. *Journal of Applied Physiology*, 112(10), pp.1637-1643.

Punjabi, N.M., 2008. The epidemiology of adult obstructive sleep apnea. *Proceedings of the American Thoracic Society*, 5(2), pp.136-143.

Quan, S.F., Gillin, J.C., Littner, M.R. and Shepard, J.W., 1999. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. editorials. *Sleep*, 22(5), pp.662-689.

Quintana-Gallego, E., Carmona-Bernal, C., Capote, F., Sánchez-Armengol, Á., Botbol-Benhamou, G., Polo-Padillo, J. and Castillo-Gómez, J., 2004. Gender differences in obstructive sleep apnea syndrome: a clinical study of 1166 patients. *Respiratory medicine*, 98(10), pp.984-989.

Rabec, C., Gonzalez-Bermejo, J., Arnold, V., Rouault, S., Gillet, V., Perrin, C., Alluin, F., Muir, J.F. and Veale, D., 2010. [Initiation of domiciliary non-invasive ventilation:

proposals of the Casavni working party]. *Revue des maladies respiratoires*, 27(8), pp.874-889.

Rajagopal, K.R., Abbrecht, P.H., Derderian, S.S., Pickett, C., Hofeldt, F., Tellis, C.J. and Zwillich, C.W., 1984. Obstructive sleep apnea in hypothyroidism. *Annals of internal medicine*, 101(4), p.491.

Rand CS, Wise RA. Measuring adherence to asthma medication regimens. *Am J Respir Crit Care Med* 1994; 149:S69.

Rauscher, H., Formanek, D., Popp, W. and Zwick, H., 1993. Self-reported vs measured compliance with nasal CPAP for obstructive sleep apnea. *CHEST Journal*, 103(6), pp.1675-1680.

Redline, S. and Tishler, P.V., 2000. The genetics of sleep apnea. *Sleep medicine reviews*, 4(6), pp.583-602.

Redline, S., Adams, N., Strauss, M.E., Roebuck, T., Winters, M. and Rosenberg, C., 1998. Improvement of mild sleep-disordered breathing with CPAP compared with conservative therapy. *American journal of respiratory and critical care medicine*, 157(3), pp.858-865.

Redline, S., Kapur, V.K., Sanders, M.H., Quan, S.F., Gottlieb, D.J., Rapoport, D.M., Bonekat, W.H., Smith, P.L., Kiley, J.P. and Iber, C., 2000. Effects of varying approaches for identifying respiratory disturbances on sleep apnea assessment. *American Journal of Respiratory and Critical Care Medicine*, 161(2), pp.369-374.

Redline, S., Kump, K., Tishler, P.V., Browner, I. and Ferrette, V., 1994. Gender differences in sleep disordered breathing in a community-based sample. *American journal of respiratory and critical care medicine*.149(3), pp.722-726.

Redline, S., Tishler, P.V., Hans, M.G., Tosteson, T.D., Strohl, K.P. and Spry, K., 1997. Racial differences in sleep-disordered breathing in African-Americans and Caucasians. *American journal of respiratory and critical care medicine*, 155(1), p.186.

Redline, S., Tishler, P.V., Tosteson, T.D., Williamson, J., Kump, K., Browner, I., Ferrette, V. and Krejci, P., 1995. The familial aggregation of obstructive sleep apnea. *American journal of respiratory and critical care medicine*, 151(3_pt_1), pp.682-687.

Reeves-Hoche, M.K., Hudgel, D.W., Meck, R., Witteman, R., Ross, A. and Zwillich, C.W., 1995. Continuous versus bilevel positive airway pressure for obstructive sleep apnea. *American journal of respiratory and critical care medicine*, 151(2), pp.443-449.

Reeves-Hoche, M.K., Meck, R. and Zwillich, C.W., 1994. Nasal CPAP: an objective evaluation of patient compliance. *American journal of respiratory and critical care medicine*, 149(1), pp.149-154.

Reid, D., Abramson, M., Raven, J. and Walters, H.E., 2000. Management and treatment perceptions among young adults with asthma in Melbourne: the Australian experience from the European Community Respiratory Health Survey. *Respirology*, 5(3), pp.281-287.

