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Obstructive Sleep Apnoea

and

Sexual Function in Men

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PREFACE:

The work described in this thesis was undertaken at the Woolcock Institute of Medical Research, Glebe and the Royal Prince Alfred Hospital, Camperdown (Sydney), as well as Department of Respiratory and Sleep Medicine, Monash Medical Centre, Clayton (Melbourne) under the supervision of A/Prof Peter Liu, Prof Ron Grunstein and A/Prof Brendon Yee.

The procedures and protocols of the research presented here were approved by the Human Research Ethics Committees of Concord Repatriation General Hospital and Royal Prince Alfred Hospital for Sydney based research and by Southern Health Human Research Ethics Committee for Melbourne based research.

This thesis represents my own work. This work has not been presented previously for the purposes of obtaining a degree.

I was responsible for the analysis of all sleep studies, co-ordinating sleep laboratory logistics and performing data analysis for the study presented in chapter 2.

I was responsible for the overall co-ordination of the study presented in Chapters 3, 4 & 5. This included performing all tasks for the Sydney site including ethics correspondence, recruitment, all patient visits and logistics, all aspects of data entry, cleaning and analysis of the study as well as overseeing the Melbourne site. I have also been involved in the collection and analysis of other data collected in this study which has not been presented in this thesis.

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SUMMARY

Sleep and sex are two fundamental human activities. The impact of having either chronically poor sleep quality from obstructive sleep apnoea (OSA) or impaired sexual function can have detrimental effects on physical and mental health, and can result in a significantly reduced quality of life. The presence of either OSA or erectile dysfunction (ED) in men can also be indicative of a high risk of developing cardiovascular disease. The two conditions are more common in overweight older men, often co-exist, and have been found to be independently associated.

Treatments for erectile dysfunction, such as testosterone supplementation or PDE-5 inhibitors, and for obstructive sleep apnoea, in terms of Continuous Positive Airways Pressure (CPAP) are both readily available. The sales of supplemental testosterone, PDE-5 inhibitors and CPAP have all substantially increased in the last 20 years. However, there are only scant small uncontrolled studies regarding the impact of treatment of one condition (OSA or ED) in the context of the other.

Testosterone prescriptions have increased 500% in the last 20 years. Given the overlap of many symptoms of obstructive sleep apnoea and testosterone deficiency; there is likelihood that men with untreated OSA are being provided supplemental testosterone. The efficacy of testosterone in untreated OSA in regards to sexual function and quality of life has not been investigated.

CPAP use, to treat OSA, has increased substantially since it was first reported in 1981. Observational and non-treatment or alternative treatment controlled studies have shown some improvement in erectile function in men with OSA; however the majority of these have been in men not specifically included on the basis of erectile function.

Since the successful use of PDE-5 inhibitors to treat erectile dysfunction, first patented in 1996, sales of PDE-5 inhibitors have substantially increased. Only two studies by the same author, both lacking an adequate placebo control, have specifically assessed the efficacy of a PDE-5 inhibitor, administered on demand, in an OSA population. There remains the possibility through theoretical mechanisms that PDE-5 administration may worsen OSA, which was confirmed by a small study. Thus the safety and efficacy of daily dose PDE-5 inhibitors in men with OSA are yet to be fully studied.

This thesis aims to investigate and report, through the use of gold-standard and well established methods, using randomised controlled protocols, the following 3 unreported questions:

1. The efficacy of testosterone on sexual function, quality of life, and neurocognition in men with OSA.
2. The effects of CPAP on sexual function, quality of life, mood and relationship in men with OSA & ED.
3. The efficacy and safety of a low daily dose PDE-5 inhibitor (Vardenafil) in men with OSA & ED

Chapter 1 provides a background and review of current literature on sleep disordered breathing, sexual function, and the relationship between the two.

Chapter 2 describes a randomised controlled study in 67 men with moderate-severe OSA who received testosterone injections 3 times over a 12 week period. In this study, testosterone was found to increase libido, but not erectile function nor any other sexual function in men with OSA.

Chapter 3 describes the methodology used in a multi-centre 2x2 factorial double blind double placebo trial of 12 weeks treatment with both CPAP and Vardenafil, a PDE-5 inhibitor in 61 men with OSA and ED. The analyses of interactions between the two treatments are reported here. No interactions were found, thus the two treatments can be presented separately.

Chapter 4 reports on the first half of the above mentioned study. Overall, CPAP, compared to Sham CPAP improved overall sexual satisfaction. However, in those who adhered to treatment, there were additional improvements in erectile function and libido, accompanied with improvements in mental health, sleepiness and several quality of life parameters.

Chapter 5 reports on the second half of the above study. This chapter describes the efficacy of 10mg daily dose Vardenafil in men with OSA and ED as well as the effects on sleep disordered breathing. This dose of Vardenafil did not worsen OSA, but did not improve erectile function at the end of the study.

The thesis concludes with a summary of findings and their implication for clinical applications.

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PUBLICATIONS

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Reviews:

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Abstracts:

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OTHER WORK PRODUCED DURING CANDIDATURE

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Lau, EMT, Yee, BJ, Wong, KK, **Melehan KL**, Celermajer, DS, Prevalence of patent foramen ovale and its impact on oxygen desaturation in obstructive sleep apnea. International Journal of Cardiology, 2013. 165(1): p. 35-40.

Terpening Z, Naismith S, **Melehan K**, Gittins, C, Bolitho S, , Lewis S, The contribution of nocturnal sleep to the consolidation of motor skill learning in healthy ageing and Parkinson's disease. Journal of Sleep Research, 2013. 22(4): p. 398-405.

Bolitho, SJ, Naismith SL, Terpening Z, **Melehan K**, Grunstein RR, Lewis SGL, Investigating REM without atonia in Parkinson's disease using the REM sleep Behaviour disorder screening questionnaire, Movement Disorders 2014. 29(6): p. 736-42

Bolitho, SJ, Naismith SL, Terpening Z, Grunstein RR **Melehan K**, Yee, BJ, Coeytaux, A, Lewis SGL, Investigating the night to night variability of REM without atonia in Parkinson's disease. Sleep Medicine, 2014 (in press)

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Abstracts:

Melehan KL Denotti, D, Marshall, N, Williams, S, Grunstein, RR, Who Sleeps With Who? The results of the ABC Big Sleep Survey, Australasian Sleep Association Annual General Meeting, Darwin NT, October 2012

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Lau EM, Yee BJ, Wong KK, **Melehan KL**, Grunstein RR, Celermajer DS, Association Between Patent Foramen Ovale and Obstructive Sleep Apnoea Proceedings from Cardiac Society of Australia and New Zealand 59th Annual Scientific Meeting, Perth, August 2011 Heart, Lung and Circulation, Volume 20, Supplement 2, 2011, Page S234

MANUSCRIPTS IN PROGRESS

Melehan KL, Hoyos CM, Yee BJ, Buchanan PR, Grunstein RR, Liu PY, Increased sexual desire with exogenous testosterone administration in men with obstructive sleep apnoea: An 18-week randomized double-blind placebo controlled study.

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2010 – 2013: NHMRC Dora Lush Biomedical Scholarship (*to support full-time study*)

2011: Travel Award, World Congress Sleep Kyoto, Japan (*to attend world congress*)

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ABBREVIATIONS

AHI **	Apnoea Hypopnoea Index
APAP	Automatic Positive Airway Pressure
BMI	Body Mass Index (kg/m^2)
BSFI	Brief Sexual Functioning Inventory
cGMP	cyclic Guanosine Monophosphate
cmH_2O	Centimetres of Water Pressure
CPAP	Continuous Positive Airway Pressure
CVD	Cardiovascular Disease
DASS	Depression Anxiety Stress Score
ED	Erectile Dysfunction
EDITS	Erectile Dysfunction Inventory of Treatment Satisfaction
EEG	Electroencephalogram
EMAS	European Male Aging Study
EMG	Electromyogram
EOG	Electrooculogram
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes of Sleep Questionnaire
FSH	Follicular Stimulating Hormone
GRISS	Golombok Rust Inventory of Sexual Satisfaction
IIEF	International Index of Erectile Function
KSS	Karolinska Sleepiness Score
LH	Luteinising Hormone
NPT	Nocturnal Penile Tumescence

NREM	Non Rapid Eye Movement
REM	Rapid Eye Movement
ODI3	Oxygen desaturation (minimum 3%) Index
OSA	Obstructive Sleep Apnoea
PAT	Peripheral Arterial Tonometry
PDE-5	Phosphodiesterase Type 5
RAU	Rigidity Activation Units
RDI **	Respiratory Disturbance Index
SaO2	Oxyhaemoglobin saturation
SERS	Self Esteem and Relationship Scale
SHBG	Sex Hormone Binding Globulin
SF-36	Short Form 36
SRE	Sleep Related Erection
SSS	Stanford Sleepiness Score
TAU	Tumescence Activation Units
TDS	Testosterone Deficiency Syndrome

** Early studies did not distinguish between RDI and AHI, using the terms interchangeably. For accuracy, all references to AHI and RDI will use the reported nomenclature.

1. Literature Review

1.1. MALE SEXUAL FUNCTION

Healthy sexual function is not only necessary for reproductive success but is also a contributor to a satisfactory quality of life [1, 2]. Male sexual health requires incorporation of biological, psychological and social factors in order to shape sexual behaviour, and to maintain sexual drive, erectile function, and overall satisfaction [3]. A classic description of sexual response is that described by Masters and Johnson, this being a four stage model of sexual desire, sexual excitement, orgasm and resolution [4]. All of these phases are required to maintain a healthy sexual function. Various aspects of sexual function such as arousal, desire, and behaviour intertwine to have influence on one another. These different facets are driven by a complex mix of neurochemical, neuroanatomical, psychological and social factors which can be difficult to report in a quantitative research [5].

1.1.1. Sexual Desire

Known by various names, including 'libido', 'sex drive', 'sexual motivation', 'sexual interest', and 'lust', sexual desire is an important aspect of human existence [6]. The intensity of sexual desire can vary between individuals and also within an individual over a given time frame [7]. Defining sexual desire and describing its manifestation is difficult, and much of the physiology is unknown [7, 8]. A particular area of difficulty is the classification of sexual desire into two separate components: dyadic and solitary desire, that is, interest in behaving sexually with a partner or by oneself, respectively, which is often not taken into account in clinical quantitative research [9].

Clinically, sexual desire can be readily understood, however there is no single accepted method used for quantitative measurement [6]. Levels of sexual desire can be difficult to measure due to reliance on self-report and self-knowledge in a complicated mix of social and psychological processes, particularly when asked retrospectively [5]. There are several questionnaire based tools which have been used in the scientific literature, however clinicians often find these difficult to accept due to the complexity of contributors to sexual desire [6]. Behavioural observations, such as documenting masturbation frequency, has been suggested as a measurement of sexual desire, as this activity is less constrained than other sexual behaviours by external factors such as partner presence, risk of pregnancy or disease [10]. However, two problems exist using this as a measurement technique. Firstly, masturbation frequency is an inferred measurement assuming there is a translation of desire into masturbation, which is not always the case, and secondly, engaging in this behaviour may be limited by an individual's social and religious beliefs.

There are many influences upon the level of sexual desire, which can include hormone levels, age, weight, gender, social situation, education, health, and the importance of sex to the individual [6, 11-15]. The presence of a relationship may have some influence in sexual desire [14], however, the length of the relationship has not been shown to affect sexual desire in males, unlike that which occurs in females [16]. If sexual desire in a relationship differs between partners which results in a discrepancy between the desire of one partner and actual levels of intercourse, relationship quality can be impacted, particularly over longer relationship lengths [17].

Suggestion has been made that an ideal method of measuring sex drive is to combine questionnaire data, behavioural data and in-depth interview. However, this is not always logistically possible in clinical trials [10]. The most available and utilised option in research is to use validated questionnaires to quantify sexual desire and related facets of sexual function.

1.1.2. Normal Erectile Function

Erectile function is a complex process, requiring input from the vascular, endocrine, and central and peripheral nervous systems. Two types of erections exist – those occurring due to a physical or psychological stimulus of some kind and those occurring without stimulus during sleep. An erection occurs when an endogenous release of nitric oxide in the nerve endings of the penis and from vascular endothelial cells promotes guanylyl cyclase to produce cyclic guanosine monophosphate (cGMP). An increase in cGMP can also occur by inhibiting phosphodiesterase type 5 (PDE-5) in the corpus cavernosum via exogenous administration of PDE-5 inhibitors. This increase in cGMP allows smooth muscle relaxation, arterial dilatation and venous constriction which results in an erection [18]. Testosterone levels also influence this function, since testosterone is thought to have effects on nitric oxide release, with insufficient amounts associated with a reduction of pressure in penile arteries during erections [19-21].

1.1.3. Sleep Related Erections

Long before described in scientific literature, the existence of nocturnal erections was common knowledge [22]. The religious community condemned their occurrence, believed to be resulting from impure thoughts, and devices were developed to prevent them [22]. Erections during sleep have been described in the scientific literature since the 1940's [23, 24]. These were

confirmed to be associated with REM sleep, some thirteen years after the discovery of this stage of sleep [25, 26]. Further investigation found that these nocturnal erections correspond with about 90% of REM sleep cycles, this being 4 or 5 periods, lasting a total of 1.5-3 hours during the sleep period [7]. The nomenclature of this phenomena was coined by Karacan in the 1960's as "Nocturnal Penile Tumescence (NPT)", rather than the phrase "penile erections during sleep", which was considered too explicit for the time [22]. In 1991, the phrase "sleep related erections (SRE's)" was adopted in the International Classification of Sleep Disorders [27]. The cause of these predictable and reliable SRE's which occurred in healthy men was found to be due to increased blood flow to the penis and were not found to be related to any sexually themed dreams, nor sexual activity [22, 28]. Neither sexual abstinence nor pre-sleep sexual activity, either intercourse or sexual arousal affect subsequent erections during sleep [22, 29]. Although the neurophysiological basis of these SRE's is not completely understood, these episodes of penile blood engorgement increase corporeal oxygenation and may function to protect the morphological integrity of the penis [30, 31]. Without regular oxygenation, fibrosis of the smooth muscle may occur leading to atrophy of the corpora cavernosa [32].

Sleep related erections can be affected by a number of biological influences. Advancing age has been shown to reduce the number of episodes of SRE's, reducing by about 25% between the ages of 13 and 70 years [7]. This reduction is more prominent after age 60 [33]. The presence of diabetes has also been shown to reduce SRE's. In a study of 100 diabetic and 400 non-diabetic men, those with diabetes had fewer SRE's, less tumescence time, diminished penile circumference increase, and lower penile rigidity than those without [34]. Similarly, smokers have a dose response relationship with increased pack year histories impairing SRE's [35].

1.1.4. Sexual Dysfunction

Estimates of the broad diagnosis of male sexual dysfunction in the community vary between 10 to 50%, however, many men are left undiagnosed and untreated due to social discomfort by either the patient or physician [36]. Sexual dysfunction, including low sexual desire and erectile or ejaculatory difficulties, can have a significant effect on quality of life. Any of these disorders can contribute to difficulty in initiating or maintaining a relationship, and can contribute to negative impact on mood, self-esteem and life satisfaction, which can also be bidirectional, by creating or worsening the level of sexual dysfunction [37].

Low desire for sexual activity can cause distress to the individual and create conflict in a relationship [38]. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines hypoactive sexual desire disorder as "deficient or absent sexual fantasies and desire for sexual activity" resulting in significant distress and is not explained by any other disorder [39]. In a large (n=1749) cohort of American adults who had been sexually active in the last year, 15% reported low sexual desire [1]. Likewise, low dyadic sexual desire found was found in 13.5% of community dwelling Australian men aged 35-80 years, whereas 68% reported low solitary sexual desire [40]. Australian data collected as part of the Global Study of Sexual Attitudes and Behaviours (n=750), found that after adjusting for age, 17% had low sexual desire [41]. In a large (n=3714) sexual dysfunction clinic population, low sexual desire was found to occur concurrently with other sexual problems of erectile dysfunction, premature and delayed ejaculation in 38%, 28% and 50% of participants respectively [13], however, causality and the direction thereof cannot be determined. In large population studies of men aged over 50, a gradual decline in sexual desire has been seen with increased age [42, 43]. A prominent

physiological association with low sexual desire is low testosterone, found to be in 40% of cases, [13] further explained in **section 1.2.5**. More recent work has also found that low estradiol, a metabolite of testosterone, also contributes to a reduction in libido [15]. Other medical contributors to low libido include side effects of anti-depressant medication [44], hyperprolactinemia [13] and lower urinary tract symptoms [45].

Erectile dysfunction (ED) is defined by the National Institutes of Health (NIH) Consensus Development Conference as the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance [7, 46, 47]. A more recent clarification of the diagnosis specifies that symptoms must have been present for at least 3 months, except when trauma or surgically induced ED is involved [48]. In the past, nomenclature of erectile dysfunction included the term "impotence", which was derived from Latin meaning "lack of power" [49] which, in a sexual sense could relate to either sexual desire or erectile function. This terminology has been used in the past to include all manner of male sexual dysfunction, including erectile dysfunction, as well as ejaculatory and orgasmic dysfunction [50, 51]. Usage of the term has changed over time, with impotence more recently referring to that of the inability to obtain an erection. Since 1992, via a consensus document from the NIH, the more precise term 'erectile dysfunction' has replaced 'impotence' due to confusion about its exact meaning [52].

Prevalence rates of ED differ between studies due to heterogeneous measurement techniques and populations, however, all have found the incidence of erectile dysfunction to increase with age. Approximately 10-17% of all men report a degree of ED, with this number increasing to approximately 50-60% of men in older age groups [1, 42, 53-57]. The Massachusetts Male

Aging study, conducted in the late 1980s on a sample of 1709 community dwelling men aged 40 to 70 years reported the incidence of at least some level of erectile dysfunction as being 52% [54]. Data from this study was used to estimate that in 1995, 150 million men across the world experienced some degree of erectile dysfunction, and this prevalence will increase to 320 million men by 2025 [58]. In a population including younger men in Brazil, overall 17% of men reported some degree of ED, ranging from 7.3% in the youngest age group (20-29 years) through to 63% in those aged over 60 [57]. Australian data, collected as part of a global study, found that of the 750 men surveyed, 21% experienced erectile difficulty [41]. A study performed in South Australia based on a community sample, found that overall, 25% of men aged over 40 were unable to achieve an erection. When stratified by age, of those men aged 40-49, about 3% reported significant erectile dysfunction, with erections being insufficient for intercourse, while those in the oldest age bracket, men aged over 90 years, 93% reported such difficulties [59]. In a general practice based sample in Perth of 1240 adult men, about 40% of men reported some degree of erectile dysfunction [60]. This higher prevalence rate found in this latter study may be due to health being slightly lower in general practice than in the community. Of those men who report ED, two studies have found that less than 30% are receiving treatment [2, 55].

Several modifiable risk factors for ED have been identified. Obesity and a sedentary lifestyle increases the likelihood of ED [61, 62] as does significant alcohol consumption (>3 drinks per day) [63]. In the Massachusetts Male Aging Study, a prospective population study of men aged 40-70, 513 men had no ED or diabetes at baseline. When these participants were reassessed 6-12 years later, those who had smoked or had a BMI greater than 28 at baseline had an

increased risk of developing ED [62]. Weight reduction strategies have been shown to improve ED [64, 65]. A high proportion (40%) of those with diabetes have ED [66], as do those with low testosterone, [67] further explained in **section 1.2.5**. Chronic periodontitis has also been correlated with ED, which may be related to atherosclerosis and its link with dental disease [68]. Additionally, the lack of a regular partner has established as a risk factor for ED [40].

In the first half of the century, prior to 1970, erectile dysfunction was thought to be solely psychogenic [22]. Although early reports of the existence of predictable nocturnal erections associated with REM sleep were described in the 1940's [24], it was not until 1970's that impaired nocturnal erections were associated with erectile dysfunction. At the time, suggestion was made that by measuring nocturnal erections, the distinction of the cause of ED being a psychological or organic basis could be identified [69]. The assumption was that if nocturnal erections are obtainable, then there is evidence that there is erectile capacity [22]. If nocturnal erections occur during sleep but not during wakefulness, then there must be psychological, behavioural or situational influences, rather than a physiological cause [22, 70]. This binary classification of ED being either of psychological or organic origin has since been considered an oversimplification, but the concept is still used [22]. Organic ED comprises 60-80% of all ED and refers to cases that are caused by underlying chronic diseases such as Parkinson's disease, stroke, diabetes, hypertension and atherosclerosis [46], as well as endocrine system disorders [71]. Psychogenic causes include performance anxiety, lack of sexual excitement, depression and schizophrenia [46]. A large population study (n=1749) found the presence of emotional issues or stress increased the risk of developing ED in the order of 3.5 times [1]. Additionally, higher scores in indexes related to anger and depression, in another

large population study (n=513) was found to increase the risk for developing ED [54]. Since the advent of and popularization of Sildenafil, in a complete turnaround from the original thought that ED was purely psychological, suggestion has now been made that sexual dysfunction has been increasingly attributed to medical causes and overlooks the contribution of psychological and social factors [11].