Reishtein, J.L., Pack, A.I., Maislin, G., Dinges, D.F., Bloxham, T.J., George, C.F., Greenberg, H., Kader, G.A., Mahowald, M.W., Younger, J.B. and Weaver, T.E., 2006. Sleepiness and relationships in obstructive sleep apnea. *Issues in mental health nursing*, 27(3), pp.319-330.

Reynolds CF, Kupfer DJ, McEachran AB, et al. Depressive psychopathology in male sleep apneics. *J Clin Psychiatry*. 1984;45:287–290.

Robinson, G.V., Smith, D.M., Langford, B.A., Davies, R.J.O. and Stradling, J.R., 2006. Continuous positive airway pressure does not reduce blood pressure in nonsleepy hypertensive OSA patients. *European Respiratory Journal*, 27(6), pp.1229-1235.

Robinson, R.W., White, D.P. and Zwillich, C.W., 1985. Moderate Alcohol Ingestion Increases Upper Airway Resistance in Normal Subjects 1–3. *American Review of Respiratory Disease*, 132(6), pp.1238-1241.

Rodríguez, G.M.J., de Lucas, R.P., Sánchez, J.M., Izquierdo, A.J., Peraíta, A.R. and Cubillo, M.J., 1996. [Usefulness of the visual analysis of night oximetry as a screening method in patients with suspected clinical obstructive sleep apnea syndrome]. *Archivos de bronconeumologia*, 32(9), pp.437-441

Rose, D. and Harrison, E., 2007. The European socio-economic classification: a new social class schema for comparative European research. *European Societies*, 9(3), pp.459-490.

Rosenthal, L., Nykamp, K., Guido, P., Syron, M.L., Day, R., Rice, F.M. and Roth, T., 1998. Daytime CPAP titration: a viable alternative for patients with severe obstructive sleep apnea. *CHEST Journal*, 114(4), pp.1056-1060.

Rudkowski, J.C., Verschelden, P. and Kimoff, R.J., 2001. Efficacy of daytime continuous positive airway pressure titration in severe obstructive sleep apnoea. *European Respiratory Journal*, 18(3), pp.535-541.

Ryan, P.J., Hilton, M.F., Boldy, D.A., Evans, A., Bradbury, S., Sapiano, S., Prowse, K. and Cayton, R.M., 1995. Validation of British Thoracic Society guidelines for the diagnosis of the sleep apnoea/hypopnoea syndrome: can polysomnography be avoided?. *Thorax*, 50(9), pp.972-975.

Ryan, S., Doherty, L.S., Nolan, G.M. and McNicholas, W.T., 2009. Effects of heated humidification and topical steroids on compliance, nasal symptoms, and quality of life in patients with obstructive sleep apnea syndrome using nasal continuous positive

airway pressure. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*, 5(5), p.422.

Sabaté, E., 2003. *Adherence to long-term therapies: evidence for action*. World Health Organization.

Salepci, B., Caglayan, B., Kiral, N., Parmaksiz, E.T., Comert, S.S., Sarac, G., Fidan, A. and Gungor, G.A., 2013. CPAP adherence of patients with obstructive sleep apnea. *Respiratory care*, 58(9), pp.1467-1473.

Salomaa, V., Niemelä, M., Miettinen, H., Ketonen, M., Immonen-Räihä, P., Koskinen, S., Mähönen, M., Lehto, S., Vuorenmaa, T., Palomäki, P. and Mustaniemi, H., 2000. Relationship of socioeconomic status to the incidence and prehospital, 28-day, and 1-year mortality rates of acute coronary events in the FINMONICA myocardial infarction register study. *Circulation*, 101(16), pp.1913-1918.

Sanders, M.H., Costantino, J.P., Strollo, P.J., Studnicki, K. and Atwood, C.W., 2000. The impact of split-night polysomnography for diagnosis and positive pressure therapy titration on treatment acceptance and adherence in sleep apnea/hypopnea. *Sleep*, 23(1), pp.17-24.

Sano, K., Nakano, H., Ohnishi, Y., Ishii, Y., Nakamura, T., Matuzawa, K., Maekawa, J. and Narita, N., 1998. [Screening of sleep apnea/hypopnea syndrome by home pulse oximetry]. *Nihon Kokyuki Gakkai zasshi= the journal of the Japanese Respiratory Society*, 36(11), pp.948-952.

Santamaria, J.D., Prior, J.C. and Fleetham, J.A., 1988. Reversible reproductive dysfunction in men with obstructive sleep apnoea. *Clinical endocrinology*, 28(5), pp.461-470.

Scanlan, M.F., Roebuck, T., Little, P.J. and Naughton, M.T., 2000. Effect of moderate alcohol upon obstructive sleep apnoea. *European Respiratory Journal*, 16(5), pp.909-913.

Schäfer, H., Ewig, S., Hasper, E. and Lüderitz, B., 1997. Predictive diagnostic value of clinical assessment and nonlaboratory monitoring system recordings in patients with symptoms suggestive of obstructive sleep apnea syndrome. *Respiration*, 64(3), pp.194-199..

Schwartz, D.J. and Karatinos, G., 2007. For individuals with obstructive sleep apnea, institution of CPAP therapy is associated with an amelioration of symptoms of depression which is sustained long term. *J Clin Sleep Med*, 3(6), pp.631-635.

Scottish Intercollegiate Guidelines Network. Management of obstructive sleep apnoea/hypopnoea syndrome in adults: a national clinical guideline Edinburgh: SIGN, 2003

Sériès, F., Plante, J. and Lacasse, Y., 2008. Reliability of home CPAP titration with different automatic CPAP devices. *Respir Res*, 9, p.56.

Shahar, E., Whitney, C.W., Redline, S., Lee, E.T., Newman, A.B., Javier Nieto, F., O'Connor, G.T., Boland, L.L., Schwartz, J.E. and Samet, J.M., 2001. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *American journal of respiratory and critical care medicine*, 163(1), pp.19-25.

Sharafkhaneh, A., Giray, N., Richardson, P., Young, T. and Hirshkowitz, M., 2005. Association of psychiatric disorders and sleep apnea in a large cohort. *Sleep*, 28(11), p.1405-11.

Sharma, S.K., Kumpawat, S., Banga, A. and Goel, A., 2006. Prevalence and risk factors of obstructive sleep apnea syndrome in a population of Delhi, India. *CHEST Journal*, 130(1), pp.149-156.

Shiomi, T., Arita, A.T., Sasanabe, R., Banno, K., Yamakawa, H., Hasegawa, R., Ozeki, K., Okada, M. and Ito, A., 2002. Falling asleep while driving and automobile accidents among patients with obstructive sleep apnea–hypopnea syndrome. *Psychiatry and Clinical neurosciences*, 56(3), pp.333-334.

Simon-Tuval, T., Reuveni, H., Greenberg-Dotan, S., Oksenberg, A., Tal, A. and Tarasiuk, A., 2009. Low socioeconomic status is a risk factor for CPAP acceptance among adult OSAS patients requiring treatment. *Sleep*, 32(4), pp.545-552.

Sin, D.D., Mayers, I., Man, G.C. and Pawluk, L., 2002. Long-term compliance rates to continuous positive airway pressure in obstructive sleep apnea: a population-based study. *CHEST Journal*, 121(2), pp.430-435.

Skomro, R.P., Gjevre, J., Reid, J., McNab, B., Ghosh, S., Stiles, M., Jokic, R., Ward, H. and Cotton, D., 2010. Outcomes of home-based diagnosis and treatment of obstructive sleep apnea. *CHEST Journal*, 138(2), pp.257-263.

Smith, A., Krishnan, J.A., Bilderback, A., Riekert, K.A., Rand, C.S. and Bartlett, S.J., 2006. Depressive symptoms and adherence to asthma therapy after hospital discharge. *CHEST Journal*, 130(4), pp.1034-1038.

Smith, I. and Lasserson, T.J., 2009. Pressure modification for improving usage of continuous positive airway pressure machines in adults with obstructive sleep apnoea. *Cochrane Database Syst Rev*, 4.

Smith, I.E. and Shneerson, J.M., 1995. Is the SF 36 sensitive to sleep disruption? A study in subjects with sleep apnoea. *Journal of sleep research*, 4(3), pp.183-188.

Socio-economic classification (United Kingdom) 2001. National Statistics website: www.statistics.gov.uk "Accessed on 26th Jan 2016.

Socio-economic classification (United Kingdom) 2010. National Statistics website: www.statistics.gov.uk "Accessed on 26th Jan 2016.