Several studies have shown that the existence of ED provides an early warning sign that there is an increased risk for developing cardiovascular disease (CVD). CVD has become the main cause of death in the developed world. Current estimates from the World Health Organisation predict that almost 23.3 million people will die of cardiovascular disease during the year of 2030 [72]. ED has been suggested as an early warning sign for cardiovascular disease, even in those men without cardiovascular symptoms [73]. Recognition that ED is an important sentinel event for CVD is growing among health professionals. ED and CVD share risk factors including older age, obesity, cigarette smoking, diabetes, hyperlipidaemia and hypertension [73, 74]. As a result, those men who present with ED should be screened for CVD and associated risk factors [75]. Two large prospective studies have shown that baseline coronary risk factors such as age, smoking, and being overweight, are associated with subsequent ED in healthy men after 8-10 [62] and 25 years follow-up [76]. More recent prospective studies [75, 77-79] and two retrospective studies [80, 81] provide further evidence that ED can predict subsequent CVD. Additionally, a large population-based longitudinal study found that self-reported ED was associated with both CVD-mortality and all-cause mortality (hazard ratios 1.43 and 1.26 respectively) after adjusting for known risk factors [82]. This high predictive association has

been shown to be as comparable as smoking or familial history of myocardial infarct as a risk factor for developing cardiovascular disease [75, 82, 83].

1.1.5. Measurement of Sexual Function

Several questionnaires have been developed to subjectively assess sexual function in the male. The European Male Aging Study (EMAS) developed a 20 item questionnaire of particular application for the aging male, with questions relating to changes in and distress caused by sexual dysfunction, as well as overall sexual functioning [84, 85]. The Golombok Rust Inventory of Sexual Satisfaction (GRISS) questionnaire comprises 28 questions and has domains for erectile dysfunction, premature ejaculation, infrequency, avoidance, non-sensuality and dissatisfaction [86, 87]. The Brief Sexual Function Inventory (BSFI) was developed for a urology based population and comprises 11 items regarding desire, erection, ejaculation and the perception of problems related to these domains [88]. The International Index of Erectile Function (IIEF) is a series of 16 questions, comprising domains of erectile function, sexual desire, orgasmic function, and overall function each rated from 0 or 1 to 5. Higher scores correspond to a higher number of events or satisfaction [89, 90]. This latter questionnaire is the recommended methodology to assess erectile function as well as the endpoint of clinical trials for ED [89, 91]. This subjective questionnaire, developed by the pharmaceutical company Pfizer in conjunction with clinical expertise, was first published in 1997 and has become the 'gold standard' measurement of ED in both clinical and research environments [89-92]. Quantification of satisfaction with treatment for ED can be measured using the Erectile Dysfunction Inventory of Treatment Satisfaction score [93].

Currently there is no accepted method of objectively measuring sexual desire [94]. The closest is the measurement of sexual arousal, by penile plethysmography, which measures erectile response to audio, visual or emotional cues, more commonly used to assess sex offenders, in order to assess patterns of arousal and treatment efficacy [95].

Several incarnations of objectively measuring erections have been developed. In the early 1960's a device which measured penile volume changes was reported, used in the context of testing the identification of an individual to homosexual or heterosexual tendencies [96, 97]. This device was found to be difficult to use during sleep. Three alternative methods to monitor erections during sleep were trialed in the mid 1960's, including a water filled cuff and a skin thermometer. The third, a mercury strain gauge, was found to be the more superior methodology [98]. This technique was further developed and found to be a cheap reliable method of monitoring SRE's [99]. A simpler technique, reported in 1980, involved placing a row of easily torn stamps, similar to postage stamps, snugly around the penis. If these stamps were torn along the perforations in the morning, erections were assumed to have occurred during sleep [70]. The late 1980's saw development of the 'Rigiscan^{TM}' device, using tension cables to monitor SRE's [100]. In a paper by Karacan in 1994, comment was made that monitoring of nocturnal erections was being used successfully by physicians around the world to determine the cause of erectile dysfunction [101]. Since the advent of successful pharmaceutical treatment for ED in the late 1990's, however, no further development of SRE measurement techniques has occurred.

Thus the most current technique to measure SRE's is the Rigiscan device, which monitors the frequency and duration of tumescence and rigidity of the penis during sleep [100]. The recording device is strapped to the participant's thigh using a commercially available strap with customised pocket to hold the device for the duration of the sleep period. Two small tension cables extend from the device to the penis, which move freely through a conduit and disposable loop covers. These loops are placed around the base and tip of the penis which gently tighten and release every 15 seconds at a force of 114 grams. After the dilatation of the loop, the penile tissue rebounds to the pre-intervention state. During this rebound, a measurement of the erectile tissue engorgement is taken. If an increase in tumescence is detected, compared to previous results and has shown at least a 6 millimetre increase, a second measurement is taken every 30 seconds. This second measurement records rigidity by tightening the loops to a linear force of 283.5 grams and determines the cross sectional response to radial compression [102].

Measurements obtained from the Rigiscan include the number of erections (defined as a 20% increase in tumescence from baseline lasting at least 3 minutes) per night, erection duration in both time and per cent of recording, and percentage rigidity (compared to 100% being a hard-rubber cylinder). Additionally, calculated variables reported are rigidity activation units (RAU's) which are a product of minutes spent at a given rigidity level in decimal form, summated for the duration of the erectile event, for both the base and the tip, as well as tumescence activation units (TAU's), which represent the duration of an erectile event multiplied by the percentage increase in circumference, as a decimal, over the baseline tumescence, again for both base and tip of the penis [103]. A study conducted in 1996, soon after these latter measurement units

were included in the assessment software, concluded that tip TAU's were the best overall measurement correlating with the diagnosis of erectile dysfunction, closely followed by both base TAU's and RAU's [104]. Repeating this study with a larger sample some 13 years later found that the diagnostic accuracy of this device did not go above 75% in any of the parameters, due to a large overlap in the RAU and TAU in that of men considered to have normal and abnormal erectile function, however, the authors recognised its utility in a research context and in documenting treatment efficacy in a clinical setting [105]. The frequency of monitoring nocturnal erections has declined since the advent of PDE-5 inhibitors, namely the release of Sildenafil in the late 1990's [22]. Due to the efficacy in treating ED using these medications, measurement of nocturnal erections generally only occurs in a clinical setting when available medications do not improve erectile function [106].

1.1.6. Treatment for Erectile Dysfunction

One of the main first line oral pharmacotherapies for men with ED is the use of PDE-5 inhibitors. Erections are normally reversed by the enzyme phosphodiesterase type 5 (PDE-5) by breaking down cyclic guanosine monophosphate (cGMP) which relaxes the corpus cavernosum muscle allowing blood to fill the muscle and an erection to occur [18]. PDE-5 inhibitors impede this process, allowing erections to occur and be maintained. The efficacy of these medications was found accidently during the development process of using PDE-5 inhibitors for the treatment of cardiac conditions in the mid 1990's due to a recurrent unintentional side effect of improved erectile function [49]. The most commonly used PDE-5 inhibitors are Sildenafil, Tadalafil, and Vardenafil, all of which have been shown to be safe, efficacious and well

tolerated [107, 108]. Less available and subsequently less studied are Avanafil, Udenafanil and Mirodenafil [109, 110]. Rates of use of PDE-5 inhibitors have substantially increased over the last 10 years, without a concomitant increase in diagnostic testing for the cause of ED [111].

In the few studies comparing PDE-5 inhibitors, the most preferred by patient is reported to be Tadalafil, possibly due to the ability to maintain sexual spontaneity [108, 112]. The half-life of Tadalafil has been found to have the longest out of the PDE-5 inhibitors, of around 17.5 hours, compared to that of Sildenafil (3.8 hours) and Vardenafil (3.9 hours) [113]. Tadalafil also has an added benefit of not being affected by food intake, whereas the efficacy of Sildenafil and Vardenafil is reduced when a high fat meal is consumed around the same time as dosage [114].

Traditionally, PDE-5 inhibitors have been taken under an 'on demand' regime. An alternate treatment is once daily administration, which can be both advantageous, by restoring the spontaneity of sexual activity, as well as disadvantageous due to an increase in burden to the patient, resulting in a potential for a reduction in adherence to treatment [110]. Several studies have found that daily administration of Tadalafil was more effective than that of an on-demand basis [115-117]. Similarly, Vardenafil has been shown to be effective when given daily for around 40% of those for whom on-demand administration was ineffective [118]. This is not a consistent result, however. In a study of men with mild to moderate ED, no benefit was found with once daily administration of 10mg Vardenafil compared with on demand dosage, with the latter regime having a trend toward a higher score in the erectile function domain of the IIEF questionnaire [119]. Similarly, in a group of patients post bilateral nerve-sparing radical

prostatectomy surgery, on-demand Vardenafil was more effective than daily administration [120].

Unfortunately, up to 30% of men who are treated with PDE-5 inhibitors for ED do not have an improvement in their symptoms [121]. For some of these men, changing the type of PDE-5 inhibitor, such as from Sildenafil to Vardenafil has been shown to improve erectile function [122]. For others, the addition of testosterone therapy has been shown to be efficacious [123-127]. The expression and function of the enzyme PDE-5 can be modulated by testosterone [128], meaning a low endogenous level of testosterone may reduce the number or efficiency of these enzymes, reducing the efficacy of PDE-5 inhibitor pharmacotherapy [129]. Testosterone is thought to have effects on nitric oxide release, with insufficient amounts associated with a reduction of pressure in penile arteries during erections [19].

The effect of PDE-5 inhibitors on sleep related erections has been inconsistent. In two studies of young healthy men with normal erectile function, a dose of 100mg of Sildenafil increased SRE parameters as measured by Rigiscan [130, 131]. In a study of men with ED, no improvement was found with Tadalafil on SRE's when measured by Nocturnal Electrobioimpedence Volumetric Assessment, which calculates penis blood flow [132]. Using the same SRE monitoring technique, another study found improvements when Sildenafil was administered to men with organic, but not psychogenic ED [133]. Also finding improvements was a study using a combination of testosterone therapy and PDE-5 inhibitors in hypogonadal men. This study found that the combination improved SRE's greater than the sum of each

therapy used on its own [134]. A similar result was found with the addition of on demand PDE-5 inhibitor for hypogonadal men using testosterone therapy for 6 months [135].

PDE-5 is the isoform generally expressed in the penile corpus cavernosum, however it is also found in other areas of the body, including the pulmonary and systemic vasculature and several other smooth muscle structures, which have been shown to be affected by PDE-5 inhibitors [136]. The low side effect profile and a greater understanding of cGMP regulated mechanisms have prompted many investigations in alternative uses of these medications. The original purpose of PDE-5 inhibitors was for cardiac related conditions before the discovery of the effects on erectile function. Since then, Sildenafil has been approved for pulmonary hypertension, and has been shown to improve flow mediated dilatation in chronic heart failure patients [136]. Additionally, a meta-analysis of PDE-5 inhibitors for Raynaud's phenomenon, a disease of excessive vasoconstriction, found that overall there is a significant but moderate effect in reducing the frequency and duration of Raynaud's exacerbations [137]. Lower urinary tract symptoms, continence after prostatectomy and urodynamic function after spinal cord injury have also all been shown to improve with PDE-5 inhibitors [138-140]. Therefore the use of daily administration of PDE-5 inhibitors may have additional positive effects apart from improved erectile function.

An alternate method of improving erectile function is by the administration of testosterone therapy, further described in **section 1.2.4.**

1.2. TESTOSTERONE

Testosterone is the main androgen which mediates pubertal maturation and preserves sexual characteristics and function in men throughout life. It is the main anabolic hormone and has wide ranging effects on human physiology. This hormone contributes toward many aspects of well-being and quality of life, including sexual function, strength, vitality, and some neurocognitive function.

The link between the testicles, now known to be the site of testosterone production, and their removal, with changes in behaviour and sexual characteristics have been noted by farmers in their livestock for at least 6000 years [141]. Historical references to human eunuchs, likewise, have noted this connection since at least the time of Ancient Greece [142]. In modern scientific literature, one of the first mentions of this phenomena was in 1849 [143]. Chemical messengers, first named “hormones” in 1905, were described in the Lancet, after experiments finding substances acted upon organs geographically distant from their place of origin [144]. Pharmaceutical companies embraced these new developments and in the early twentieth century three of these companies competed to isolate the hormone from the testicles [141]. The first team to succeed in 1935 was supported by Organon, and named the hormone “testosterone” [145], with another team, funded by Schering, synthesizing the hormone later that same year [146]. The third team published their data one week later, having also synthesized testosterone from cholesterol [147].

Since this early work, significant advances have been made in the understanding of testosterone secretion. Leydig cells within the testes are responsible for the production of the

majority of testosterone. The hypothalamus produces gonadatropin releasing hormone (GnRH), which binds with the gonadatropins in the anterior pituitary. This then releases both luteinsing hormone (LH) and follicular stimulating hormone (FSH). The FSH stimulates spermatogenis in the testes, while the LH stimulates the Leydig cells to produce testosterone. The testosterone then feeds back to suppress the production of the gonadatrophin [148]. About 2% of total testosterone is freely available to perform its functions ("free testosterone"), while the remaining is bound to either sex hormone binding globulin (SHBG) or albumin. The levels of these two proteins can therefore affect the bioavailability of testosterone [148].

1.2.1. Normal Testosterone Levels

Defining clinically normative testosterone levels across the entire adult lifespan has so far been elusive, with no clear consensus regarding the level at which a man is considered to have a low testosterone concentration. There is wide spread acceptance that there is a gradual decline in serum total and free testosterone levels associated with age in healthy adult men [149]. A decline of 1-2% per year for those aged over 40 is expected, with a faster decline, in the order of 4 nmol/L per year in those aged 61 – 87 years has been described [150, 151]. With an increasing life expectancy and a subsequent greater proportion of the older generation, the prevalence of low testosterone levels, and its accompanying symptomatology is likely to increase [152].

Extreme cases of intentional testosterone change, such as in athletes and body builders hoping for sporting enhancement and male singers castrated to maintain a soprano range, especially during the 16^{th} to 18^{th} centuries, as well as transgender individuals undergoing gender

reassignment, provide an interesting, but not generalisable, understanding of the effects of supraphysiological or complete absence of testosterone.

1.2.2. Influences on Testosterone Levels

Many concomitant pharmacotherapies as well as endogenous, situational and lifestyle factors can influence testosterone levels. In addition to age, several endogenous factors controlling testosterone exist. A substantial hereditary influence on testosterone levels has been shown in the Framingham Heart study [153]. By studying father/son and brother/brother pairs, a significant genetic correlation was found for testosterone levels, which included adjustment for known risk factors of age, BMI, as well as smoking and diabetic status [153]. The circadian rhythm also has a profound effect, with peak values occurring early in the morning and nadirs in the early evening [154]. This circadian pattern in the release of testosterone is so well established that standard practices require blood samples be taken in the early morning to ensure the sample reflects the peak testosterone level achieved throughout the day [155]. This diurnal variation, however, may not be as strong in those aged over 40 [156]. The influence of sleep on testosterone levels is further discussed in **section 1.4.1.**

Several modifiable factors have also been identified to influence testosterone levels. Firstly, increased body weight has been shown to decrease testosterone. A prospective cohort study of 1667 men showed that an increase in BMI of 4-5kg/m2 was comparable to that of the expected decline in testosterone over 10 years [157]. Likewise a large (n=890) longitudinal study found a decrease in total testosterone levels, but not free testosterone, with increase in

BMI [158]. In a large (n=991) long-term (20 year) study, those who gained more weight had lower levels of testosterone than those who lost or did not change weight [159].

Medications can have effects on testosterone levels. Statins, used to lower cholesterol, were found to reduce testosterone by 0.7 nmol/L, calculated with a meta-analysis of 6 studies, however, the clinical significance of this reduction is difficult to determine [160]. In contrast, a recent meta-analysis of 6 studies found statins improved erectile function [161]. Another common medication, glucocorticoids, which are often chronically used in the context of asthma, have also been shown to reduce testosterone with one small study (n=11) showing an inverse dose relationship, resulting in testosterone levels 60% that of the control group [162, 163].

A factor which is often overlooked is that of the influence of domestic situations on testosterone in men, which has been investigated in many studies with consistent results [164]. Relationship factors can alter testosterone, with the loss of a spouse reducing testosterone levels by more than 10nmol/L [157]. "Falling in love" in the first six months of a relationship can reduce testosterone levels compared to single men or those in long-term relationships (14.2 vs 23.6 nmol/L, p> 0.003). These levels were observed to rise after 1-2 years to the level previously seen in the control group [165]. A similar reduction in testosterone was found in heterosexual men (but not homosexual men) who had long term partners compared to those without partners (17.3 vs 27.0nmol/L, p=0.013) [166]. Several studies have documented lower testosterone levels in men in committed relationships, compared to single men [167-169]. There has also been consistent findings that becoming a father and being involved in child

rearing, reduces testosterone levels [169-171], suggesting that higher levels are associated with mating effort, and inversely correlated with parenting [171].

Social interactions have also been shown to affect the testosterone levels of men. In young college students, a short conversation with a female increased testosterone, but this was not significantly different than after a conversation with a male, however, the degree to which the male was trying to impress the female, as rated by the female, correlated with the increase in testosterone [172]. A woman's fertility has also been shown to influence a man's testosterone level, with the scent of premenopausal women who are in their most fertile phase, ovulation, producing an increase in testosterone [173].

Sexual thoughts, in the absence of sexual behaviour, has also been shown to affect testosterone levels, however this finding is not consistent. Watching a sexually explicit film has been shown to increase testosterone levels by 35%, compared with a sexually neutral film [174], however, a similar study did not find such an increase [175]. Sexual thoughts, elicited by imagining and writing about a sexual situation, did not produce an increase in testosterone compared to those who wrote about a control non-sexual situation, however an increase in cortisol levels was found, prompting a hypothesis that cortisol may facilitate sexual arousal by directing efforts toward a sexual situation [176].

Involvement in competitive sporting events can also influence testosterone levels in men. Several studies have shown winning compared to losing, increases testosterone, not only for players but for supporters [177-179]. Another study found that the level of participation in the game, rather than the outcome, correlated with the level of testosterone [180]. Anticipation for

an important match also increases testosterone levels, such as those seen in the supporters of the Spanish team participating in the lead up to the 2010 soccer World Cup final [181].

1.2.3. Testosterone Deficiency

Clinically, testosterone deficiency is defined as low testosterone levels in conjunction with clinical symptoms. Six such symptoms have been identified as characterising androgen deficiency – reduced sexual function, reduced intellectual ability, decreased body mass, changes in hair and skin, reduced bone mineral density and increased visceral fat [182]. In the older man, late onset hypogonadism can be defined by three or more sexual symptoms (such as poor morning erection, ED or low sexual desire) in addition to a total testosterone level of less than 11nmol/L and free testosterone level of less than 220pmol/L [183]. There have been inconsistent reports of the testosterone levels at which symptoms appear [183], suggesting that a significant amount of clinical decision making based on comprehensive medical history taking is essential.

Reported prevalence rates of testosterone deficiency differ. In a longitudinal study of 890 men, 20% of those over 60, 30% of those over 70 and 50% of those in their 80s have testosterone lower than that of a young healthy man [158]. In a large cross sectional study of almost 3000 men, the European Aging Male Study (EMAS), 2.1% of 40-79 year old males were found to have late-onset hypogonadism, and were found to be older and more obese than eugonadal men [184]. A population based decline of testosterone levels has been found in the United States, independent of age, in a large (n=1532) prospective cohort study, suggesting an unidentified health or environmental effect on testosterone levels in the overall population [185].

1.2.4. Testosterone Therapy

Testosterone therapy involves supplementation via transdermal, injected or implanted means [186]. Ideally, a sustained consistent release is ideal to avoid fluctuations of symptomatology [187]. Testosterone supplementation has been investigated in regard to many different clinical outcomes, using a variety of methodologies, and there remains a significant amount of conflicting information in regard to its efficacy. Baseline serum testosterone levels below which androgen supplementation is suggested varies between 8-17 nmol/L [155, 188, 189]. Although official guidelines avoid clearly identifying an exact cut off, reference is made to less than 10 nmol/L, laboratory dependent, as defining a low testosterone level [105]. There is increasing recognition that there is variation between individuals regarding the threshold of testosterone concentration and the appearance of or reduction in particular symptoms [190]. The decision to commence testosterone therapy must be based on clinical symptoms in the context of the risks involved with treatment [155]. Recent reports suggest that younger men, but not older men, with classic hypogonadism generally have a positive benefit to risk ratio with testosterone therapy [191].

The rates of prescribed testosterone supplementation in the general Australian community are substantially increasing with a nine-fold increase in the last 20 years [192]. This replicates the rapid increase in America, of 500% over the same timeframe [105]. The sale of testosterone globally has increased from $150 million in 2000 to $1.8 billion in 2011 [193]. This rapid increase in testosterone usage has not been associated with any increase in the diagnosis of androgen deficiency, and has been speculated to be viewed as a non-specific treatment for declining well-being and sexual dysfunction [192, 194]. Indeed, one survey of doctors in 5

countries regarding reasons for prescribing testosterone reported that symptoms, rather than laboratory values, drove their decision to prescribe testosterone supplementation [195].

From a clinical perspective, the effectiveness of testosterone supplementation on sexual function is generally accepted via 70 years of experience [191]. This is supported by systematic reviews, which report a consistent finding that testosterone treatment increases sexual desire, and also erectile function, although to a lesser degree [141, 196]. Separating sexual function into its various aspects, these differing facets appear to be affected by differing levels of testosterone; however there is not a clear consensus on the exact level of testosterone below which a symptom will become apparent. There is also variation between individuals regarding the influence of testosterone upon sexual function [197]. Long term observation of hypoandrogenic men receiving testosterone pellets (which declined in efficacy with time) showed a reproducible return of symptoms (lack of energy, motivation and reduced sexual desire) within individuals, however these levels varied markedly between men, suggesting that each man has a threshold at which androgen deficient symptoms become apparent [190].