Somers, M.L., Peterson, E., Sharma, S. and Yaremchuk, K., 2011. Continuous positive airway pressure adherence for obstructive sleep apnea. *ISRN otolaryngology*, 2011.

Spitzer, R.L., Kroenke, K., Linzer, M., Hahn, S.R., Williams, J.B., Verloin deGruy, F., Brody, D. and Davies, M., 1995. Health-related quality of life in primary care patients with mental disorders: results from the PRIME-MD 1000 Study. *Jama*, 274(19), pp.1511-1517.

Stammnitz, A., Jerrentrup, A., Penzel, T., Peter, J.H., Vogelmeier, C. and Becker, H.F., 2004. Automatic CPAP titration with different self-setting devices in patients with obstructive sleep apnoea. *European Respiratory Journal*, 24(2), pp.273-278.

Stepnowsky, C.J., Marler, M.R. and Ancoli-Israel, S., 2002. Determinants of nasal CPAP compliance. *Sleep medicine*, 3(3), pp.239-247.

Stewart, R.B., Moore, M.T., May, F.E., Marks, R.G. and Hale, W.E., 1992. Nocturia: a risk factor for falls in the elderly. *Journal of the American Geriatrics Society*, 40(12), pp.1217-1220.

Stradling, J.R. and Crosby, J.H., 1991. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men. *Thorax*, 46(2), pp.85-90.

Stradling, J.R., Barbour, C., Pitson, D.J. and Davies, R.J., 1997. Automatic nasal continuous positive airway pressure titration in the laboratory: patient outcomes. *Thorax*, 52(1), pp.72-75.

Strohl, K.P. and Redline, S., 1996. Recognition of obstructive sleep apnea. *American journal of respiratory and critical care medicine*, 154(2), pp.279-289.

Strollo Jr, P.J., Sanders, M.H., Costantino, J.P., Walsh, S.K., Stiller, R.A. and Atwood Jr, C.W., 1996. Split-night studies for the diagnosis and treatment of sleep-disordered breathing. *Sleep*, 19(10 Suppl), pp.S255-9.

Sullivan, C., Berthon-Jones, M., Issa, F. and Eves, L., 1981. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *The Lancet*, 317(8225), pp.862-865.

Syme SL, *Am J Epidemiol* 1976; Marmot, M.G. and Syme, S.L., 1976. Acculturation and coronary heart disease in Japanese-Americans. *American Journal of Epidemiology*, 104(3), pp.225-247.

Tarasiuk, A., Greenberg-Dotan, S., Simon, T., Tal, A., Oksenberg, A. and Reuveni, H., 2006. Low socioeconomic status is a risk factor for cardiovascular disease among adult obstructive sleep apnea syndrome patients requiring treatment. *CHEST Journal*, 130(3), pp.766-773.

Teran-Santos, J., Jimenez-Gomez, A. and Cordero-Guevara, J., 1999. The association between sleep apnea and the risk of traffic accidents. *New England Journal of Medicine*, 340(11), pp.847-851.

Tregear, S., Reston, J., Schoelles, K. and Phillips, B., 2009. Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*, 5(6), p.573.

Tregear, S., Tiller, M., Fontanarrosa, J., Price, N. and Akafo, C., 2007. Executive summary: obstructive sleep apnea and commercial motor vehicle driver safety. *Washington, DC: Federal Motor Carrier Safety Administration*.

Turkington, P.M., Sircar, M., Saralaya, D. and Elliott, M.W., 2004. Time course of changes in driving simulator performance with and without treatment in patients with sleep apnoea hypopnoea syndrome. *Thorax*, 59(1), pp.56-59.

Udwadia, Z.F., Doshi, A.V., Lonkar, S.G. and Singh, C.I., 2004. Prevalence of sleep-disordered breathing and sleep apnea in middle-aged urban Indian men. *American journal of respiratory and critical care medicine*, 169(2), pp.168-173.

Ulfberg J, Carter N, Talback M, Edling C. Excessive daytime sleepiness at work and subjective work performance in the general population and among heavy snorers and patients with obstructive sleep apnea. *Occupational Health and Industrial Medicine*. 1997;3(36):129.

Umlauf, M.G., Chasens, E.R. and Greevy, R.A., 2004. Obstructive sleep apnea, nocturia and polyuria in older adults. *SLEEP*, 27(1), pp.139-44.