1.2.5. Testosterone and Sexual Function

Traditionally, testosterone has long been strongly associated with virility. Healthy sexual function in males comprises sexual desire as well as satisfactory erectile and ejaculatory capabilities, and the production of sperm, all of which may be influenced by testosterone [198, 199]. Low levels of testosterone appear to have an inverse relationship with symptoms of sexual problems including poor morning erection, low sexual desire, erectile dysfunction, as

well as contributors to the ability to maintain healthy sexual function, including inability to perform vigorous activity, depression and fatigue [183].

Questionnaire data published by various authors regarding sexual functioning, including sexual desire, erectile function and orgasmic function have suggested differing threshold levels of testosterone to be associated with reduced sexual functioning, ranging from 8nmol/L to 12nmol/L [105, 183, 190, 200]. Testosterone levels below 8, 11 and 12, nmol/L have all been associated with decline in various aspects of functioning [189]. Below 12 nmol/L, less sexual activity occurs and there is a reduction in nocturnal erections [105, 141]. Self-reported morning erections decrease at testosterone levels below 11 nmol/L [183]. With testosterone concentrations under 8 nmol/L, men have been found to have reduced sexual desire and erectile function and an increase in depression [183, 201, 202].

1.2.5.1. Testosterone and Sexual Desire

Sexual desire has been reported to reduce at a variety of thresholds, including 8, 10, 11, 12 and 17, 20 nmol/L [183, 203, 204]. Adding to this uncertainty, two separate studies in which testosterone levels were artificially adjusted in healthy young eugonadal men found opposing results, with one reporting no association with levels of serum testosterone and measurements of any sexual function parameter [205] and the other finding a significant reduction in the amount of sexual desire, number of fantasies and frequency of sexual encounters [206]. Although reports regarding the relationship between testosterone levels and sexual desire have been inconsistent, the majority point to a link between the two. Compared to age matched controls, for men with testosterone lower than 9 nmol/L, dyadic but not solitary, sexual desire

was reduced [207]. In a study of 1632 men, sexual desire measured via self-report on a 14 point scale, showed a significant association with testosterone, however, the difference in mean testosterone between those whom reported low sexual desire (defined as a score less than 14) versus those whom did not, was small, with only 0.12 nmol/L difference between unit increases of sexual desire [203].

In the 16th century, young boys, destined to become singers, were castrated prior to their voice breaking, in order to maintain voices in the high octave ranges [208]. Depending upon the timing of the spermatic cord being severed, these 'castrati' were known to have a complete lack of sex drive if the procedure was performed prior to puberty [209], and presumably, before adult testosterone levels were reached.

In more recent times, the effects of testosterone therapy on sexual desire have been investigated. Meta-analyses of clinical trials of pharmacotherapy have shown a large effect of testosterone supplementation on sexual desire, but only in those with low baseline levels [196, 210]. In one of the few studies examining both aspects of sexual interest, those with low testosterone were found to have lower overall desire than a matched control group, however, there was no difference in solitary sexual desire, that is, interest in behaving sexually by oneself [207]. When these men were administered androgen therapy, dyadic sexual desire, the interest in behaving sexually with a partner, increased to levels similar to that of the control group. Additionally, solitary desire was increased compared to baseline, but was not different than that of the control group [207]. Testosterone replacement, via patch or gel, for those with low baseline testosterone has been shown to increase sexual desire. This increase has been

found to occur once a low normal range of testosterone has been reached, and no further increase was seen by increasing the serum level to beyond this threshold [211]. In a dose finding study, 100 mg/day but not 50 mg/day was found to increase in sexual desire in hypogonadal men [204].

When men with testosterone within the normal ranges are given supplemental androgens, sexual desire has been found to be both unchanged and increased. In a placebo controlled study of eugonadal men presenting with low sexual desire, testosterone was successful in increasing desire compared to placebo [212]. A meta-analysis of 7 placebo controlled studies in eugonadal men found that testosterone administration slightly increased sexual desire [213]. When supraphysiological doses were given to eugonadal men in a study investigating androgen use in contraception, an increase in sexual desire without a corresponding change in sexual encounters occurred, however this increase was attributed to one individual, without whom the result was no longer significant [214]. However, in a randomised controlled study, in which eugonadal men with ED received exogenous testosterone, increases in sexual desire were reported, but these were not statistically different than placebo [215]. An explanation posed regarding the relationship between testosterone and libido is that there is not a linear relationship at which there is a threshold level above which desire increases, rather, relative to regular levels, a transient increase in circulating hormones may be a more influential factor [213].

1.2.5.2. Testosterone and Erectile Function

The two forms of erection, those occurring as a result of sexual stimulation and those occurring during sleep, appear to have differing relationships with testosterone levels, although this is not a consistent finding [71, 216]. In two studies, erections in response to stimuli were not affected by levels of testosterone, however those occurring during sleep were [217, 218]. In a case series of seven transgender individuals, undergoing male to female gender reassignment, the suppression of testosterone through oestrogen therapy was accompanied by a distinct, but statistically insignificant, reduction in erections during both wake and sleep [219].

The relationship with erections during wakefulness due to stimuli with testosterone levels are not clear, with studies differing regarding the relationship between erectile function and testosterone. A large population study (n=1071) found there was no difference in serum total testosterone levels between groups classified as having or not having ED [220]. Additionally, a large population study (n=1195), showed that severe, but not mild, ED, had an increased risk of a low testosterone level [221].

Pharmaceutical studies allow an insight into the relationship of testosterone with erectile function. In a small (n=10) early study of five men with low sexual interest and five men with erectile dysfunction, testosterone did not improve erectile function compared with placebo [212]. In a systematic review and meta-analysis of placebo controlled trials of testosterone use a small improvement in erectile function was found, however, there were several unexplained and inconsistent results within these studies [196]. Similarly, a meta-analysis of 17 clinical trials showed an inverse relationship between testosterone levels and erectile function, however,

they identified several caveats regarding these effects being mediated by baseline levels, duration of treatment and identified a lack of information on long-term safety of androgen therapy [213].

For nocturnal erections there appears to be a closer relationship with testosterone levels. In an early study reported in 1977, simultaneous measurement of penile tumescence via a mercury strain gauge and testosterone by 10-20 minute blood sampling found a relationship between the two, although this crude study did not correlate the two using modern methods [222]. A few years later, similar measurements were taken in men with lifelong problems with erections, and found no relationship between REM cycles, testosterone and tumescence, however, those with erectile difficulties exhibited both reduced testosterone and reduced nocturnal erections compared to controls [223]. In a study of five men with epilepsy and low testosterone, and five age matched controls, penile activity during sleep was found to be correlated with free testosterone levels [224]. Similarly, in a study of hypogonadal men, lower levels of testosterone were associated with nocturnal erections that were either absent, or of very low amplitude and duration compared to controls [225]. For eight healthy young eugonadal men, a single injection of testosterone increased the rigidity but not the duration of nocturnal erections compared to placebo [226], however, this is not replicated in another similar study finding no such change [227]. Aspects of sleep related erections had varying levels of association with testosterone when measured in 201 men including both hypogonadal and eugonadal participants. This study concluded that the testosterone threshold for sleep related erections is less than that of the lower end of normal range [228]. In agreement with this concept is a study that found the threshold for nighttime erections to be lower than that of sexual intercourse frequency and

sexual desire, however this study found a higher threshold, within the normal range, that of around 14nmol/L [204]. The effect of testosterone supplementation upon nocturnal erections appears to take some time, according to one study, in which, despite a rapid (3 months) increase to normalised levels of serum testosterone concentration, nocturnal erections increased steadily over 6-12 months of testosterone supplementation [225]. In contrast, the association between testosterone levels and nocturnal erections was assessed in hypogonadal men immediately after dosage of androgen supplementation and 7-8 weeks later, which found that with the declining levels of circulating testosterone, a reduction in nocturnal erections in terms of rigidity and duration was seen [229]. In a group of 29 men with COPD, not selected for baseline levels of testosterone or erectile function, testosterone supplementation was administered in a study examining the effect on body composition and pulmonary function. Improvements in overall sexual function as well as erectile function were noted, however, the difference between the treatment group and the placebo group was largely due to a decline in both testosterone levels and sexual function in the control group, suggesting testosterone may prevent decline, rather than improve function in this population [230].

The pathway between low testosterone and impaired erectile function has not been established [200], however, some animal evidence suggests that testosterone may regulate nitric oxide mediated validation in the vasculature of the penis [20]. Indeed, one human study has found evidence for a relationship between cavernous vasodilation and free testosterone in men with ED, using dynamic colour duplex ultrasound to distinguish between arteriogenic or corporeal venocclusive or psychogenic erectile dysfunction [21]. Low testosterone may be found in conjunction with ED, however, it may not be the only contributing factor, with only 5-

15% of those with ED having a low testosterone level [216]. Indeed, not all patients with ED and a low testosterone level have improvement in symptomatology with exogenous testosterone administration [71].

In summary, the amount of androgen required to maintain sexual function is not well established, and has individual variation. As a result, men with testosterone above or below a pre-set threshold value may result in quite different presentations.

1.2.6. Testosterone and Neurocognitive function

The role of testosterone in neurocognition is complex and not completely understood [231]. Various studies, using different methodologies to measure cognitive function under differing conditions, age, levels of baseline cognitive functioning, age and duration of treatment, as well as a unclear definition of testosterone deficiency, have so far found inconsistent results regarding the exact influence that testosterone has upon cognition. Supporting the notion that testosterone can have effects on cognition are some observations of brain biology and function. Androgen receptors are found in brain regions responsible for learning and memory, which may mean that testosterone can influence cognitive processes [231]. Indeed, higher levels of testosterone were related to increased amygdala activation in men as measured by brain functional magnetic resonance imaging (fMRI) during mental work, which translated to better memory performance [232]. An intentional reduction of testosterone in prostate cancer patients revealed a reduction in activation of the right parietal-occipital region of the brain, compared to baseline, during periods of spatial reasoning and memory tasks on fMRI, in the absence of detriments in performance [233]. Additionally, cerebral perfusion has been noted

to be predicted by the level of free testosterone and also to increase with testosterone supplementation when measured by single-photon emission computed tomography [234, 235]. By artificially adjusting testosterone levels in healthy young eugonadal men, no association was found with levels of serum testosterone and measurements of spatial cognition [205]. Very few studies have investigated younger, healthy men, rather, the majority of studies regarding the association between neurocognition and testosterone have focused on elderly men [231]. In a large (n=407) longitudinal study, higher levels of free testosterone were associated with higher scores associated with visual and verbal memory, as well as visuospatial functioning [236]. In this study, men classified as being hypogonadal had lower scores on memory and visuospatial performance than those who were eugonadal [236]. In the Massachusetts Male Aging study, there were associations between all measures of cognition with free testosterone; however, this effect was not significant once adjusted for age [237]. In another study of 54 men aged 61-77 years, testosterone was shown to be associated with working memory in but not with spatial abilities, verbal memory and visuomotor processing speed, however the influence of age was not reported [238]. In men aged 40-80, lower bioavailable levels of testosterone were associated with lower scores on processing capacity and speed, whereas executive function and memory showed only a weak correlation [239]. After stratification, only those in the oldest age group, 71 – 80 years, were found to benefit from higher testosterone levels in processing speed, executive and global cognitive function but not memory [239].

Some studies have found a quadratic (U-shaped) relationship between testosterone and cognition, suggesting an optimal hormone range for particular cognitive tasks [240, 241]. Older males aged 59 - 89 years were found to have a U-shaped relationship between total

testosterone and the World backwards test, as well as free testosterone with the visual reproduction test. Both a linear and a quadratic relationship were found for mental control and verbal memory with free, but only a linear relationship with total, testosterone. The magnitude of these relationships may have, however, been affected by a 5 year interval between blood sampling and cognitive testing [240].

The effect of androgen supplementation on neurocognition has received a reasonable amount of attention, with differing results. Recent work in older men found no change in executive function, memory and spatial cognition with physiological or supraphysiological doses of testosterone [242, 243]. Similarly, in women with surgically induced menopause, testosterone levels were not found to be correlated with cognitive performance as measured by digit symbol substitution task, paired and free recall, or the presence of cognitive fatigue [244]. In contrast, improvements in spatial memory, special reasoning and verbal fluency were seen with testosterone administration compared to placebo in a small (n=25) study [245]. Several other small studies have reported improvements in memory and spatial cognition for older men treated with androgen supplementation but with only those who had an initial lower level of testosterone [246, 247]. Supporting the data showing a U-shaped relationship of testosterone and cognition in non-supplemented men, moderate to large increases (11 - 50 nmol/L) in serum testosterone were associated with improvements in verbal and partial memory in older men from the community given supraphysological doses of testosterone, however, those with either very large (>51 nmol/L) or low (<10 nmol/L) increases did not show such change [248]. Similarly, higher levels of testosterone in 30 elderly men were associated with a decline in

learning in regard to verbal fluency with testosterone treatment, but not in other verbal or spatial tasks [249].

The use of anabolic steroids in those aiming to increase testosterone levels with resultant increases in muscle mass or athletic performance has increased in the last 30 years [250, 251]. Users can reach supraphysiologic testosterone levels at least 50 times the level of normal adult male, including a case described having serum testosterone level of over 700 nmol/L [252]. These men may be at risk of cognitive deficit, with visuospatial memory of steroid using weight lifters in a small study (n = 31) shown to be significantly worse than in their counterparts whom did not use steroids. No difference was found for reaction time, rapid visual information processing or immediate free recall [252]. Again this may support the theory of a U-shaped relationship and an optimal functioning level of testosterone.

1.2.7. Testosterone and Quality of Life

Few studies have investigated the relationship between testosterone and quality of life measurements such as the SF-36 quality of life assessment tool. In a population study of 47 older men, of which 57% had testosterone levels lower than the normal range, no relationship was found between testosterone and scores in any domain of the SF-36 [253]. In a study of 3369 older (age 40-79 years) men, testosterone levels were associated with the Beck Depression Inventory and individual questions of the SF-36, although the SF-36 domain scores were not reported [183]. The questions reported to be associated with testosterone levels were related to vigour, walking more than 1km, bending and stooping, feeling downhearted, loss of energy and fatigue. Further analysis of these individual questions found a threshold of

below 13nmol/L to significantly increase the likelihood of having reduced vigour. Similarly, less than 160pmol /L of free testosterone increased the probability of feeling down and of having increased fatigue. These results suggest that there may be varying thresholds for the appearance of androgen deficient symptoms in the general male population. Several studies of pharmaceutical intervention have reported improvements in differing domains of the SF-36 due to testosterone replacement [254, 255], however, other studies have found either no or minimal improvement in these domains [256-260], again suggesting a heterogeneous relationship with testosterone.

1.2.8. Testosterone and Cardiovascular Disease

Men have a higher risk of cardiovascular disease than women, suggesting testosterone being a mediating factor in this relationship [261-263]. However, this is not a linear, or clear, association [19, 148, 263-268]. Both a low level of endogenous testosterone as well as the administration of exogenous testosterone appear to have an increase in cardiovascular risk, but there is no clear evidence that restoring low testosterone to normal levels increases the likelihood of cardiovascular disease [261, 264]. A recent review, has identified testosterone to have some protective effects against cardiovascular disease, in regard to the properties of being a vasodilator, anti-inflammatory, anti-atherosclerotic, and anti-coagulant agent [269]. Likewise, a meta-analysis of 19 studies showed older, but not younger, men were weakly protected by a higher level of endogenous testosterone [267]. A cross–sectional analysis of 54 studies showed that those with cardiovascular disease had lower levels of testosterone than those without, however, concluded that the association may or may not be that of cause and

effect [265]. An often cited study was terminated early due an increase in cardiovascular complications in those men randomly assigned to receive testosterone supplementation [270]. Indeed, a meta-analysis of 27 clinical trials of testosterone found a greater risk of cardiovascular events for those taking active testosterone compared to placebo, with a greater risk in non-pharmaceutical funded clinical trials compared to those funded by pharmaceutical companies [271]. A recent retrospective study in men who had undergone coronary angiography found a 5.8% higher incidence of cardiovascular events in men whom had received testosterone therapy [268]. Similar reports of increased cardiovascular events have been described in men taking anabolic steroids for sporting enhancement [272]. On the other hand, other authors, including those whom have performed meta-analyses, have not shown this relationship and reported testosterone replacement therapy as having no or little effect on cardiovascular events, but observed that the quality of this data is less than ideal, due to the short duration of the studies, lack of allocation concealment, and the small numbers of both events and participants [264, 266, 273]. Several authors consider the current literature, particularly in older men, to be inadequate to accurately assess the risks of testosterone therapy on cardiovascular outcomes [191, 264, 266, 273].

1.3. OBSTRUCTIVE SLEEP APNOEA

1.3.1. Description

Obstructive sleep apnoea (OSA) is a sleep disorder characterised by repetitive periods of complete absence ("apnoea") or reduction ("hypopnoea") of respiration caused by a narrowing of the upper airway. Periods of apnoea and hypopnoea are accompanied by futile respiratory effort against a constricted upper airway [274]. This is terminated by a brief arousal from sleep which clears the airway blockage and normal breathing is resumed. As a result, there are repeated disruptions to sleep continuity, drops in blood oxygen levels, momentary increases in blood pressure, and numerous other parasympathetic and sympathetic responses. These pauses in breathing can occur up to several hundred times during the sleep period, causing in a variety of physiological, psychosocial and psychological outcomes.

The most common symptoms of OSA are snoring and excessive sleepiness. Bed partners, family members and travelling companions of the patient often observe and report episodes of snoring and apnoea [275]. Other features include unrefreshing sleep, nocturia, dry mouth, mood disturbance, morning headache, poor concentration, fatigue, choking or gasping, recurrent awakenings during sleep and erectile dysfunction [276-278].

1.3.2. Diagnosis

The International Classification of Sleep Disorders defines OSA as, in the absence of any other disorder, having more than 5 respiratory events (apnoeas, hypopnoeas and respiratory effort

related arousals) per hour was well as clinical symptoms. If no symptoms are present, more than 15 respiratory events per hour are required to make the diagnosis [279] and can be referred to as obstructive sleep apnoea syndrome (OSAS).

The most thorough method to clinically document OSA is full attended in laboratory polysomnography [280, 281]. This test involves overnight observation at a sleep laboratory while several physiological parameters are concurrently recorded during sleep. Typical monitoring configurations to identify sleep stages and arousals from sleep include electroencephalography (EEG) and electrooculography (EOG) and electromyography (EMG). Respiration parameters are recorded using plethysmography to monitor respiratory effort, pressure and temperature changes for nasal and oral respiration and pulse oximetry for blood oxygen saturation. Recordings are analysed and summated to describe sleep efficiency, the amount of time in different sleep stages, namely Rapid Eye Movement (REM) and non-Rapid Eye Movement (NREM) sleep, degree of hypoxia and the frequency of cortical arousal and breathing irregularities per hour of sleep [282]. Monitoring sleep in the home environment is becoming increasingly prevalent due to improvements in technology, validation and acceptance [283].

The severity of OSA is generally based on the frequency of apnoeas and hypopnoeas per hour, known as the apnoea hypopnoea index (AHI), with less than 5 breathing disturbances per hour considered normative, from 5 - 15 mild, 15 - 30 moderate and more than 30 is considered severe OSA [276]. The respiratory disturbance index (RDI), is often used interchangeably with

AHI, however, this former term should be used when apnoeas, hypopnoeas as well as respiratory event related arousals per hour are reported [282]. **Prevalence**

The definition of OSA is somewhat inconsistent across studies, which can contribute to variation in prevalence rates. Dividing a population into the presence and absence of OSA can be influenced by the equipment used, analysis techniques employed, AHI selected and the decision to include or exclude associated symptomatology [284-288]. Notwithstanding, by any criteria, obstructive sleep apnoea is a relatively common condition with all the hallmarks of a chronic condition [289].

A study commonly cited describing the prevalence of obstructive sleep apnoea is that of Young, 1993 [286]. In this study, OSA, defined as an AHI of more than 5 per hour as well as concurrent excessive daytime sleepiness, occurred in 4% and 2% of middle-aged western men and women respectively. Based on polysomnographic criteria alone, an AHI of greater than 5 exists in approximately 24% and 9% of men and women respectively when measured more than 20 years ago [286]. This prevalence rate is likely to have increased [287].

1.3.4. Risk Factors

One of the main risk factors for developing OSA is excessive weight. Longitudinal data regarding obesity showed a dose response relationship, with a 1% increase in weight being associated with a 3% increase in the AHI [290], hence, the current obesity epidemic will translate into a greater number of individuals with OSA. A recent study in 400 women from the Swedish community (age 48 years, BMI 25kg/m^2) found that 50% had an AHI greater than 5, with BMI and age being the major contributors to incidence rates [291]. On average, world-

wide, body mass index (BMI) has increased by 0.4 kg/m^2 per decade over the last 30 years [292]. The United States has the highest average BMI of high income countries, with an average of 28.4 kg/m^2, with 69% of the population classified as being overweight (BMI>25) and 35% being obese (BMI>30) [292]. Australian body habitus is almost as large, with 60% classified as being overweight and 25% obese [293]. This increase in body size is particularly more prevalent for men, with a yearly increase in the rate of obesity by 0.8%, with no such change for women [294]. Although not currently directly documented, the prevalence rate of OSA is likely to increase given the rising rate of obesity and the link between these two conditions [287, 295]. Incorporating the recent trajectory in obesity, a strong causal factor for OSA, using the same AHI and symptomatology criteria as Young's study, the current estimate of OSA prevalence rates is 14% of men and 5% of women [286, 287].

Increasing age inflates the incidence of OSA [296, 297]. In a study of 741 men, using a definition of an AHI greater than 10, OSA existed in 3.2% of those aged between 20-44 years, 11.3% of 45-64 year olds, and 18.1% in the oldest category, ages 65-100 [296]. When these polysomnographic findings were combined with clinical features of at least one symptom, OSA syndrome was prevalent in 1.2%, 4.7% and 1.7% respectively [296]. As this study suggests, as does several others, there is a high prevalence of obstructed breathing during sleep in the elderly, however, this is not accompanied by clinical symptoms [295, 298]. Possible explanations suggested for this incongruence include theories that OSA in older age may be a condition distinct from that of middle age, or that those who exhibit symptoms have not survived to older age [299]. Indeed, mortality data from the long term Bussleton study shows that the presence of OSA is indicative of early death [300].

Physical anatomy can contribute to the narrowing of the upper airway and thus the risk of developing OSA. There is an increase in the risk of developing OSA for those with increased neck size, enlarged tonsils (particularly in children), anomalies of the craniofacial structure or upper airway soft tissue and nasal congestion [301-306]. Alcohol intake can also reduce upper airway muscle tone, increasing the likelihood of OSA [304].

Hormonal factors have also been suggested to influence the incidence of OSA. The higher prevalence of OSA in males has been suggested to be due to higher testosterone levels [306, 307]. Women experience many hormonal changes as part of the menstrual cycle, pregnancy, menopause and hormone replacement therapy. All of these circumstances have been shown to impact upon levels of sleep disordered breathing [307-310]. In a case report, a woman with a testosterone producing tumour with higher than expected levels of testosterone was found to have significant OSA, which resolved once the tumour was removed [311].

1.3.5. Consequences

Untreated OSA is associated with a number of established outcomes, including excessive daytime sleepiness, increased cardiovascular risk, mood disturbance, neurocognitive deficit, hormone imbalance and impaired sexual function. OSA is independently associated with increased risk of all-cause mortality [300, 312], cardiovascular mortality [312-314] and cardiovascular events [313, 315]. Hypertension, heart failure, coronary heart disease, stroke and arrhythmia are all established consequences of OSA [299, 316-318]. Additionally, those with OSA may also be at greater risk of diabetes [319], through the increase of glucose intolerance and insulin resistance [320, 321] in this population.

One of the most common daytime symptoms of OSA is excessive sleepiness. Those with OSA have been shown to be sleepier than well matched controls, however the relationship between severity of OSA and sleepiness levels are weak [286, 322]. The level of sleepiness in an individual can often be difficult to ascertain through clinical evaluation [323]. Subjective methods for quantifying sleepiness are available. Sleepiness over recent times can be subjectively measured in using the Epworth Sleepiness Scale (ESS), first described by Johns 1991 [324]. This self-reported 8 item scale assesses the likelihood of falling asleep in various scenarios commonly encountered in daily life, such as sitting and reading, watching TV and lying down in the afternoon. Subjects are asked to rate the chance of falling asleep in each circumstance from 0 (no chance of dozing) to 3 (high chance of dozing). The scores are tallied to give a total between 0 – 24, with those above 12 indicating excessive sleepiness [325]. The ESS focuses on levels of sleepiness over the preceding two weeks and can be used to subjectively quantify sleepiness and assess change due to treatment effects [325]. Two measures of 'present moment' sleepiness are available for use in the research setting. The Karolinska Sleepiness Scale (KSS), a single item with nine possible responses is presented to respondents to assess instantaneous levels of subjective sleepiness from 1 (extremely alert) to 9 (extremely sleepy – fighting sleep) [326]. Higher scores represent greater subjective sleepiness and have been correlated with behavioural and EEG changes [327]. The Stanford Sleepiness Scale (SSS) is also a single item measurement of sleepiness with seven possible responses ranging from 1 (feeling active and vital; alert; wide awake) to 7 (almost in reverie; sleep onset soon; lost struggle to remain awake) [328, 329]. This score assesses momentary levels of sleepiness and can be used repeatedly to measure changes across the day [329].

1.3.6. Impact on Quality of Life

Patients with OSA often experience an impaired quality of life [330-332], and this impairment is often the reason for seeking and possibly adhering to treatment [331]. General quality of life can be measured using the Short Form 36 (SF-36) questionnaire, which can be compared to number of reference ranges, including the largest set obtained from over 13,000 subjects from the United Kingdom [333, 334]. A large sleep related study (Wisconsin Sleep Cohort) of a general population found the entire group to have similar results to that of the English reference range, however, those with even mild sleep disordered breathing had much lower general health comparable to that experienced with other chronic disease states such as arthritis and diabetes [335]. Another study found that, compared to the normative population, those with OSA scored lower in all domains of physical function, mental health, role limitation, pain, general health, vitality and social function [336]. The latter two domains were noted to be the most significantly different [336]. Of all the domains in the SF-36, that of vitality has been reported by one study to be the most affected in those with OSA [337]. Likewise, vitality was shown to be the only domain correlated with OSA severity in the Sleep Heart Health study [330]. Some studies have shown no or minimal correlation of any numerical parameter of OSA, such as AHI or minimum oxygen levels, with the scores of any domain of the SF-36 [332, 338], which may suggest an interpersonal difference in susceptibility to symptoms.

A disease specific quality of life measurement, the Functional Outcomes of Sleep Questionnaire (FOSQ) has been developed to identify the functional impact of sleep disorders on quality of life [339]. This consists of five subscales (Vigilance, Activity, Intimacy and Social Relationships, Social Outcome and General Productivity) as well as a total score and can successfully

distinguish between those seeking treatment for a sleep disorder and the normal population [339].

More than half of patients with OSA have depression, either doctor diagnosed or via questionnaire [340]. This may not be a direct link, however, rather this may be a result of the reduced quality of life seen in OSA [338]. Correlation of ESS and quality of life scores with depression scores have been documented, but the only parameter of OSA found to have an association with levels of depression is hypoxaemia [338, 340].

Manifestations of OSA, such as sleepiness, mood changes and irritability [341] may collectively impact on mental health and interpersonal relationship quality with one's spouse. Indeed one of the earliest descriptions of OSA in a case series of 25 men included marital breakdown as one outcome of sleep apnoea [342]. In a study of obese men in Sweden, men with OSA and excessive sleepiness were found to be 3 times more likely to be twice (or more) divorced than those with neither OSA or sleepiness [343]. A later study showed that men with OSA are almost 3 times as likely to sleep separately from their wives [344]. In this study there was no difference in marital satisfaction between those with and without OSA, and it was speculated that by sleeping separately, marital harmony was maintained [344].

1.3.7. Treatment of OSA with CPAP

Continuous positive airway pressure (CPAP) is the standard first-line treatment for OSA. CPAP delivers pressurised air via a mask which splints the upper airway open during sleep and re-establishes normal breathing and sleep patterns. In several reviews focusing on the efficacy of CPAP, this treatment is recognised as being effective in eliminating airway obstruction in sleep,

thereby improving daytime sleepiness, blood pressure levels and quality of life [345, 346]. In a 10 year observational study found that, compared to healthy controls, men with untreated severe OSA had a higher risk of fatal and non-fatal cardiovascular outcomes, and CPAP use reduced this risk [313]. In OSA patients whom have already had a stroke, CPAP has been shown in a 5 year follow up study to reduce mortality, compared to those who did not use CPAP [347]. Potentially, this reduced risk of cardiovascular disease may be attributable to a reduction in blood pressure. A meta-analysis of 10 pooled randomised controlled trials found a statistically significant reduction with CPAP, however, this reduction was small, in the order of 1-2mmHg, but was more substantial in subjects with more severe OSA, resulting in a 2-3mmHg reduction [348]. Currently, a multicentre, long term study on cardiovascular outcomes (SAVE study) is underway to determine the efficacy of CPAP in the prevention of cardiovascular disease [349].

Although the efficacy of CPAP on health outcomes is high, adherence to CPAP usage is low. The World Health Organisation defines adherence as "the extent to which a person's behavior … corresponds with agreed recommendations from a health care provider". In a meta-analysis of adherence to recommended medical treatment, categorised by 17 different disease conditions, compliance to therapy for sleep disorders was the lowest of all disease categories (65%). Complexity of the treatment regimen was suggested as a reason for low adherence [350]. In a Cochrane review, the highest reported average nightly usage in any randomised trial was 5.9 hours per night for all participants [346]. This is likely to represent best case scenario. A commonly used definition of adherence is that of a minimum of four hours every night. This duration was found to be the threshold at which longer use was unlikely to result in further improvements in levels of sleepiness [351]. Using this definition, only 46 – 83 % of patients

would be considered adherent in a variety of reviewed trials [352]. Given that even one night without usage results in the recurrence of OSA [353], studying the effects of CPAP on health and social outcomes may be limited by participants adherence to CPAP therapy.

Partner influence on CPAP adherence can be both beneficial and detrimental. Patients in one study whom had sought treatment for OSA due to their spouse rather than being self-referred were less adherent to CPAP therapy [354]. Relationship quality also has an influence, with levels of conflict in the relationship, as well as perceived pressure from partners, having an inverse relationship with hours of CPAP use [355, 356]. In comparison, another study showed that those patients whom were living with a partner tended to have a higher adherence rate to treatment, with an odds ratio of 1.5 of being adherent (>4hours/night) with CPAP therapy [357]. In a small, 2 week study, the number of nights in which a man with OSA slept in the same bed as his wife was positively correlated with CPAP adherence [358]. In a longer term (6 month) sham controlled study, those who were more adherent to therapy, in both active and placebo arms, were more likely to be married [359]. Indeed having a partner at home has been identified as being a positive predictor in adherence to therapy [360].

CPAP treatment has repeatedly been shown to reduce sleepiness, more so for patients whom were sleepier pre-treatment [346]. Improvements were seen on ESS scores in a long-term randomised controlled study using sham CPAP, particularly in those who had moderate-severe OSA and who were more adherent to therapy [359]. In mild OSA (AHI 5-15) a randomised control study using an oral placebo, CPAP treatment showed a greater improvement in ESS than

that of placebo, however stratification showed those with very mild OSA (AHI 5-10) did not show such improvement [361].

Improvements in other parameters of quality of life have also been noted in CPAP use, particularly for those who experience more symptoms pre-treatment [346]. A meta-analysis of 16 studies using the SF-36 questionnaire found that CPAP does not improve general quality of life, however it does improve physical function and vitality [362]. Some studies have found these improvements to be more pronounced for those who adhere to CPAP therapy [361, 363].

In regards to sleep specific quality of life, the Functional Outcomes of Sleep Questionnaire (FOSQ) has been used in a several sham CPAP controlled studies, finding improvements in vigilance [364-366], general productivity [364, 366], activity level [365, 366] and social outcomes [365]. However, no improvement in any domain in the FOSQ was seen for patients with moderate OSA (AHI 10-30) in a conservative treatment (weight loss and sleep hygiene) controlled study [367]. In a study assessing dosage, that is, CPAP adherence, with overall FOSQ scores, increasing usage of CPAP saw greater improvements in the number of patients with normative scores, up to 7 hours usage, after which, no further improvement was seen [351].

Improvements in depression scores have been noted even with low usage of CPAP (2.8 ± 2.1 hours) compared to an oral placebo [361]. In contrast, in another oral placebo randomised controlled study of those with mild-moderate (AHI 5-30) OSA, no change was seen in any parameter of the SF-35 or FOSQ questionnaire by the use of CPAP [368]. Limitations in interpreting this result include low usage of CPAP (3.5±2.1 hours/night) and a placebo effect was noted in the control arm, which may have contributed to this result [368]. However, a sub-

analysis of those whom were adherent to CPAP therapy (>4hours) also showed no improvement in any domain of the SF36 or FOSQ questionnaires in this mild OSA group [368]. Potentially this may be due to lower symptomatology in this group.

Relationship quality may improve with CPAP use, with one study showing CPAP users, compared to those recommended conservative treatment in the same sleep clinic population, found to show improvements in marital satisfaction, happiness and communication, all of which were correlated with CPAP usage, as well as a reduction in frequency of conflict in the relationship to reduce with adequate CPAP use [355, 369]. A potential contributor to an improved relationship may be due to an improved quality of life for the patient but also due to a better quality sleep for the partner if they share sleeping space. Both patient and partner have been shown to be less sleepy after the implementation of CPAP therapy, as measured by the ESS [363]. After the commencement of CPAP therapy, bed partners of CPAP users have been shown to improve in both objectively measured sleep efficiency and subjective sleep quality [370].

1.4. SLEEP AND SEXUAL FUNCTION

Sleep and sex are both essential human experiences. Several medical conditions exist in which sleep and sex intertwine, such as Kleine-Levine Syndrome, in which periods of hypersomnolence occur in conjunction with hypersexuality [371]. Links between REM sleep deprivation and sexual behavior changes have been noted in animal models. Sleep deprived rats have been shown to have increased erectile function with 24 hours of no REM sleep, but this phenomena declines after 96 hours of REM sleep deprivation [372]. Sexsomnia, a distinct parasomnia in which sexual acts are performed during sleep, has received increased attention through case reports, although research is lacking [373, 374]. No intervention studies on humans have investigated the influence of sleep deprivation on sexual function have been reported. Cross-sectional data investigating lifestyle driven sleep restriction in teenagers has shown increased risk taking behaviour, including sexual activity related behaviours [375].

1.4.1. Sleep and Testosterone

There is increasing recognition of the role sleep plays in metabolic and endocrine processes. The circadian pattern in the release of testosterone is so well established that standard practices require blood samples be taken at the same time of day – early morning – to ensure the sample reflects the peak testosterone level achieved throughout the day [148, 155].

During sleep, surges of testosterone are seen when frequent (every 10-20 minutes) blood samples are drawn [376, 377]. A testosterone surge is initiated by a rise in luteinising hormone, which has been shown to peak around 2 hours prior the peak of testosterone, however, this diurnal variation is not seen for those administered exogenous testosterone [378].

Confirmation of a relationship between sleep stages and testosterone has not yet been fully documented. Some studies relate a surge in testosterone with sleep onset, others relating it with REM sleep, still others report no relationship with any sleep stage [376, 379, 380]. One small study of 6 healthy males found vast interpersonal variability with regards to hormone pulsatility, with these pulses maintained for the individual over time [381]. One limitation with the correlations made between sleep stages and testosterone release is the differing sampling rate between the two parameters. Sleep studies are analysed on the basis of each 30-second block, each allocated a particular stage of sleep, which are dynamic and can change frequently around a basic regular pattern in a healthy adult. Blood samples were collected every 30 minutes in some protocols, during which time it is feasible that several sleep stages had occurred between samples. The closest blood sampling time interval to that of the 30 second sleep staging is that of 2.5 minutely. This study described testosterone increases as being tightly related to sleep stage, in that surges occurred 2.5 minutes prior, and up to 25 minutes after, sleep "deepened" but fails to describe which sleep stage, named in the conventional manner, this refers to, but may refer to NREM sleep in general [382].

Testosterone concentrations are at their peak at the beginning of the waking day, and fall as the day progresses [383]. To determine whether this is circadian or sleep stage dependent, several studies have misaligned sleep and circadian phase. One study allowed 7 minute sleep opportunities within every 20 minutes, which allowed for a normal sleep total duration over a 24 hour period. This study found that although the levels of testosterone remained the same as during continuous sleep, testosterone secretion was delayed, and was only exhibited by those who had REM sleep during the short sleep bout [384]. In another study, which

misaligned sleep periods so that sleep occurred during the day, testosterone was found to be highest after a full sleep period, whether that was during the day or night, and circadian effects were only marginal [385]. This concept of testosterone secretion being mediated by sleep is confirmed by studies relating reduced sleep efficiency, or reduced time spent asleep with reduced testosterone levels. In extreme cases, such as several days of sleep deprivation in military operations, androgen levels have been reported to fall as much as 70-90% [386]. Reduced testosterone levels have been associated with decrease in sleep efficiency, sleep duration, lower number of REM sleep episodes and altered REM sleep latency [387, 388], however, this finding is not consistent, with another study of healthy men with artificially reduced testosterone levels showing no change in REM duration or latency [227], suggesting a unidirectional relationship of sleep influencing testosterone. This relationship, however, is not consistent, with other authors finding no such association between sleep duration and testosterone levels [389]. At the other end of the spectrum, supraphysiological doses of exogenous testosterone have been shown to reduce sleep time, in the context of an increased severity of OSA [260].

Suggestion has been made there may also be a seasonal variation in testosterone levels. For example, 915 men living in Northern Norway, exposed to extremes of light and dark across the year, were found to have peak testosterone levels in the winter and nadir in the summer, with a range of 31% difference between them [390]. The same authors then studied a group of men living in California, who are not exposed to such extremes of light and dark, and found no such relationship [391]. A large (n=11,000) study in the south-west of United States of America, which also lacks light extremes, categorized blood samples in a mens health practice by month

and season, and found seasonal variation in oestradiol, follicular stimulating hormone, and sex hormone binding globule, but not testosterone [392]. A recent review, however, was unable to confirm or deny this relationship, given the vast amount of variables unaccounted for [393].

1.4.2. OSA and Testosterone

Potentially, there is a bidirectional relationship between testosterone and OSA – namely sleep disordered breathing may reduce levels of testosterone and supraphysiologically high levels of testosterone may increase sleep disordered breathing. Many symptoms of OSA and reduced testosterone overlap, including low sexual desire, erectile dysfunction, mood disturbance and lack of energy. A marked preponderance for males to develop obstructive sleep apnoea over females is suggestive of a hormonal, namely testosterone, influence in the pathogenesis of this condition.

An independent association between the presence of OSA and a reduced level of total testosterone has been previously shown by several authors [384, 389, 394-396]. Compared with snorers, those with OSA as measured via exhaled CO2 and pulse oximetry, were found to have reduced levels of testosterone [389]. Similarly, reduced levels of testosterone were found in a sleep clinic sample of those who had AHI greater than 5 compared with those with an AHI less than 5, even after excluding those with diabetes, previous ED treatment, abnormal hormonal status and endocrine disturbance, however, the level of testosterone did not differ between those diagnosed with mild, moderate or severe OSA based on AHI [396]. Additionally, although age did not differ between the two groups, those with an AHI greater than 5 had a

higher BMI (32 vs 28), and since increased weight is known to reduce testosterone [157], this result should be interpreted with caution.

A reduction in testosterone due to OSA may be due to a several factors. A proposed mechanism for this relationship is the interruption to normal sleep related endocrine processes, namely the pulsatility of luteinizing hormone and subsequent testosterone release [384]. Indeed repeated measurement of testosterone during sleep via frequent sampling (every 20 minutes) found a relationship between the degree of sleep apnoea in terms of AHI and reduced bioavailable but not total testosterone, however this association was lost after adjusting for age [387]. Sleep efficiency, was however, positively associated with circulating testosterone [387]. The frequent interruptions to sleep by OSA, may lead to a subsequent reduction in overall sleep time obtained, which, as several authors have established, reduces testosterone levels [385, 397].

Alternately, the repetitive oxygen desaturation and resaturation which occurs due to repetitive apnoeic events may be a contributing factor. This frequent intermittent hypoxia has been associated with reduced serum testosterone [389], whereas other physiological measurements associated with OSA, such as frequency of respiratory events or their associated arousals have not shown any such association [389, 394]. Stratification of OSA severity by minimum saturated oxygen levels showed a lower level of testosterone with those who desaturated to a lower level, an association which remained after adjusting for age and obesity [398].

Many men with OSA will unfortunately remain untreated due to difficulties with current treatment modalities. Adherence with the most effective treatment for OSA, CPAP, is poor,

with estimated non-adherence rates of between 46-83 percent [352]. These untreated men, as well as those yet to be diagnosed, will continue to exhibit symptoms and be at risk of the cardiovascular consequences of OSA. Unfortunately, many symptoms of OSA are also common to androgen deficiency – fatigue, low mood, poor concentration and erectile difficulties, which may lead to treatment directed toward restoring androgen levels without addressing underlying sleep apnoea.

1.4.3. OSA and Sexual Desire

The original mention in the scientific literature of sexual problems being present in those with OSA is in Guilleminault's paper describing 25 OSA cases in 1977 [342]. This paper refers to 48% of men having "sexual problems" namely "impotence" and proceeds to discuss this in terms of a reduction in both erectile function and sexual drive, which can create confusion for the modern reader.

Some studies in the literature state that low sexual desire is a symptom of obstructive sleep apnoea, a fact assumed to be so well-known that no reference is given [399, 400]. Many other papers refer to Guilleminault's paper as the proof that men with OSA have low sexual desire [57, 401-404], however, there is a paucity of modern research utilising best practice techniques, such as using validated measurement techniques and control groups to confirm this relationship (**see Table 1.1**).

Studies which have looked at the link between OSA and sexual desire have been small and with mixed results. In one survey study, which included only those men with partners, questionnaire data was used to classify men into either mild, moderate or heavy snorers, and found no

difference between these groups in terms of sexual desire [405]. In a study of men having polysomnography for suspected OSA, no difference was found in regards to desire for tenderness, intercourse or masturbation between those who did and did not have OSA, however those whom had severe OSA (AHI>30) reported less masturbation than those in the no, mild and moderate OSA groups [406]. Age was, however, found to be associated with a reduction in desire [406]. In a study in which data was stratified by age, only in the age group of 40-49 years was there a difference in sexual drive between OSA and controls [407]. In a study using questionnaire data to determine the presence of OSA, the group was divided into those with low and regular sexual desire, and the group of low sexual desire were found to have a greater likelihood of OSA than those in the regular sexual desire group [221]. Studies using the Golombok Rust Inventory of Sexual Satisfaction questionnaire found that in the domain closest to that of sexual desire, 'nonsensuality', no difference was found between those with OSA and a control group, or between groups of no, mild, moderate and severe OSA [396, 408]. Only one study has reported a relationship between the severity of OSA, in terms of lowest recorded nocturnal SaO2 with a reduction of sexual desire [409]. In this study, there was a trend toward a relationship with AHI ($p=0.062$) and mean SaO2 ($p=0.062$) when data was stratified into quartiles [409]. One major symptom of OSA, sleepiness, may in theory affect sexual desire. In a study of 176 men with OSA, 69% of participants reported reduced sexual desire due to sleepiness, as measured in the FOSQ Intimacy and Sexual Relationships domain; however no control group exists to compare this result [410]. Survey data in the US in 2008 (National Sleep Foundation Poll) investigating this relationship found that 20% of people surveyed have sex less often or have lost interest in sex because they are too sleepy [411].