Vagiakis E, *Sleep Med* 2006; Smith R, *Chest* 2002; Ip MS, *Chest* 2004; Tarasiuk A, *Chest* 2004; Guilleminault C, *Ann Intern Med* 1995; Valipour A, *Sleep* 2007

Van de Graaff, W.B., 1991. Thoracic traction on the trachea: mechanisms and magnitude. *Journal of Applied Physiology*, 70(3), pp.1328-1336.

Van Dieren, S., Beulens, J.W., van der Schouw, Y.T., Grobbee, D.E. and Neal, B., 2010. The global burden of diabetes and its complications: an emerging pandemic. *European journal of cardiovascular prevention and rehabilitation: official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*, 17, p.S3.

Vázquez, J.C., Tsai, W.H., Flemons, W.W., Masuda, A., Brant, R., Hajduk, E., Whitelaw, W.A. and Remmers, J.E., 2000. Automated analysis of digital oximetry in the diagnosis of obstructive sleep apnoea. *Thorax*, 55(4), pp.302-307.

- Verbraecken J., 2007 Continuous positive airway pressure compliance - Is socioeconomic background relevant? *European respiratory Disease, Touch Briefings* 1;1-2
- Verse, T., Pirsig, W., Junge-Hulsing, B. and Kroker, B., 2000. Validation of the POLY-MESAM seven-channel ambulatory recording unit. *CHEST Journal*, 117(6), pp.1613-1618.
- Vesin, A., Azoulay, E., Ruckly, S., Vignoud, L., Rusinovà, K., Benoit, D., Soares, M., Azevedo-Maia, P., Abroug, F., Benbenishty, J. and Timsit, J.F., 2013. Reporting and handling missing values in clinical studies in intensive care units. *Intensive care medicine*, 39(8), pp.1396-1404.
- Vgontzas, A.N., Legro, R.S., Bixler, E.O., Grayev, A., Kales, A. and Chrousos, G.P., 2001. Polycystic Ovary Syndrome Is Associated with Obstructive Sleep Apnea and Daytime Sleepiness: Role of Insulin Resistance 1. *The Journal of Clinical Endocrinology & Metabolism*, 86(2), pp.517-520.
- Viegi, G., Scognamiglio, A., Baldacci, S., Pistelli, F. and Carrozzi, L., 2001. Epidemiology of chronic obstructive pulmonary disease (COPD). *Respiration; international review of thoracic diseases*, 68(1), p.4.
- Waldhorn, R.E., Herrick, T.W., Nguyen, M.C., O'Donnell, A.E., Sodero, J. and Potolicchio, S.J., 1990. Long-term compliance with nasal continuous positive airway pressure therapy of obstructive sleep apnea. *CHEST Journal*, 97(1), pp.33-38.
- Wang W, He G, Wang M, Liu L, Tang H., 2012. Effects of patient education and progressive muscle relaxation alone or combined on adherence to continuous positive airway pressure treatment in obstructive sleep apnea patients. *Sleep & Breathing* 16(4):1049–57.
- Wang, Y., Gao, W., Sun, M. and Chen, B., 2012. Adherence to CPAP in patients with obstructive sleep apnea in a Chinese population. *Respiratory care*, 57(2), pp.238-243.
- Flemons, W.W. and Reimer, M.A., 1998. Development of a disease-specific health-related quality of life questionnaire for sleep apnea. *American journal of respiratory and critical care medicine*, 158(2), pp.494-503.
- Watson, R., Greenberg, G. and Bakos, L., 1987. Sleep apnea and depression. *Sleep Res*, 16(6), p.7.
- Weaver, T.E., Kribbs, N.B., Pack, A.I., Kline, L.R., Chugh, D.K., Maislin, G., Smith, P.L., Schwartz, A.R., Schubert, N.M., Gillen, K.A. and Dinges, D.F., 1997. Night-to-night variability in CPAP use over the first three months of treatment. *Sleep*, 20(4), pp.278-283.

Weaver, T.E., Maislin, G., Dinges, D.F., Bloxham, T., George, C.F., Greenberg, H., Kader, G., Mahowald, M., Younger, J. and Pack, A.I., 2007. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep*, 30(6), p.711.