Clinical trials of treatment for OSA provide an insight into the effect of OSA upon sexual desire. In a small study (n=12), men who had undergone surgery for OSA (uvulopalatopharyngoplasty), those who reported low sexual desire pre-surgery via interview, reported improvements to normal levels 3 months post-surgery [389]. The results from this study are limited since it was uncontrolled, and had no numerical validated measurement of sexual function. In a larger study (n=83) of men prescribed CPAP, those whom adhered to therapy over 3 years (n=56) had improved sexual desire, as measured by the IIEF questionnaire, compared to those men whom did not use CPAP as recommended [412]. This may have been due to the decline in sexual desire in those whom did not use CPAP, but also, those who chose to continue with CPAP may have done so because have received a greater treatment effect. In a separate study comparing CPAP with a mandibular advancement splint, no improvement from baseline for either treatment was found in any facets of sexuality other than ED after usage for 2-3 months [408].

The hypoxia experienced by those with OSA may influence levels of sexual desire. In mice models, chronic intermittent hypoxia of reduction of oxygen in the air from 21% to 7% for 6 minutely intervals, leading to a minimum blood oxygen level of 76%, reduced the number of sexual behaviours, although there was notable individual differences between mice [413].

Table 1.1 Studies investigating OSA and sexual desire relationship

Author	N	Age (years)	Desire Measure	OSA Measure	Results	Comments
Guilleminault (1977) [342]	25	44 (25-65)	Self-report	PSG	48% reported 'impotence'	Terminology: "sexual problems", "impotence" and "abatement of sexual drive" used interchangeably.
Hoekema (2007)[408]	96	OSA: 49±9 (n=48) Control: 48±8 (n=48)	GRISS	PSG	No difference in non-sensuality between OSA and controls	Treatment with either CPAP or MAS did not improve non-sensuality scores
Hanak (2008) [405]	827	64 (51-90)	BSFI	Questionnaire	No difference in sexual desire between non-snorers, moderate snorers or heavy snorers	Only men with partners included in the study. Older age group.
Stannek (2009) [406]	158	OSA: 51±11 (n=131) Control: 47±14 (n=27)	MMAS	PSG	No difference in sexual desire between OSA and control.	No difference in sexual desire between OSA severity categories. Age reduced sexual desire.
Budweiser (2009) [409]	401	No ED: 50 (42,55) ED: 62 (54,70)	IIEF-15	PSG	No difference in sexual desire between OSA and controls	No differences between OSA severity categories.
Petersen (2010) [407]	308	51 ± 10	BSFI	Limited PSG (no EEG)	No difference in sexual desire between OSA and controls for ages 30-39, 50-69 Only at age 40-49 years showed OSA less desire than controls *	No correlation with severity of OSA

(Continued over)

Table 1.1 Studies investigating OSA and sexual desire relationship (continued)

Author	N	Age (years)	Desire Measure	OSA Measure	Results	Comments
Reishtein (2010) [410]	123	46 ± 8	FOSQ	PSG	69% reported reduced desire	No differences between OSA severity categories. CPAP treatment improved number of men with reduced desire compared to baseline (69% to 40%) **
Martin (2012) [221]	1195	35-80	Sexual Desire inventory	Maislin Questionnaire	The probability of having OSA increased risk of low sexual desire.*	13.5% of all men had low dyadic desire 68% of all men had low solitary desire.
Ak (2013) [396]	85	38 ± 8	GRISS	PSG	No difference in non-sensuality between OSA and controls	No differences between OSA severity categories.

Note: *p<0.05, **p<0.01, Age data are mean ± SD, mean (range), median (25th, 75th) or range. Abbreviations: BSFI = Brief Male Sexual Functioning Inventory, ED = Erectile Dysfunction, FOSQ = Functional Outcomes of Sleep Questionnaire, GRISS = Golombok Rust inventory of sexual function questionnaire, IIEF = International Index of Erectile Function, MMAS = Massachusetts Male Aging Study questionnaire, N=number of study participants, OSA = Obstructive Sleep Apnoea, PSG = Polysomnography.

1.4.4. OSA and Erectile Function

Many authors have interpreted Guilleminault's original 1977 paper as being 48% of the 25 men with OSA (n=12) had erectile dysfunction [342, 414-417]. Guilleminault further stated in a later article which reported the success of tracheostomy as a treatment for sleep apnoea, that 44% had erectile or ejaculatory difficulties, while 4% had impotence [418]. Some early case reports in the early 1980's of men with OSA also state that these patients had erectile dysfunction [419, 420]. In more recent times, there has however, been uncertainty regarding this link. Prevalence studies have been conducted in patients presenting in general populations (see **table 1.2**), ED clinics (see **table 1.3**), and sleep clinics (see **table 1.4)**, with differing results.

One early study on 70 healthy older men (aged 45-74), recruited via media advertisement, came to the conclusion there was no link between erectile dysfunction and sleep disordered breathing [421]. This study however, used inadequate techniques to establish the presence of OSA, such as the use of a single measurement of breathing via a thermister – now known to have significant limitations – and no measurement of oxygen saturation levels. Later research found this latter measurement relevant, in that oxygen saturation parameters were to be strongly correlated with erectile dysfunction [409, 414, 422]. In another study of healthy community based men, there was no association found between no, mild, moderate and heavy snoring and either erectile function or sexual desire. Although snoring is not indicative of the degree of apnoea, the authors however did find that heavy snorers tended to have reduced sexual satisfaction compared to the non- and mild snorers [405]. A study of 3,363 defense force personnel found an association between sleep quality and sexual function, including

when data was adjusted for known risk factors of OSA and ED [423]. This correlation, however, was not specific to OSA, rather sleep disorders in general, suggesting that other factors causing sleepiness may also be a contributor to sexual dysfunction. Although questionnaire based determinants of both erectile function and sleep disorders provide limited evidence, they contribute to the overall understanding of the association.

The risk of developing ED in the context of OSA was determined in a recent large population study of 467 men in the city of Sao Paulo, Brazil. For those men with an AHI of greater than 15, the odds ratio of having ED was 2.75 times that of men who had an AHI of less than 15. Similarly, for men who exhibited both an AHI of greater than 15 and symptoms of OSA, this risk is 2.12 that of men without the OSA syndrome [57].

Patients presenting with ED to sexual health clinics, urologists, and other related services, have been studied in relation to OSA. As recently as 1999, however, a comprehensive review of the current literature regarding pathophysiology of ED did not list OSA as a risk factor, or mention it in any context [50]. At around this time, ED was sometimes investigated using nocturnal penile tumescence measurement during sleep in order to determine if ED was due to a physiological or psychological problem [101]. A clinic in Florida performed only 37 such overnight studies over 5 years (1990-1995) and found that 60-70% of men had an AHI of greater than 5 [424]. This may not be representative of prevalence rates since this convenience sample of an erectile dysfunction clinic population, which may have advanced age, higher prevalence of diabetes and other risk factors common to both conditions. Consecutive patients who presented at a urology clinic were administered a Berlin questionnaire regarding symptoms of sleep disorders. Of

these 285 men, 27% were considered to have a high risk for OSA. Initial univariate analysis suggested snoring as being correlated with ED, however, once age and pre-existing medical conditions were added to the analysis, there was no longer a correlation [416].

In men presenting to a sleep clinic, subjective sleepiness, a common symptom of OSA, as assessed by the Epworth Sleepiness Score (ESS), was shown to be positively correlated with ED severity on the IIEF questionnaire [425]. A study using a limited channel PSG (no EEG), and a single questionnaire in 98 men with OSA, found 25% had ED, however, there were no correlations between ED and OSA severities [426]. Men undergoing full polysomnographic evaluation in sleep clinics have also been assessed regarding sexual function using a variety of subjective questionnaires. Using an abridged form of the IIEF to evaluate erectile function, of those 209 men with an RDI greater than 5, the occurrence of ED was higher than those with an RDI of less than 5 [427], however, when this group of patients was stratified on the basis of severity of OSA, only those with severe OSA (RDI >40) were found to have ED [427]. This study was performed using a thermistor to quantify sleep apnoea, now known to underestimate the degree of sleep disordered breathing [428]. In a similar study of 85 snoring men being assessed at a sleep clinic, no difference was found regards erectile function, as measured by the GRISS questionnaire between those with an AHI above and below 5, however, this study excluded all participants with previous history of diabetes, endocrine disturbance and hormonal imbalance which may have diluted the outcome [396]. This study did not describe the method used to assess sleep or breathing, apart from having a sleep test, which limits interpretation.

In order to firmly establish the link between OSA and ED, both best practice measurement and research techniques needed to be utilized, while accounting for known risk factors. The gold standard method of diagnosing obstructive sleep apnoea is a multiple channel nocturnal polysomnograph [429], using pressure transduced airflow [282, 428]. The International Index of Erectile Function questionnaire has been established as being one of the most robust measurements of ED [89, 90, 430]. The most thorough research methodologies would utilize both of these measurements. To date, there have been three such studies. Budweiser (2009) studied patients attending a sleep clinic for suspected OSA. In men with at least mild obstructive sleep apnoea with an AHI of greater than 5, 65% reported at least mild ED as measured by the erectile function domain of the IIEF questionnaire, compared to 34% of men without OSA. This higher prevalence remained even after the comorbidities of obesity, diabetes, hypertension and age were accounted for [409]. Similarly, 44% of patients presenting to a sleep clinic were found to have ED, also measured via the IIEF as well as NPT [431]. In the largest study done to date (n=1025) in men with erectile complaints, 44% of them were found to have at least mild obstructive sleep apnoea (AHI>5) as measured via polysomnography [415]. In contrast, in a recent study of 62 men, although 64% of men with OSA were found to have ED, there was no difference in prevalence of ED between those with and without OSA once BMI and age was accounted for [432]. These high quality studies suggest there is a high association between OSA and ED, although obesity and age may be contributing factors.

A potential explanation of the association between OSA and ED is that of disruption of REM sleep caused by OSA reducing the quality of sleep related erections, which normally occur during each REM sleep period [30]. These episodes of penile blood engorgement increase

corporeal oxygenation and may function to protect the morphological integrity of the penis [30, 31]. The first study to report impaired NPT with patients with OSA was in 1981 [433]. This study found that half of patients with apnoea or hypoventilation (n=7) showed impaired NPT [433]. Likewise, on review in 1986 of 31 patients being investigated for ED with NPT, 10 of these patients had sleep apnoea, resulting in disturbed nocturnal erections. The conclusion of this study was that full sleep studies should be performed in conjunction with NPT to ensure that there is not an incorrect diagnosis of an abnormal NPT, rather than commenting on a potential causal pathway [434]. In the same year, another clinic found that the addition of respiratory channels facilitated the diagnosis of sleep apnoea, in that 5 of 30 patients had OSA [435]. As recently as 1994, the accuracy of NPT monitoring was said to be reduced, indeed "erroneous", when sleep disturbances such as apnoea are present, rather than a potential cause of erectile dysfunction [436]. One of the first studies to report a link between the two was in 1989, when a small correlation was found between apnoea index and penile rigidity in a study of 285 patients [437]. In contrast, a study performed around the same time, which did not monitor oxygen levels, found no association between NPT results and AHI [421]. However, this lack of oxygen monitoring severely limits both the accuracy of the measurement of OSA. In a later observational study of the effects of CPAP treatment, of 22 patients with ED symptoms and OSA, 15 (68%) had abnormal NPT readings [438]. Although this study does not have a control group with which to compare frequency of impaired NPT, the presence of 7 men who had both OSA and ED who did not have an impaired NPT, suggests there may be other contributing factors to this relationship. A more recent study found that morning erection, assessed

subjectively, was the characteristic of sleep related erections most affected by the severity of OSA, as measured by PSG [427].

In a review of literature current at the time (2003), data was suggestive of a link between OSA & ED, suggestion was made that research into direct correlations between severity of each was required, once common risk factors had been removed [439]. Several studies have since investigated which parameters of OSA have the most positive correlation with ED. Although a higher incidence of ED in men with OSA was reported, three studies have been unable to identify any measured OSA parameter to be correlated with ED severity [406-408]. This may be due to patient selection including those OSA but without ED, making correlative findings difficult. In contrast, several more studies have found correlates. Studies using NPT have reported that OSA severity was associated with ED aetiology, with the mean AHI significantly higher in those with organic compared to psychogenic ED [407, 415, 433]. Margel et al (2004) reported that in their OSA sample the respiratory disturbance index (RDI), but not the number of oxygen desaturations, predicted ED as measured by the abridged IIEF [427]. Additionally, morning tiredness has also been identified as a predictor of ED [427]. The majority of studies however, report the highest indicator has been those variables associated with nocturnal saturation. The minimum observed SaO2 overnight was found to be correlated with ED prevalence in one study, while in another, a minimum SaO2 of less than 77% was found to be highly predictive of ED [414, 422]. In a study of 401 men, categories of OSA severity based on quartiles of mean (<91%, >91-93%, >93-94%, and >94%) and minimum (≤74%, >74-81%, >81-85% and >85%) oxygen saturation correlated with the severity of ED, however no such correlation was found with AHI [409]. Several studies have found minimum nocturnal SaO_2

levels to be strongly correlated with ED incidence rates [409, 414, 422]. Furthermore, a recent study identified that mean nocturnal SaO_2 levels independently predicted ED [409]. The theory of intermittent hypoxia causing ED has been tested in mice models, by adjusting oxygen levels in the air, leading to 10 hypoxic episodes per hour to a minimum of 76%. This study found that intermittent hypoxia reduced the number of spontaneous erections by 55%, without change in testosterone levels, in mice, [413]. One suggested mechanism is that the repeated hypoxia of OSA may have an impact on endothelial function, which translates into a reduced ability to transport sufficient blood for erections [417]. Alternatively, another author suggests the hypoxia of OSA is associated in nerve dysfunction, thereby affecting erectile capacity [404]. Another theory is that hypoxia reduced testosterone levels, thereby impacting on erectile function [440].

The relationship between low oxygen levels and gonadal dysfunction was reported more than 50 years ago after Sir Edmond Hillary's expedition to the Himalayas, although the exact meaning of dysfunction is unclear [441]. A recently case study reported a mountaineer in Nepal monitoring his nocturnal erections for 42 consecutive nights via Rigiscan measurement found a decline in erection duration and tumescence with ascent to higher altitude with lower atmospheric oxygen [442]. Given the preservation of REM sleep at altitude, unlike that of slow wave sleep, [443] this is more likely to be due to the reduction in the partial pressure of oxygen at altitude and thus overnight oxygen saturation levels.

There is some evidence that those with respiratory failure have an impaired hypothalamic-pituitary function which may lead to erectile dysfunction [444, 445]. Nocturnal penile

tumescent monitoring of a small group (n=20) of men with chronic obstructive pulmonary disease found a relationship between erectile function and pulmonary impairment [446]. The influence of testosterone differed in these studies, with one finding no difference in those with and without erectile function [446], while another did [447]. Oxygen treatment in these patients has been shown to improve erectile function in some cases. In a group of 12 men with chronic obstructive respiratory disease and erectile dysfunction, who received oxygen therapy for one month, 5 of these men (42%) regained erectile function, defined as a reappearance of a morning erection. Both testosterone and PaO2 was higher in these patients than in those who did not respond to therapy. A single 24 hour period was insufficient to improve erectile function in these patients, suggesting longer term therapy is required for effective treatment [448]. The effects of oxygen therapy in patients with ED but without respiratory disease have not been investigated [444].

Overall, the literature, though limited by studies being conducted in varying populations, using different outcome measurement tools, and often in small study populations, suggests an association between ED and OSA, with reduced oxygen levels being one of more likely explanatory variables. Potential other variables include a reduction of testosterone, due to sleep disruption and hypoxia, depression, and a disruption to sleep related erections, as schematically described in **figure 1.1**.

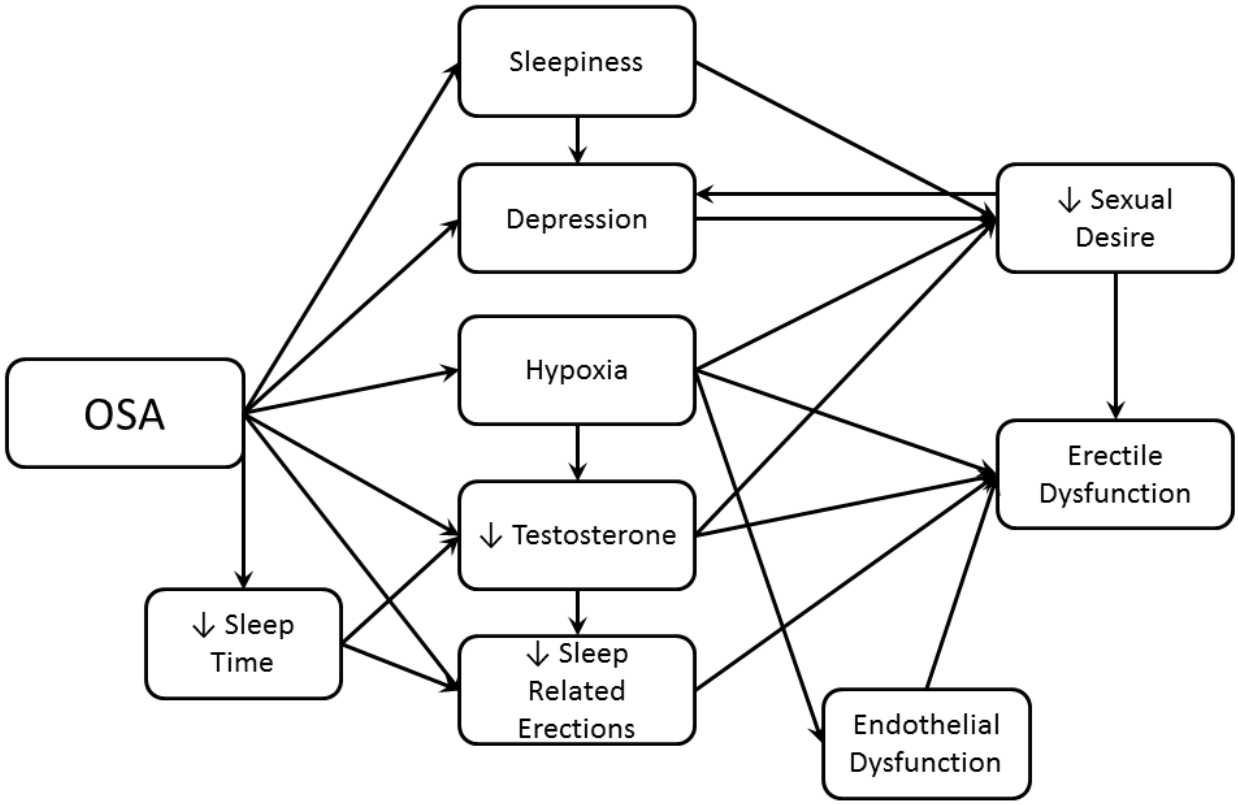


Figure 1.1 Potential mechanisms between OSA, ED and low sexual desire

Table 1.2 Population studies investigating OSA and ED relationship

Author	N	Age (years)	ED Measure	OSA Measure	Results
Schiavi (1991) [421]	70	Range: 45 - 75	NPT & psychosexual interview	Partial PSG (no SaO2 or respiratory effort)	No correlation between sleep disordered breathing parameters and NPT/sexual function parameters once age was accounted for.
Heruti (2005) [423]	3363	36 ± 7 (mean ± SD)	IIEF-5	Sleep Quality questionnaire	Correlation between IIEF-5 and SQ (r=-0.21, p<0.00001) after adjusting for age and excluding men with HT, diabetes & obesity. Sleep quality questionnaire not specific to sleep apnoea.
Hanak (2008) [405]	827	64 (51,90) median (25^{th}, 75^{th} percentiles)	BMSFI	Snoring Questionnaire	Heavy snorers twice as likely to have lower sexual satisfaction compared to mild/non-snorers, after adjustment for potential confounders. No association between degree of snoring and erectile function.
Andersen (2010) [57]	467	Range: 20-80	MMAS single question	PSG	Odds ratio 2.75 of having ED if OSA (AHI>15) compared to no OSA (AHI<5) (p=0.0001) Odds ratio 2.19 of having ED if OSA (AHI>15) & sleepiness if have ED compared to no OSA (AHI<5) (p=0.003)

AHI = Apnoea Hypopnoea Index, BMSFI=Brief Male Sexual Functioning Inventory, ED = Erectile Dysfunction, HT=hypertension, IIEF-5 = The 5-item International Index of Erectile Function, MMAS = Massachusetts Male Aging Study, N=number of study participants,NPT = Nocturnal Penile Tumescence, OSA=Obstructive sleep apnoea, PSG = polysomnography, SD=Standard deviation,

Table 1.3 Studies investigating prevalence of OSA in ED populations

Author	N	Study population	Age (years) (mean ± SD)	ED Measure	OSA definition	OSA Measure	Prevalence of OSA (%)	Comments
Pressman (1986) [434]	31	NPT clinic	58 ± 6.8	NPT	AHI ≥ 5	Limited PSG	32	Reviewed 31 men undergoing NPT. 9 had OSA. Concluded OSA disrupted NPT recording, if OSA exists, it may give a false reading on NPT.
Foreman (1986) [435]	30	NPT clinic: Both for ED and painful erections	NR	NPT	NR	Limited PSG	17	5 of 30 patients had sleep apnoea. Case reports of these 5 patients presented. AI range: 10-89
Hirshkowitz (1990) [415]	1025	NPT clinic	54 (NR)	NPT	AI ≥ 5 AI ≥ 10 AI ≥ 15	Limited PSG	44 28 20	AI was 10.5 for men with "organic" ED, and 8.3 for men with "non-organic" ED
Chediak (1996) [424]	37	NPT clinic	52 ± 14	NPT	AHI > 10 AHI > 5	PSG	49 57 then 70	Result consistent across 2 nights 1st night then 2nd night
Seftel (2002) [416]	285	Urology clinic	53 ± 13	Physician diagnosed	NR	Cleveland Sleep Habits questionnaire	27 (at high risk of OSA)	63% of sample had ED (n=168) 57% of sample snored

Abbreviations: AI=Apnoea Index, AHI = apnoea hypopnoea index, ED = Erectile Dysfunction, ESS = Epworth Sleepiness Scale, , scale, IIEF= international index of erectile function, OSA = obstructive sleep apnoea, N=number of study participants, NPT = nocturnal penile tumescence, NR=Not reported, PSG = Polysomnography.

Table 1.4 Studies investigating prevalence of ED in sleep clinic populations

Author	N	OSA definition	Age (years)	ED Measure	OSA Measure	Prevalence of ED (%)	Comments
Guilleminault (1977) [342]	25	NR	44 (25-65)	Self-report	PSG	48	Terminology: "sexual problems", "impotence" and "abatement of sexual drive" used interchangeably. Case report series.
Guilleminault (1981) [418]	49	NR	47 (12-66)	Self-report	PSG	44	4% had "impotence" 44% had "erectile or ejaculatory difficulties"
Fanfulla (2000) [404]	25	AHI>10	48 ± 12	Self-report	PSG	72 (any ED) 44 (severe ED)	Study assessed bulbocavernosus reflex and somato-sensory evoked potentials of pudendal nerve in assessing possible involvement in cause of ED. Concluded nerve dysfunction may be involved in association between OSA & ED.
Margel (2004) [427]	209	AHI 5-20 (n=80) AHI 20-40 (n=60) AHI>40 (n=46) AHI<5 (n=23)	44 ± 12 44 ± 12 50 ± 10 50 ± 8	IIEF-5	PSG (no oximetry)	79 (any ED)	All aspects of erectile function declined with increased OSA severity*. Severe OSA (AHI>40) had increased ED compared to all other groups*. Those with severe ED had the greatest AHI.
Goncalves (2005) [414]	98	AHI>10	47 ± 10	Sexologist Interview	PSG	29	MVA: $MinSaO_2$* and age* not AHI, BMI or SaO_2 predicted ED. $MinSaO_2$>80%: 15% with ED $MinSaO_2$≤80%: 40% with ED. Different between groups**.
Hoekema (2007) [408]	96	AHI>5 (n=48) ND (controls, n=48)	49 ± 9 48 ± 8	GRISS	PSG	NR	More ED* in OSA than controls. Correlation between AHI and nonsensuality score of the GRISS (r=0.311)*

(Continued over)

Table 1.4: Studies investigating prevalence of ED in sleep clinic populations (continued)

Author	N	OSA definition	Age (years)	ED Measure	OSA Measure	Prevalence of ED (%)	Comments
Budweiser (2009)[409]	401	AHI>5 (n=369) AHI<5 (controls, n=32)	62 (54, 70) (ED) 50 (42, 55) (No ED)	IIEF-15	PSG (23% had "split night")	66 (any) 30 (severe)	34% of controls had ED. Different to OSA group**. Erectile function decreased with worsening quartiles of AHI**, Minimum SaO_2** and mean SaO_2** associated with ED: MeanSaO_2** predicted erectile function after adjustment for risk factors.
Zhuravlev (2009) [431]	72	NR	44 (32-56)	IIEF-5 & NPT	PSG	44	25% of those with OSA & ED had normal testosterone levels
Stannek (2009) [406]	158	AHI>5 (n=116) AHI<5 (controls,n=42)	51 ± 11 47 ± 14	Single IIEF question	PSG	NR	More frequent ED in OSA than controls* Severity of OSA not correlated to incidence of sexual dysfunction.
Petersen (2010) [407]	308 1185	AHI>5 ND (controls, collected separately)	51 ± 10	BMSFI & LiSat	PSG	NR	Erectile function worse in OSA compared to controls*. AHI not correlated with any outcomes.
Cruz (2012) [426]	98	AHI>20	55 ± 11	Single question	Limited PSG	25	No correlations or predictive parameters reported.
Santos (2012) [432]	62	AHI>5	52 (NR)	IIEF-5	PSG	64.4	After controlling for BMI & Age, no difference between those with and without OSA in terms of ED, sexual satisfaction
Ak (2013) [396]	85	AHI>5 (n=42) AHI<5 (controls, n=43)	38 ± 8	GRISS	NR : "sleep test"	NR	No difference in ED between apnoea and non-apnoea groups after controlling for age and BMI.

Note: *p<0.05, **p<0.01, Age data are mean ± SD, mean (range), median (25th, 75th). Abbreviations: AHI = Apnoea Hypopnoea Index, BMSFI = Brief Male Sexual Functioning Inventory, ED = Erectile Dysfunction, GRISS = Golombok Rust inventory of sexual function questionnaire, IIEF = International Index of Erectile Function, LiSat = Fugl-Meyer Life satisfaction checklist, N=number of study participants, ND=Not Described, NPT = Nocturnal Penile Tumescence, NR = Not reported, OSA = Obstructive Sleep Apnoea, PSG = Polysomnography, RDI = Respiratory Disturbance Index, SaO2 = Blood Oxygen Saturation, Split Night = ½ of night was diagnostic, other ½ was CPAP titration.

1.5. TREATMENT

Conservative treatments for both OSA and ED include modifications to lifestyle factors which may contribute to the severity of the condition, such as weight loss, smoking cessation and a reduction of alcohol intake. If these lifestyle changes are insufficient, several treatment options exist. Obstructive sleep apnoea can be treated using mechanical means such as continuous positive airway pressure (CPAP) or a mandibular advancement splint (MAS) or via surgery of the upper airway. Erectile dysfunction is often treated using pharmacotherapy, including PDE-5 inhibitors and androgen therapy. There is evidence that in the presence of both conditions, CPAP therapy may have positive effects on ED. Treatment of ED using pharmacotherapy, however, may have detrimental effects on the severity of OSA. Treating the two conditions simultaneously may be the optimal treatment choice.

1.5.1. Testosterone Therapy and OSA

There has been much discussion in the literature regarding the effects of testosterone treatment in untreated OSA due to the risk of increasing the severity of sleep disordered breathing. Worsening of sleep disordered breathing with exogenous testosterone was first described in a case report in 1983 [449], and further investigations later that decade finding a high degree of individual variability, with some men experiencing worsening, while others did not change [450, 451]. A case report on a 13 year old boy in 1994 similarly documented the phenomena [452]. At present, current guidelines recommend against using exogenous testosterone in men with untreated OSA [155, 453]. Two recent reviews investigated the evidence for these recommendations and found little to support such guidelines [454, 455].

The only exception noted is in the use of supraphysiological doses [260]. A recent study, using clinically appropriate doses, further investigated the relationship and showed an increase in the ODI in the short-term, which returned to normal levels in the longer term, with no change in AHI at any timepoint [456]. Several mechanisms have been posed as mediating factors between the exacerbation of OSA by testosterone supplementation. Testosterone may stimulate breathing directly at the level of the CNS or peripheral chemoreceptors, resulting in an increase in ventilator response to hypoxia, thereby reducing carbon dioxide levels below the apnoea threshold [457, 458]. Indeed, changes in serum testosterone due to androgen administration have been correlated with changes in the hyperoxic ventilatory recruitment threshold in men with OSA. These changes have been shown to have a time course similar to that seen during sleep, with a worsening of ventilatory drive correlating with serum testosterone levels [459]. In addition to affecting apnoeic thresholds, testosterone has also been shown to increase the collapsibility of the upper airway [310]. Both of these effects occurring simultaneously can explain a theoretical increase in the likelihood of sleep disordered breathing with increased levels of testosterone, however, apart from supraphysiological doses, this has not been substantiated.

1.5.2. PDE-5 Inhibitors and OSA

PDE-5 inhibitors allow blood flow to increase, enhancing the ability to obtain and maintain an erection. However, for those susceptible to sleep disordered breathing, this increase in blood flow creates a theoretical risk of an impaired airway size due to engorgement of upper airway tissues, a reduction of nasal patency and an increase in the tendency for relaxation of the soft

tissue in the pharyngeal muscles [460-462]. These factors thereby suggest a theoretical increased risk of OSA, or worsening thereof. Indeed, a randomised placebo-controlled study of 13 men with severe OSA showed a 50mg dose of Sildenafil prior to sleep increased the AHI, ODI, and amount of time hypoxic while asleep [463, 464]. This small study requires further investigation to determine if a lower dose of PDE-5 inhibitors is safe for those with OSA [465].

1.5.3. Effect of Treatment for OSA on Sexual Function

CPAP treatment for OSA has shown mixed results in regard to the effect on testosterone levels, however, as with all CPAP studies, adherence to therapy can be as low as less than 50%, which limits our understanding of the effect of CPAP on testosterone [352]. An early trial, only 8 years after CPAP was first described [466] showed that three months CPAP, total, but not free, testosterone increased [398]. This study was performed when the CPAP mask was glued on, rather than the current straps which are easily removed, which may have resulted in a high adherence rate, however this cannot be verified. Also showing an increase in testosterone was a study in which blood samples were taken every 20 minutes during sleep on men who had been treated with CPAP for nine months [467]. This increase was on the basis of mean testosterone levels and area under the curve of the frequent overnight sampling, rather than the more commonly used one-off morning sample. Men undergoing UPPP surgery to alleviate OSA have been shown to have an improvement in testosterone levels [389]. On the other hand, several studies have found treatment of OSA using CPAP did not raise levels of testosterone. In a study of men with low (<12 nmol/L) baseline testosterone, no improvement with CPAP was seen after three months [431]. However, in that study, the adherence to CPAP

therapy was not described, nor exploratory statistics of those men adherent to therapy reported. A single night of CPAP therapy was insufficient to improve testosterone levels of 28 men with OSA [468]. In a sham controlled study of 3 months duration, no change in testosterone was seen before and after CPAP use, however, there was a decline in testosterone for those allocated to placebo treatment, resulting in a difference between groups [469]. A study of patients for whom CPAP therapy was documented as being more than 5 hours usage per night for 11-36 months also did not show an increase in testosterone levels [470]. Likewise, no change in testosterone levels was found in a study of 16 men after 6-10 months of CPAP therapy [471]. Similarly a study comparing the efficacy of CPAP and Mandibular Advancement Splints found that neither increased testosterone levels [408]. The majority of these studies do not show an increase in total testosterone, with the exception of that seen in frequent overnight sampling and those with potentially higher efficacy of therapy, that is, surgery or higher adherence with therapy.

Studies of the effect of CPAP on erectile function have been performed in general OSA populations, as well as in men with OSA and ED, the distinction of which should be noted (see **table 1.5**). A recent review, using theoretical mechanisms together with observational and uncontrolled studies concluded that CPAP therapy for OSA improves ED [30]. These studies have used objective measures such as nocturnal erection monitoring, or subjective measurement, or a combination of the two.

One of the first studies to report on the effect of CPAP treatment upon erectile function used mercury strain gauges to monitor sleep related erections. Of the 22 OSA patients presenting

with ED, 15 had impaired NPT recordings on a night without CPAP, defined as penile rigidity less than 500 grams and a tip circumference change of less than 16 millimeters. Overall, there was no change in NPT parameters with one night of CPAP. There were five individuals who no longer had an impaired reading when CPAP was used [438]. However, there was still a moderate degree of OSA (RDI 18/hour) despite CPAP treatment. Potentially, a more effective CPAP treatment may have further improved erectile function. Due to the small observational nature of this study, interpretation of this result is limited. Additionally, considerable night-to-night variability in NPT recordings have been reported [472], which may go some way in accounting for the change in NPT, rather than the treatment used. In the only other study assessing the impact of CPAP on nocturnal erections, three months of treatment which included participants using CPAP or who had undergone surgery, only the change in percentage rigidity was reported, which showed an improvement from 13.8% to 40% for rigidity greater than 80% [354]. Commonly cited measurements of the Rigiscan device, such as duration, rigidity activation units and tumescence activation units were not reported in this study, however.

Several within-individual, before and after studies have also shown improvements in sexual function with 2 weeks to 12 months of CPAP therapy [410, 414, 438, 473-475]. Improvements in the FOSQ Intimacy and Sexual Relationships domain, as well as its component parts, that is, the effect of sleepiness on desire, intimacy, arousal and orgasm, were seen with CPAP use for a minimum of 3 months in all OSA patients (n=123) studied. When stratified by AHI severity, only those with AHI greater than 60 had significant improvement [410]. In a study assessing the efficacy of a hypnotic medication in relation to CPAP adherence, there was an overall

improvement in the domain of intimacy in the FOSQ questionnaire after 2 weeks of CPAP use in 72 men with OSA, not selected on the basis of ED [476], however, a much larger randomised control trial of 113 men and women with mild to moderate OSA (AHI 5-30) did not show any improvement in this domain after 8 weeks of CPAP treatment [366]. Another study of 17 men with OSA and ED found that ED resolved after one month of CPAP in 13 subjects; however ED assessment was by sexologist interview and not a validated instrument [414]. Using the IIEF questionnaire, a study in a group of 15 men with OSA and ED also found improvements in erectile function after 3 months of CPAP [473]. In contrast, one study, which included diabetic men with and without ED did not find an improvement in erectile function after 3 months of CPAP usage, a result which may be influenced by the presence of diabetes, a condition known to worsen erectile function [477, 478]. Limitations to these studies, however, include having a small number of participants, a lack of placebo control and being of short duration.

Longer term (6-12 months) uncontrolled studies of men with OSA also show improvement in erectile function with continued CPAP treatment, at least in those with severe OSA [479, 480]. In a study of 98 OSA patients, 25 had symptoms of ED, assessed clinically. Of these, one in three men had resolution of their ED with 6 months of automatic CPAP (APAP) use however this was not statistically significant [426]. In a study of 209 men with OSA, which included those with and without ED, erectile function improved after 12 months of CPAP treatment in 20% of subjects, and this improvement was positively correlated with CPAP compliance, baseline AHI and minimum oxygen saturation [479]. One year of adherent CPAP treatment (usage > 4 hours) in 147 men, again with and without ED, improved scores in erectile function, and sexual drive, as measured by the BSFI, however this result comprised 50% no change, 13% scored worse, and

37% had improved [474]. One longer term (3 year) study found that in men with OSA, who were prescribed CPAP, of which 61% had ED, erectile function declined overall. This was due to a poor adherence rate to CPAP (38% did not use CPAP), and those men who did not use CPAP had a decline in erectile function, compared to those who used CPAP having no change overall, suggesting that CPAP prevented a decline in erectile function. In the subset of patients who had moderate-severe ED, there was a very slight improvement in erectile function with CPAP. Although there was minimal effects on erectile function, this study did show that CPAP users, compared to non-users showed a significant increase in overall sexual function as measured by the IIEF, as well as individual subdomains 'orgasmic function' and 'overall satisfaction' [412].

Prospective studies of CPAP treatment have shown mixed results. A small (n=27) randomised no-treatment controlled study showed a significant improvement in ED after one month of CPAP despite a significant residual OSA (AHI = 29) persisting in those randomised to CPAP therapy [481]. The lack of an adequate placebo, however, does not allow for the patient to be blinded to therapy and limits the interpretation of this result. Another one month prospective randomised study of CPAP therapy, using an unnamed selective serotonin reuptake inhibitor antidepressant, as a control, found that CPAP therapy in those with severe sleep apnoea was sufficient to increase IIEF scores from 15 to 19, compared with a change from 13 to 14 with the antidepressant, however, the significance of this difference was not reported [417]. Given that some anti-depressants are known to cause or worsen erectile dysfunction [482], this comparison group makes interpretation difficult. No change in erectile function was seen in another study of one month duration which compared the effect of CPAP against mandibular advancement by oral splint in a crossover design, however, this study did not assess ED by IIEF,

and included men with and without ED [408]. In a study using either CPAP, mandibular advancement splint, or surgery (uvulopalatopharyngoplasty), as selected by the patient, only those who had surgery were found to have improvements in the Korean version of the IIEF, however surgery improved but did not resolve OSA (AHI at baseline 29.6±21.6, at follow up 18.5±15.6, p=0.027) [483]. Similarly, a study using CPAP, and surgery of varying types for those not adherent to therapy, in men with OSA and ED, found an overall improvement in both subjective (IIEF) and objective (Rigiscan) measurements of ED, however the improvements per treatment were not reported [354].

Two randomised studies of CPAP and Sildenafil, in men with OSA and ED, have been reported by the same author [484, 485]. The first randomised 30 men to either Sildenafil on demand or CPAP use nightly for 12 weeks. All domains in the IIEF improved from baseline for both treatments. For those allocated to Sildenafil, the IIEF-ED domain improved by 5 points, 54% of intercourse attempts were successful, and 53% of participants satisfied with treatment. For those allocated to CPAP, the IIEF-ED domain improved by 2.3 points, 24% of intercourse attempts were successful, and 20% were satisfied with treatment. Differences between treatments at week 12 were reported, with all domains of the IIEF, except sexual desire, being higher with Sildenafil than with CPAP [484]. The second study of 40 men compared nightly CPAP use with Sildenafil, taken on demand, for 12 weeks [485]. This study reported 27% of intercourse attempts were successful with CPAP, compared to 51% with Sildenafil, which was statistically significant. Similarly, the IIEF-ED domain improved for both groups compared to baseline, with the scores for Sildenafil being higher than that of CPAP after 12 weeks. The degree of OSA in this study was mild, with an AHI of 9, which may limit the effects seen due to

CPAP. Neither of these studies reported CPAP adherence rates, which may limit the interpretation of these studies. Additionally, there was no placebo control, nor baseline measurement with which to compare successful intercourse attempts.

A randomised sham-controlled study showing that CPAP improves ED has yet to be performed. Sham-control is essential, because the primary outcome of therapy is self-reported [486], but none of the available studies are sham-controlled. Additionally, many of the studies in the current literature include men who do not have erectile dysfunction, which may or may not dilute the efficacy of CPAP on erectile dysfunction.

The effect of CPAP on sexual function is not widely acknowledged. Amidst a questionnaire regarding expected outcomes from CPAP usage, 53% of patients about to undergo CPAP therapy acknowledged that there may be an increase in sexual desire and performance. About two thirds of these same respondents recognized that there would be a positive effect from the use of CPAP in regards to feeling better, allowing their partner to sleep better, and have less chance of a motor vehicle accident among other factors [487].

Table 1.5 Trials investigating effects of OSA treatment on Erectile Dysfunction

Author	N	Population	Treatment	Study Design	AHI (events/h)	Duration	Erectile Function measure	Change in Erectile Function
Guillimenault (1981) [418]	50	OSA	Tracheostomy	Observation	81 (65-120)	9months -6years	Self-report	98% "sexual problems" disappeared
Karacan and Karatas (1995) [438]	22	OSA & ED	CPAP	Observation	49.2 ± 28	1 night	NPT	33% of those with previously abnormal NPT had normal NPT with CPAP
Li (2004) [481]	27	OSA & ED	CPAP (n=15) Control (n=12)	Randomised parallel, no treatment control	45 ± 11 42 ± 14	1 month	IIEF-5	↑* compared to controls (non-English text)
Perimenis (2004) [484]	30	Mild OSA & ED	CPAP (n=15) Sildenafil (n=15)	Randomised parallel	7.3 ± 1.2 7.4 ± 1.4	12 weeks	IIEF-5, SIA	Sildenafil was superior to CPAP **. Both numerically improved from baseline but p-value was not reported.
Goncalves (2005) [414]	17	OSA & ED	CPAP	Observation	71.4 ± 26.8	1 month	Sexologist Interview	ED resolved in 76%* (13 out of 17 patients). OSA parameters did not predict ED change

(Continued over)

Table 1.5: Trials investigating effects of OSA treatment on Erectile Dysfunction (continued)

Author	N	Population	Treatment	Study Design	Age	AHI (events/h)	Duration	Erectile Function measure	Change in Erectile Function
Margel (2005) [479]	60	OSA	CPAP	Observation	54 ± 10 (↔) 54 ± 11 (↑) 59 ± 10 (↓)	40.6 ± 18 .1 (↔) 53.7 ± 15.2 (↑) 38.4 ± 18.9 (↓)	17 months (range 12-26)	IIEF-5	62% no change 20% ↑(**from baseline) 18% ↓(**from baseline), UCA: ΔIIEF vs Baseline MinSaO2 (r=-0.37**), CPAP adherence (r=0.69*). ΔIIEF not correlated with RDI (NS).
Karkoulias (2007) [473]	15	Mild OSA & ED	CPAP	Observation	56 ± 4	7.3 ± 1.2	12 weeks	IIEF, SIA	↑ Erectile function improved * but sexual desire did not.
Hoekema (2007) [408]	48	OSA	CPAP (n=27) MAS (n=21)	Randomised parallel	51 ± 9 48 ± 8	46.7 (10-64.4) 20.6 (9.5-31.1)	2-3 months,	GRISS	↔CPAP, ↔MAS. Between-group NR
Perimenis (2007) [480]	48	OSA & ED & COPD	CPAP & bronchodilators	Observation	53 ± 10	28.3 ± 23.2	6 months	ED Intensity Score	↑** compared to baseline. Erectile function improved in 25% AHI greater in patients who ↑**. ΔIIEF positively correlated with age, AHI.