Wells, R.D., Freedland, K.E., Carney, R.M., Duntley, S.P. and Stepanski, E.J., 2007. Adherence, reports of benefits, and depression among patients treated with continuous positive airway pressure. *Psychosomatic medicine*, 69(5), pp.449-454.

Wenzel, M., Kerl, J., Dellweg, D., Barchfeld, T., Wenzel, G. and Köhler, D., 2007. [Expiratory pressure reduction (C-Flex Method) versus fix CPAP in the therapy for obstructive sleep apnoea]. *Pneumologie (Stuttgart, Germany)*, 61(11), pp.692-695.

Wetter, D.W., Young, T.B., Bidwell, T.R., Badr, M.S. and Palta, M., 1994. Smoking as a risk factor for sleep-disordered breathing. *Archives of internal medicine*, 154(19), pp.2219-2224.

White, L.H. and Bradley, T.D., 2013. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnoea. *The Journal of physiology*, 591(5), pp.1179-1193.

White, L.H., Lyons, O.D., Yadollahi, A., Ryan, C.M. and Bradley, T.D., 2015. Night-to-night variability in obstructive sleep apnea severity: relationship to overnight rostral fluid shift. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*, 11(2), pp.149-156.

Whitelaw, W.A., Brant, R.F. and Flemons, W.W., 2005. Clinical usefulness of home oximetry compared with polysomnography for assessment of sleep apnea. *American journal of respiratory and critical care medicine*, 171(2), pp.188-193.

Whittle, A.T., Finch, S.P., Mortimore, I.L., MacKay, T.W. and Douglas, N.J., 1997. Use of home sleep studies for diagnosis of the sleep apnoea/hypopnoea syndrome. *Thorax*, 52(12), pp.1068-1073.

Whyte, K.F., Allen, M.B., Jeffrey, A.A., Gould, G.A. and Douglas, N.J., 1989. Clinical features of the sleep apnoea/hypopnoea syndrome. *QJM*, 72(1), pp.659-666.

Williams, L., O'Connor, R.C., Grubb, N. and O'Carroll, R., 2011. Type D personality predicts poor medication adherence in myocardial infarction patients. *Psychology & health*, 26(6), pp.703-712.

Wolkove, N., Baltzan, M., Kamel, H., Dabrusin, R. and Palayew, M., 2008. Long-term compliance with continuous positive airway pressure in patients with obstructive sleep apnea. *Canadian respiratory journal: journal of the Canadian Thoracic Society*, 15(7), p.365.

Yamashiro Y, Kryger MH. CPAP titration for sleep apnea using split-night protocol. *Chest*. 1995;107:62-6.

Ye, L., Pien, G.W., Ratcliffe, S.J. and Weaver, T.E., 2009. Gender differences in obstructive sleep apnea and treatment response to continuous positive airway pressure. *J Clin Sleep Med*, 5(6), pp.512-518.

Young, T., Blustein, J., Finn, L. and Palta, M., 1997. Sleepiness, driving and accidents: sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. *Sleep*, 20(8), pp.608-613.

Young, T., Peppard, P., Palta, M., Hla, K.M., Finn, L., Morgan, B. and Skatrud, J., 1997. Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Archives of Internal Medicine*, 157(15), pp.1746-1752.

Young, T., Evans, L., Finn, L. and Palta, M., 1997. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep*, 20(9), pp.705-706.

Young, T., Finn, L., Hla, K.M., Morgan, B. and Palta, M., 1996. Snoring as part of a dose-response relationship between sleep-disordered breathing and blood pressure. *Sleep*, 19(10 Suppl), pp.S202-5.

Young, T., Palta, M., Badr, M.S. and Barsh, L.I., 1993. Sleep-disordered breathing. *N Engl J Med*, 329, pp.1429-1430.

Young, T., Shahar, E., Nieto, F.J., Redline, S., Newman, A.B., Gottlieb, D.J., Walsleben, J.A., Finn, L., Enright, P. and Samet, J.M., 2002. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. *Archives of internal medicine*, 162(8), pp.893-900.

Yue, H.J., Bardwell, W., Ancoli-Israel, S., Loreda, J.S. and Dimsdale, J.E., 2009. Arousal frequency is associated with increased fatigue in obstructive sleep apnea. *Sleep and Breathing*, 13(4), pp.331-339.

Zung WW. A self-rating depression scale. *Arch Gen Psychiatry*. 1965; 12:63–70.