(Continued over)

Table 1.5: Trials investigating effects of OSA treatment on Erectile Dysfunction (continued)

Author	N	Population	Treatment	Study Design	AHI (events/h)	Duration	Erectile Function measure	Change in Erectile Function
Perimenis (2007) [488]	40	OSA & ED	CPAP (n=20) CPAP + Sildenafil (n=20)	Cross-over	56 ± 5	6 weeks each arm	SIA	SIA greater with Sildenafil than CPAP**.
Perimenis (2007) [485]	40	Mild OSA & ED	CPAP (n=20) Sildenafil (n=20)	Randomised parallel	8.9 (6–25) 9.9 (6–24)	12 weeks	IIEF, SIA	↑**CPAP, ↑**Sildenafil but Sildenafil was superior SIA greater with Sildenafil than CPAP**
Taskin (2010)[417]	40	Severe OSA (AHI>30)	CPAP (n=20) Anti-Depressant (n=20)	Randomised parallel	35 ± 19.3 33 ± 21.7	1 month	IIEF-5	↑**CPAP, ↔ (NS) antidepressant Stratifying by MinSaO2 of 80% did not show correlation with ΔIIEF.
Petersen (2012) [474]	146	OSA	CPAP (only >4hrs use included)	Observation	43.3 ± 26.3	12 months	LiSat, BMSFI	↑* Sexual life, erectile function, sexual desire all improved with CPAP overall but half unchanged, 37% improved, 13% scored lower.
Cruz (2012) [426]	98	OSA	Auto-PAP	Observation	52.2 ± 21.4	6 months	Likert scale	↔ in ED with AutoPAP overall (25% to 18%, NS) 12%↑ (NS from baseline) 5%↓ (NS from baseline)

(Continued over)

Table 1.5: Trials investigating effects of OSA treatment on Erectile Dysfunction (continued)

Author	N	Population	Treatment	Study Design	AHI (events/h)	Duration	Erectile Function measure	Change in Erectile Function
Khafagy (2012) [354]	80	OSA & ED	CPAP (n=57) Surgery (n=23)	Observation CPAP used <4hrs, surgery performed.	33.4 ± 1.7 37.0 ± 7.6	3 months	NPT + IIEF-5	Results combined for both treatments. ↑**. ED resolved in 22.5% (IIEF-5) ↑* Percentage rigidity (NPT) Commonly reported NPT parameters not reported. OSA not treated completely (AHI 12 & 14 for CPAP and surgery respectively)
Shin 2013 [483]	56	OSA	UPPP (n=30) CPAP (n=16) MAS (n=10)	Observation Patient preference determined treatment	29.6 ± 21.6 51.6 ± 17.1 29.3 ± 10.6	7 (4, 15) months	IIEF-5	↑UPPP (*from baseline) ↔CPAP (NS) ↔MAS (NS)
Budweiser (2013) [412]	91	OSA	CPAP users (any use, n=56) Non-CPAP users (n=35)	Observation	28.1 (18.0, 40.0) 14.7 (6.8, 23.7)	3 years	IIEF-15	↔CPAP users, ↓ non-users. Between-group NS. Sub-Analysis (1): No difference in those with moderate/severe ED. (2): CPAP↑* compared to non-users in those with both moderate-severe ED and mean nocturnal SaO_2<93%.

(Continued over)

Table 1.5: Trials investigating effects of OSA treatment on Erectile Dysfunction (continued)

Author	N	Population	Treatment	Study Design	AHI (events/h)	Duration	Erectile Function measure	Change in Erectile Function
Knapp (2014) [477]	35	OSA & Diabetes	CPAP	Observation	NR. Inclusion was AHI >15	3 months	SHIM ADAM	↔ in ED with CPAP. CPAP reduced number of androgen deficient symptoms (as measured by ADAM) but this was not sexual function.

Note: ↑denotes an improvement ↓denotes a worsening ↔ denotes no change. Data are mean ± standard deviation or mean (range). *p<0.05, **p<0.01. Δ=change Abbreviations: ADAM: Androgen Deficiency in the Aging Male questionnaire, AHI = Apnoea Hypopnea Index, CPAP = Continuous positive airway pressure, BMSFI = Brief Male Sexual Functioning Questionnaire, COPD = Chronic Obstructive Pulmonary Disease, ED = erectile dysfunction, EF=erectile function, IIEF = International index of erectile function, IIEF-5 = The 5-item International index of erectile function, GRISS = Golombok Rust inventory of sexual function, IIEF-15 = The 15-item International index of erectile function, LiSat11= Life satisfaction 11, MAS = mandibular advancement splint, NPT=Nocturnal Penile Tumescence, NR = not reported, NS = not significant, OSA = Obstructive Sleep Apnoea, RDI = Respiratory Disturbance Index, SaO_2 =oxygen saturation levels, SHIM = Sexual Health Inventory for Men questionnaire, SIA = Successful intercourse attempts, UCA= Univariate Correlational Analysis, UPPP = uvulopalatopharyngoplasty.

1.5.4. Simultaneous Treatment for OSA & ED

The efficacy of using both CPAP and PDE-5 inhibitors as treatment modalities for men with OSA and ED have been reported in 2 studies [431, 488]. In 40 men with mild-moderate OSA (AHI 15.1±3.9), the effects of CPAP alone was compared to CPAP plus on-demand 100mg Sildenafil, in a cross over design [488]. In this study, which included heavy smokers (87% of participants), the use of both treatments resulted in a greater number of successful intercourse attempts (61%) compared to using CPAP alone (25%). A run-in phase using CPAP alone was conducted for 4 weeks, followed by 6 weeks of the allocated treatment. There was no baseline measurement on successful attempts on which to base any change data, nor was CPAP usage reported, however there was a slight increase in successful intercourse attempts from 19% during the run-in phase to 25% during the treatment period, the difference of which was not discussed. In the only other report of combination therapy in OSA and ED, a small observational study reported outcomes for 32 men with OSA and ED, using various combinations of CPAP, testosterone and PDE-5 inhibitors, depending on patient presentation. Six out of eight patients with OSA and ED, but with normal testosterone levels improved erectile function, and of the five patients who received all three treatments, all were reported to have normal erectile function after 3 months [431]. Although this pilot study shows good efficacy of treatment, the study was not conducted in a randomised fashion, and lacks placebo control, as well as being a small study. Further studies of the use of polytherapy in men with OSA and ED using a rigorous protocol design are needed.

1.5.5 Summary of treatment options

Three treatment options exist for a man with obstructive sleep apnoea and erectile dysfunction – testosterone therapy, PDE-5 inhibitor use or CPAP. The majority of the literature shows that testosterone improves erectile function and sexual desire, however testosterone may worsen OSA. PDE-5 inhibitors are an effective treatment, in the majority of cases, for ED, but there is some thought that these also have the potential to worsen OSA. CPAP is an established treatment for OSA, and there is some evidence regarding its effect on erectile function and sexual desire. See **figure 1.2** below:

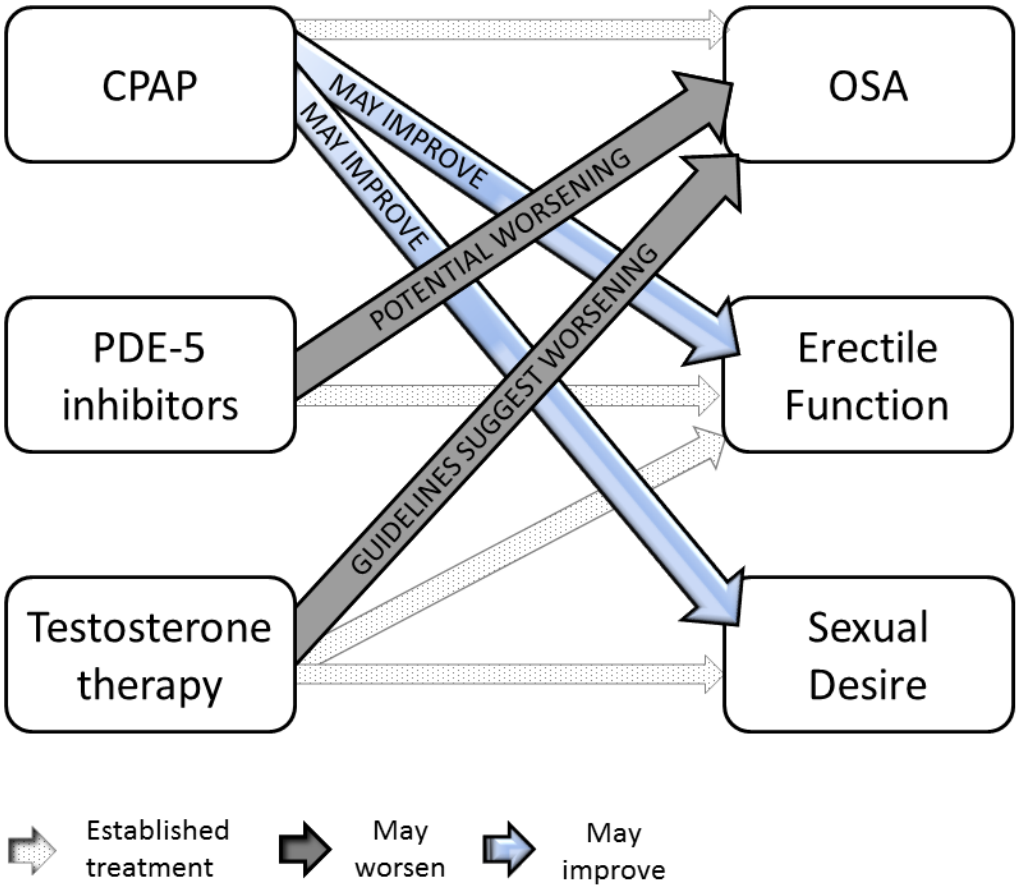


Figure 1.2: Effects of treatment on OSA, Erectile Function & Sexual Desire

1.6 CONCLUSION

Sexual function is an important part of quality of life, which can be affected by a number of lifestyle and disease factors. Evidence suggests that there is a link between OSA and both low testosterone and ED. The causal pathway between these conditions has not yet been established, however, there is increasing suggestion that this may be due to hypoxia related factors. There is a strong belief there is a relationship between OSA and low libido; however there is a lack of compelling evidence linking the two. The establishment of clinical guidelines recommending against testosterone supplementation in men with OSA is increasingly shown as having little evidence to warrant such advice. Together with the increasing prescriptions of testosterone in the general population, and potentially, if guidelines change due to evidence against them, in men with OSA, there is a need to establish the efficacy of testosterone in men with untreated OSA in regard to sexual function as this has not yet been investigated in a randomised controlled setting.

There also remain unanswered questions regarding the efficacy of CPAP treatment on testosterone, sexual desire, and erectile function in men with OSA and ED, due to the lack of adequately controlled studies, in which participants are blinded to treatment allocation. Placebo controlled studies are absolutely required in this field to elucidate the effects of therapy upon the subjective matter of sexual function.

The best clinical treatment plan for men with both OSA and sexual dysfunction has yet to be established. Would testosterone therapy be efficacious? Would testosterone supplementation worsen sleep disordered breathing? Will CPAP treat erectile function and improve testosterone levels? Would a PDE-5 inhibitor be effective in treating ED without worsening OSA? Would a combination of these therapies be optimal? This thesis aims to

contribute to answering this clinical scenario by conducting two randomised controlled trials to assess the efficacy of testosterone, CPAP, and a PDE-5 inhibitor in men with OSA.

2. Effects of testosterone administration on sexual function, quality of life and neurocognitive performance in untreated obstructive sleep apnoea.

2.1 CHAPTER SUMMARY:

Background: Sexual dysfunction, testosterone deficiency, obesity and obstructive sleep apnoea (OSA) all have high prevalence rates and often coexist. Exogenous testosterone prescription frequency is increasing in the general community and may be given to those with untreated OSA. This study comprehensively assessed the impact of testosterone administration on sexual function, general and sleep specific quality of life and neurocognitive performance in obese men with untreated OSA.

Methods: Sixty-seven middle aged obese men with moderate to severe OSA received intramuscular injections of 1000 mg testosterone undecanoate or placebo at baseline, week 6 and week 12. General and sleep related quality of life questionnaires, sleepiness levels, neurocognitive performance and sexual function were assessed at baseline, 6, 12 and 18 weeks.

Results: Testosterone administration, compared with placebo, significantly suppressed gonadotropins and increased blood testosterone concentrations ($p<0.001$). Testosterone, compared to placebo increased sexual desire by 16% (mean difference between groups, 95%CI: 5.4-26.8, $p=0.004$), independently of baseline testosterone levels. There was no change in erectile function, frequency of sexual attempts, orgasmic ability, quality of life, sleepiness levels or neurocognitive function. Post-hoc analysis in participants with low testosterone levels at baseline (<8nmol) found testosterone increase vitality ($p = 0.004$), and reports of both feeling down and nervousness were reduced ($p = 0.002$ and $p = 0.032$ respectively).

Conclusions: Testosterone therapy does not improve erectile function in men with OSA but does increase sexual desire. Exogenous testosterone variably controls different facets of quality of life, with benefits seen only for those with lower baseline levels (< 8 nmol/L) in the areas of vitality, nervousness and feeling down. Neurocognition was not changed.

2.2 INTRODUCTION:

Obstructive sleep apnoea (OSA) and testosterone (or androgen) deficiency are common conditions which often co-exist in men [57, 158, 184, 286, 289, 401, 409], and are associated with increased age and obesity [290, 296, 489, 490]. Approximately 25% of middle aged-men have OSA [286] and around 2% have testosterone deficiency [158, 184]. Recent studies have found both conditions to be increasing in prevalence in the general community [185, 287].

An independent association between the presence of OSA and a reduced level of total testosterone has been previously shown by several authors [384, 389, 394-396]. Additionally, levels of free and total testosterone have been shown to decline with increases in parameters describing OSA severity, particularly the level of hypoxaemia [398]. Potential mechanisms of untreated OSA leading to low testosterone levels include the impact of sleep restriction, known to reduce testosterone levels [385, 397], interruption of the normal pulsatility of luteinizing hormone and subsequent testosterone release in sleep [384] and repetitive hypoxia due to sleep apnoea [394].

The most effective treatment for OSA is continuous positive airway pressure (CPAP), however, adherence rates to CPAP treatment are low, with estimations of take up rates being between 46-83% [352]. Reasons attributed this low adherence include the intrusive nature of the treatment, discomfort, as well as psychological and social reasons [352]. An alternative treatment, using a mandibular advancement splint (MAS), has been shown to be less efficacious but is more likely to be used than CPAP [491]. The low adherence rates to CPAP and the incomplete elimination of OSA with MAS leaves many people with OSA with either suboptimal treatment or no treatment at all.

Symptoms such as reduced erectile quality, low mood and increased cognitive impairment are common to both OSA [57, 404, 409, 492-496] and testosterone deficiency [40, 198, 201, 242, 246, 497-499]. Given the overlap of symptoms, if OSA and low testosterone co-exist in an individual, there is potential for symptoms to be attributed to low testosterone alone, and treatment administered without addressing underlying sleep apnoea.

Symptoms of testosterone deficiency have been shown to become apparent below varying thresholds [190]. Serum testosterone levels below 8, 11, 12, and 13 nmol/L have all been associated with decline in various aspects of sexual functioning and quality of life [189]. One of the earliest symptoms to appear is that of reduced vigour when serum testosterone is less than 13 nmol/L [183], whereas below 12 nmol/L, less sexual activity occurs and there is a reduction in nocturnal erections [105, 213]. Morning erections decrease at testosterone levels below 11 nmol/L [183]. With testosterone concentrations under 8nmol/L, men have been found to have reduced sexual desire and subjective erectile function and increased rates of depression [183, 202, 500]. These varying thresholds for the appearance of androgen deficient symptoms in the general male population need to be considered when examining the association between testosterone levels and sexual function and quality of life as well as changes after treatment.

Therapy for testosterone deficiency has been suggested to begin at various level of serum testosterone, including below 8, 10, 11 and 13 nmol/L [105, 155, 188, 189]. Treatment for low testosterone is via the administration of supplemental testosterone, in various formats including transdermal patches, injection and pellets. The rates of physician prescribed testosterone have substantially increased in the general community of Australia at up to a nine-fold increase in the last 20 years [192]. Similarly, a 500% increase over the same timeframe has been seen in America [188]. This rapid increase in testosterone has not been

associated with an increase in the diagnosis of androgen deficiency, and has been speculated to be viewed as a non-specific treatment for declining well-being and sexual dysfunction [192, 194]. In any case, this increase in usage necessitates greater understanding of the effects in populations other than the general healthy population.

Potentially, there may be a bidirectional relationship between testosterone and OSA. Testosterone replacement has been shown to worsen OSA at supraphysiological doses [260] and as such, there has been considerable discussion in the literature regarding the effects of testosterone treatment in untreated obstructive sleep apnoea, with the current guidelines recommending against usage in this population [155, 453]. However, reviews of the evidence do not support the idea that conventional doses of exogenous testosterone worsen OSA [454, 455]. The results of the current study in regard to testosterones effect on sleep disordered breathing have recently been published, which found an initial worsening of OSA which was not sustained [456]. Despite studies investigating the effects of testosterone administration on OSA severity [260, 450] these studies have not reported the impact any purported change in OSA has upon outcomes known to be affected by OSA severity, the effect of sleep disruption on activities of daily living, quality of life as well as reaction time and neurocognition [32, 339, 492, 501, 502]. Some of these outcomes have been investigated in relation to serum testosterone, as well as testosterone supplementation, but not in the context of untreated OSA, in which there may be some overlap.

Of the few studies which have investigated the relationship between testosterone and quality of life measurements such as the SF-36 quality of life assessment tool, no studies have been performed in an OSA population, rather, they have been performed in a general

population with OSA status undefined, or not listed as an exclusion criterion. Some of the bigger studies investigating the relationship between endogenous testosterone and SF-36 domain scores have not reported any association between the two [183, 253]. An analysis of individual questions on the SF-36, rather than the conventional domain scores, found a testosterone threshold of below 13nmol/L significantly increased the incidence of having reduced vigour. Similarly, less than 160pmol/L of free testosterone increased the prevalence of feeling down and of having increased fatigue [183]. Pharmaceutical intervention studies have reported improvements in differing domains of the SF-36 due to testosterone replacement [254, 255, 503], however, other studies have found either no or minimal improvement [256-260].

The role of testosterone in neurocognition is complex and not completely understood [231]. Androgen receptors are found in brain regions responsible for learning and memory, which may mean that testosterone can influence cognitive processes [231]. Differences in spatial abilities due to gender suggest that there is an influence of testosterone on this aspect of neurocognition [504]. Indeed, testosterone levels in males have been correlated with various aspects of neurocognition, and a link has been made with the decline in testosterone with the development of Alzheimer's disease, however, there does remain some differing opinion on the extent to which this occurs [505, 506]. Some studies have found a quadratic (U-shaped) relationship between serum testosterone and cognition, suggesting an optimal hormone range for particular cognitive tasks [240, 241]. The effect of androgen supplementation on neurocognition has received a reasonable amount of attention, with differing results. Recent work in older men found no change in executive function, memory and spatial cognition with physiological or supraphysiological doses of testosterone [242, 243]. Several small studies have reported improvements in memory and

spatial cognition after testosterone administration in older men but generally only in those who had a lower level of testosterone initially, suggesting a possible baseline threshold for improvement [246, 247, 497]. In contrast a recent study found no change in executive function, memory and spatial cognition with large doses of testosterone [242]. In men with OSA, these cognitive processes , such as executive function, reaction time and memory, may be detrimentally affected by repetitive hypoxia from untreated OSA in regards to executive function and reaction time [492]. No previous study has investigated the impact of testosterone on men with untreated OSA who are already at an increased risk of neurocognitive impairment.

The effectiveness of administration of exogenous testosterone to men with untreated OSA upon sexual function, quality of life and neurocognition has not been assessed. No randomised placebo controlled studies have reported the association between exogenous testosterone administration and sexual function in men with sleep apnoea while assessing the effects on sleep disordered breathing. Therefore, this study aimed to comprehensively assess the impact of testosterone administration in men with untreated OSA in the realms of sexual function, neurocognitive performance and quality of life, both general and sleep related. The impact of baseline testosterone levels upon these parameters was also assessed.

2.3 METHODS

2.3.1 Study Design

This study was a randomised double-blind, placebo controlled parallel group study. All participants were randomly assigned to receive 3 doses of either Reandron (Testosterone undecanoate 1000 mg in 4 ml castor oil vehicle, Bayer Schering) or 4 ml volume-matched oil vehicle placebo via intramuscular injection. A registered nurse administered these injections at baseline, week 6 and week 12. In addition, all participants undertook a concurrent weight loss programme, consisting of a dietician prescribed low calorie (< 2500 kJ) diet and exercise advice (at least 30 minutes brisk walking per day). Clinical assessments were performed at baseline, weeks 6, 12 and 18.

2.3.2 Participants

Participants were recruited via sleep clinics at Royal Prince Alfred Hospital and the Woolcock Institute of Medical Research, Sydney, Australia and were deemed eligible to take part if they were men aged over 18, obese with body mass index (BMI) greater than 30 kg/m^2 and had polysomnographically determined mild or greater OSA, defined as an apnoea/hypopnoea index (AHI) greater than 10 per hour. Excluded from the study were those who had uncontrolled medial or psychiatric illness, severe OSA (SaO2 minimum less than 65% or AHI greater than 80 events per hour) or requiring immediate CPAP treatment, or who were currently on CPAP treatment, concurrent medication known to alter sleep, body weight or androgen action, a desire for paternity in the next 12 months, participation in sports that ban supplemental testosterone and require drug monitoring, fasting haematocrit greater than 52%, prostate-specific antigen greater than 4 ng/mL [456]. A standard medical history, physical examination and blood sample were obtained upon entry to the study. All subjects provided written informed consent and the study was approved by

the Sydney South West Area Health Service Human Research and Ethics Committee (Royal Prince Alfred Hospital Zone). All procedures complied with Good Clinical Practice guidelines, applicable regulatory requirements and the Declaration of Helsinki. The study is registered with the Australia New Zealand Clinical Trials Network, number ACTRN12606000404527.

2.3.3 Hormone Analysis

Venous blood samples were collected in the early morning at baseline, weeks 6, 7, 12, and 18. Blood samples were stored at -80 and batched for assaying. All samples of each individual participant were run in the same assay. Luteinizing hormone, follicle-stimulating hormone were analysed by commercially available Delfia assays (Perkin-Elmer Life Sciences, Rowville, Australia). Total testosterone was measured by mass spectrometry (API-5000 triple-quadruple; Applied Biosystems/MDS SCIEX, Ontario, Canada). Free testosterone was calculated using Vermeulen mass equations [507].

2.3.4 Sexual function and quality of life

A series of computerised questionnaires regarding quality of life, levels of sleepiness and sexual function were administered in an isolated room to maintain privacy at baseline, weeks 6, 12 and 18. General and sleep-related quality of life was assessed using the Short Form 36 (SF-36) [333] and Functional Outcome of Sleep (FOSQ) [339] questionnaires respectively. Analysis was performed using established scoring methodologies for various domains, as well as assessment of individual questions previously found to have an association with testosterone levels [183, 339]. Self-rated levels of sleepiness over the last two week was assessed by the Epworth Sleepiness Scale [324] and momentary sleepiness was assessed by the Karolinska and Stanford Sleepiness Scales [326, 328].

Various facets of sexual function were assessed using a Sexual Activity Questionnaire, using a visual analogue scale, as previously utilised in a testosterone treatment study [187].

Participants were asked 8 questions regarding their degree of sexual thought, desire, erectile and ejaculatory function, as well as sexual frequency and satisfaction **(Figure 2.1)**. Responses were quantified and expressed as a percentage.

Please mark on the line how you have been feeling in the last month:

Have had no sexual thoughts	----------	Have had many sexual thoughts
Have had no sexual desire	----------	Have had strong sexual desire
Have had no erections on wakening	----------	have had erections on wakening
Have not engaged in sexual activity by myself	----------	Have engaged in sexual activity by myself
Have not had sexual activity with a partner	----------	Have had sexual activity with a partner
Have not had sexual satisfaction	----------	have had strong sexual satisfaction
Have not ejaculated	----------	Have ejaculated

Figure 2.1 Sexual Activity Questionnaire

2.3.5 Neurocognitive Function

Computerised neurocognitive function testing was conducted at the same time of day for each participant. Spatial cognition was assessed using the 'Tower of London' [508], a task-based test in which balls must be moved into a pre-specified position in the least amount of moves. Executive memory was measured by the 'Stroop' test in which a series of words describing colours were presented in differing coloured fonts. These words were to be identified by the participant in terms of the colour of the word rather than the word itself – for example the word '*RED*' may be presented in green font so the correct answer is green [509]. Reaction time, which is reduced in untreated OSA [32, 353, 492], was assessed using the psychomotor vigilance task (PVT) in which the subject pressed a button in response to a stimuli which recorded as well as displayed to the subject each reaction time in milliseconds [510]. These neurocognitive tests were performed at weeks 6, 12 and 18 weeks.

2.3.6 Statistical Analysis

Statistical analysis was performed using SAS statistical package version 9.2 (SAS Institute, Cary, North Carolina, USA). Significant difference was defined as $p<0.05$. As this was part of a larger study, an estimation of 60 patients completed would have 90% power to detect a clinically relevant change in the primary outcome of the larger study, this being weight loss of 10% compared to placebo, with α set at 0.05, based on preliminary data obtained at the study location. The current analyses presented as part of this thesis were secondary endpoints and accordingly, unpowered. The randomisation code was broken only after all data were collected and the database cleaned and locked. Outcome variables were differences from baseline at 6, 12 and 18 weeks with all analyses performed using an intention-to-treat analysis. Overall and individual time point differences between groups were assessed from mixed model analyses of treatment, time and the interaction between these. Normality of residuals was confirmed.

The influence of baseline testosterone (total and free) on the effectiveness of testosterone treatment was also explored. Baseline total and free testosterone were included in separate mixed models as dichotomised factors using predefined cut points of baseline total testosterone (8, 11 and 13nmol/L) and free testosterone (160, 220 and 280pmol/L)[183]. The statistical significance of the interaction terms of treatment and each variable were examined. Results of those with a significant interaction term are shown as stratified by the variable. Additionally baseline total and free testosterone were included as linear covariate variables, as was age.

2.4 RESULTS

The flow of participants through the study is shown in **figure 2.2**. Sixty-seven men were recruited into the study. Of these participants, 33 were randomised to receive testosterone, 34 to receive placebo. The baseline characteristics of these men are shown in **Table 2.1**. There were no significant differences between the groups at baseline. There were 13 withdrawals: 7 from the testosterone group, 6 from the placebo group. Withdrawal was due to pain from injection (n=2), time commitments (n=5), personal reasons (n=3) and unspecified (n=1). There was no difference in any demographic, sleep or hormone level between those who withdrew and those who completed the study (data not shown). One adverse event also resulted in withdrawal. This was due to the development of basal cell carcinoma, which was considered to have an unlikely relationship to study drug. A total of 54 men completed all protocol procedures. Weight decreased during the study due to the weight loss programme (1.8kg) but there was no significant difference between the groups at any timepoint or overall.

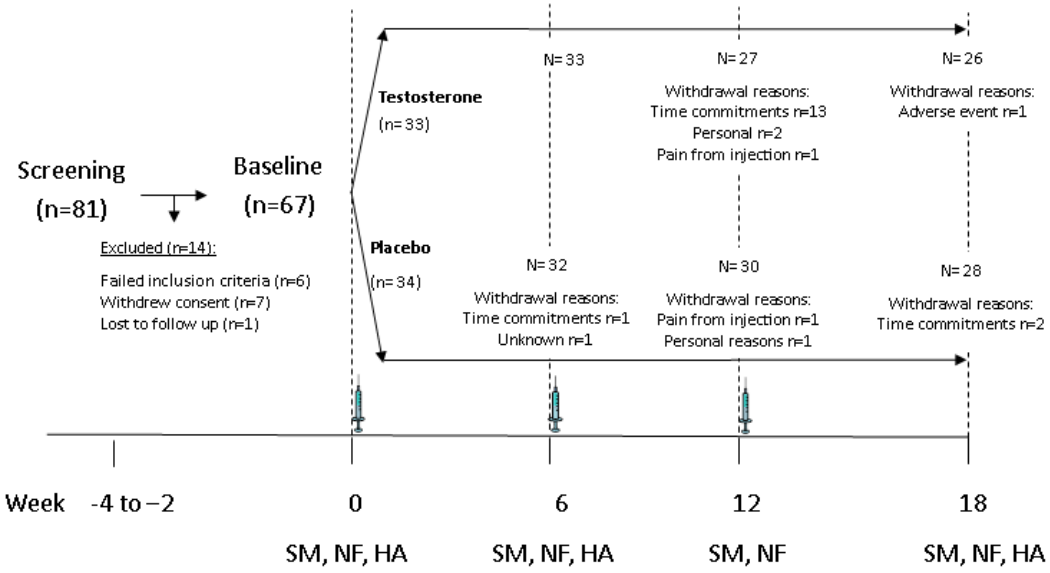


Figure 2.2 Study Flow.

NOTE: =injection given of either testosterone undecanoate or placebo as appropriate.
SM = Subjective measurements, NF=Neurocognitive Function, HA=Hormone Analysis

Table 2.1 Baseline Characteristics

	Testosterone (n = 33)	Placebo (n = 34)	p-value
Age (years)	48.2 ± 2.5	49.2 ± 2.6	0.50
BMI (kg/m2)	34.9 ± 4.3	36.6 ± 4.9	0.15
Weight (kg)	108.0 ± 15.3	114.7 ± 17.8	0.10
Total AHI (events/hour)	30.3 ± 15.8	33.2 ± 22.5	0.55
REM AHI (events/hour)	32.2 ± 22.7	42.8 ± 24.1	0.07
NREM AHI (events/hour)	29.7 ± 17.2	29.8 ± 23.3	0.95
ODI (events/hour)	21.6 ± 16.1	29.6 ± 24.3	0.12
Minimum SpO_2 (%)	82.3 ± 9.0	78.6 ± 8.3	0.08
LH (IU/L)	3.3 ± 2.2	3.4 ± 1.4	0.82
FSH (IU/L)	4.3 ± 3.7	4.5 ± 2.5	0.76
Testosterone (nmol/L)	13.2 ± 5.3	13.4 ± 5.1	0.77
Free Testosterone (nmol/L)	0.29 ± 0.02	0.28 ± 0.07	0.81
Sex Hormone Binding Globule (nM)	22.2 ± 8.0	21.9 ± 8.6	0.90

Note: Values are mean ± SD. p-values were calculated by Student's t-test. Abbreviations: BMI=body mass index; AHI=apnoea hypopnoea index; REM = Rapid Eye Movement sleep, NREM = Non-Rapid Eye Movement Sleep, ODI=oxygen desaturation index; Sp02= arterial oxygen saturation; LH=luteinizing hormone; FSH=follicle-stimulating hormone, IU/L =international units per litre, nmol/L=nanomoles per litre, nM=nanomoles.

2.4.1 Hormone profile

Baseline testosterone level was 13.3 ± 5.2 nmol/L. In this population of obese men with OSA, 62% were incidentally found to have testosterone less than 13nmol/L. Alternate thresholds of 11nmol/L and 8nmol/L yielded prevalence rates of 47% and 23% respectively. As expected, men who were randomised to active treatment showed an increase in serum testosterone and a decrease in both follicular stimulating hormone and luteinizing hormone from baseline compared to those in the placebo group ($p \leq 0.001$).

2.4.2 Sexual Function

Testosterone treatment increased sexual desire by 16% compared to placebo ($p = 0.004$) (**Figure 2.3**). There were no between-group differences in any other sexual function outcome including the number of sexual encounters, erectile or ejaculatory function. The increase in sexual desire occurred from the first assessment period (week 6) and remained elevated for the duration of the study and was independent of baseline testosterone levels (**figure 2.4**). To determine if the degree of baseline testosterone influenced response to androgen therapy, the data was then stratified using predetermined cut points of 8, 11 & 13 nmol/L. No difference was found in treatment response between those above or below any cut point in any sexual function parameter.

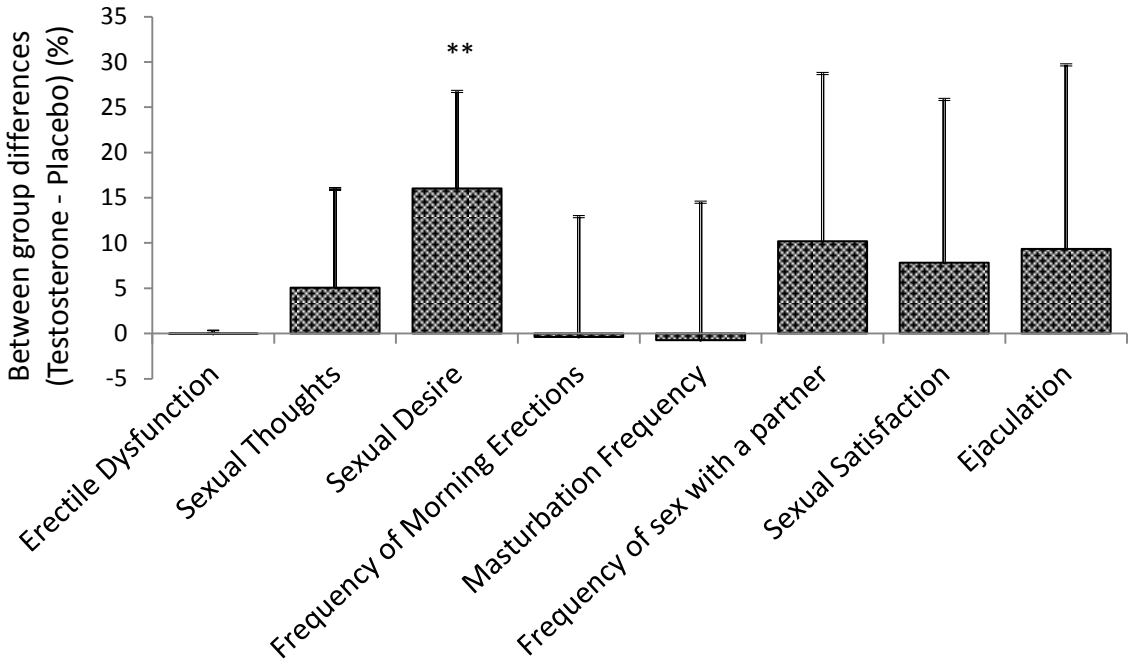


Figure 2.3 Sexual Function change from baseline with Testosterone.

Note: This figure shows the mean and 95% confidence interval for testosterone minus placebo changes from baseline scores for each parameter. The bar marked ** shows a significant difference between testosterone and placebo (p=0.004).

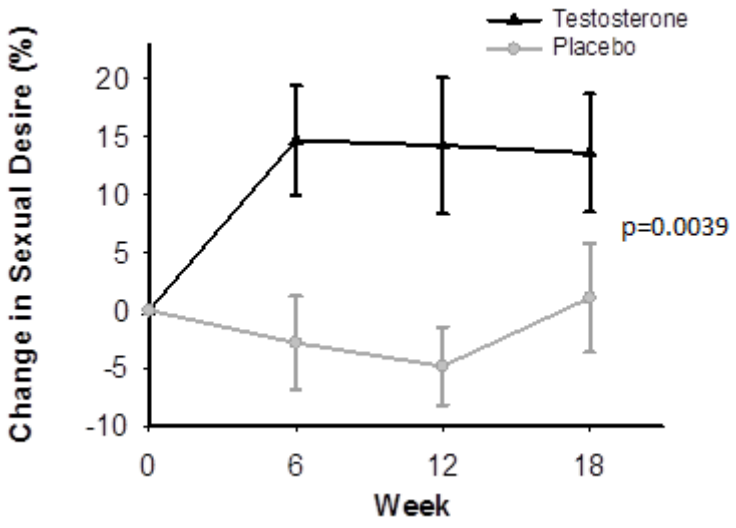


Figure 2.4 Changes in sexual desire over time with testosterone versus placebo

Note: This figure shows mean change from baseline plus standard deviation for each time point for both testosterone and placebo. This had an overall difference between groups (p=0.0039).

2.4.3 Quality of Life

Testosterone therapy did not change subjective sleepiness or any of the overall domains in the SF-36 and FOSQ questionnaires compared to placebo. Furthermore there were no between-group differences in the change for the single items of interest from the SF-36 and FOSQ questionnaires (**Table 2.2)**. When the results for quality of life, as measured by the SF36 were stratified, the interaction term of treatment and the dichotomised factor for baseline testosterone at a level of 8 nmol/L was significant for vitality (p=0.01), degree of feeling down (p=0.004), and nervousness (p=0.04) (**Figure 2.5)**. Further analysis showed the improvement after active treatment was only in those with baseline testosterone of less than 8nmol/L. Of these men, nine were in the treatment group and six were from the control group.

Table 2.2 Effect of testosterone on quality of life

	Testosterone (n = 33) Baseline Mean ± SD	Mean change from baseline	Placebo (n = 34) Baseline Mean ± SD	Mean change from baseline	Mean differences (95% CI)	Effect size (d)	p-value
SF-36 Domains							
Physical health	66.1 ± 15.0	6.3	66.1 ± 16.6	5.3	1.0 (-4.4 to 6.4)	0.06	0.71
Mental health	70.8 ± 14.1	10.3	79.3 ± 11.8	4.5	5.7(-2.4 to 13.9)	0.48	0.16
Physical function	76.7 ± 19.4	7.3	75.2 ± 16.3	6.2	1.1(-5.0 to 7.3)	0.07	0.71
Role – Physical	71.2 ± 29.4	6.7	73.5 ± 33.1	7.8	-1.1(-14.9 to 12.6)	-0.03	0.87
Body Pain	82.7 ± 21.4	-1.8	72.1 ± 26.8	2.5	-4.3(-12.0 to 3.1)	-0.16	0.27
Vitality	44.8 ± 23.6	9.4	48.7 ± 17.2	4.0	5.4(-1.9 to 12.7)	0.31	0.14
General Health	55.9 ± 19.5	10.2	62.0 ± 17.8	5.8	4.4(-2.6 to 11.3)	0.25	0.21
Social Functioning	72.9 ± 22.0	7.9	78.8 ± 21.0	6.9	1.0(-8.7 to 10.7)	0.05	0.83
Role – Emotional	63.6 ± 38.6	17.8	78.4 ± 33.8	6.8	11.0(-3.7 to 25.7)	0.33	0.14
SF-36 Single questions of interest*							
"During a typical day, did your health limit you :							
-doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?"	1.9 ± 0.8	0.2	1.6 ± 0.6	0.2	-0.2(-0.4 to 0.3)	-0.33	0.68
-walking more than one kilometer?"	2.5 ± 0.7	0.3	2.6 ± 0.6	0.2	0.0(-0.3 to 0.4)	0.00	0.80
-bending, kneeling or stooping"	2.5 ± 0.7	0.2	2.4 ± 0.7	0.2	0.0(-0.3 to 0.3)	0.00	0.91
"Have you felt down during the past month?"	4.6 ± 1.0	0.4	5.1 ± 0.8	0.1	0.3(-0.2 to 0.8)	0.38	0.24

Note: Values are mean ± standard deviation * Single questions of interest - as reported by Wu, 2010 as being indicative of symptoms associated with low testosterone levels. The p values of the change from baseline were calculated by mixed model analysis, Effect size (Cohen's d) calculated by dividing difference between testosterone and placebo by the standard deviation of placebo standard deviation at baseline.

(Continued over)

Table 2.2 Change in quality of life between testosterone and placebo (continued).

	Testosterone (n = 33)		Placebo (n = 34)				
	Baseline Mean ± SD	Mean change from Baseline	Baseline Mean ± SD	Mean change from Baseline	Mean differences (95% CI)	Effect size (d)	p-value
Epworth Sleepiness Scale	10.8 ± 5.0	-1.6	12.0 ± 4.3	-1.6	0.0 (-1.4 to 1.4)	0.00	0.99
Karolinska Sleepiness Scale	4.9 ± 2.2	-0.4	4.9 ± 1.9	0.0	-0.4(-1.4 to 0.7)	-0.21	0.48
Stanford Sleepiness Scale	2.8 ± 1.1	-0.1	2.6 ± 1.1	0.2	-0.4(-0.9 to 0.1)	-0.36	0.15
FOSQ Domains							
General Productivity	3.2 ± 0.6	0.2	3.2 ± 0.5	0.2	0.0(-0.2 to 0.2)	0.00	0.93
Social Outcome	3.4 ± 0.8	0.2	3.2 ± 0.7	0.3	-0.1(-0.4 to 0.2)	-0.14	0.34
Activity Level	2.8 ± 0.8	0.2	2.8 ± 0.6	0.3	0.1(-0.3 to 0.2)	0.17	0.59
Vigilance	2.8 ± 0.7	0.2	2.8 ± 0.6	0.2	0.0(-0.2 to 0.2)	0.00	0.71
Intimate Relationships and Sexual Activity	3.0 ± 0.9	0.3	3.2 ± 0.7	0.2	0.1(-0.2 to 0.5)	0.14	0.50
FOSQ single questions of interest							
"Has sleepiness or tiredness affected your…"							
Intimate or sexual relationship	2.7 ± 1.2	0.4	2.9 ± 0.8	0.4	0.0 (-0.8 to 0.8)	0.00	0.94
Desire for intimacy or sex	2.8 ± 1.2	0.3	3.1 ± 0.9	0.1	0.3(-0.5 to 1.1)	0.33	0.49
Ability to become sexually aroused	2.9 ± 1.2	0.5	3.2 ± 1.0	0.3	0.2 (-0.7 to 1.1)	0.20	0.67
Ability to orgasm	3.2 ± 1.1	0.3	3.6 ± 0.8	-0.5	0.8 (-0.4 to 2.1)	1.00	0.19

Note: Values are mean ± standard deviation. * Single questions of interest - as reported by Wu, 2010 as being indicative of symptoms associated with low testosterone levels. The p values of the change from baseline were calculated mixed model analysis. Effect size (Cohen's d) calculated by dividing difference between testosterone and placebo by the standard deviation of placebo standard deviation at baseline.

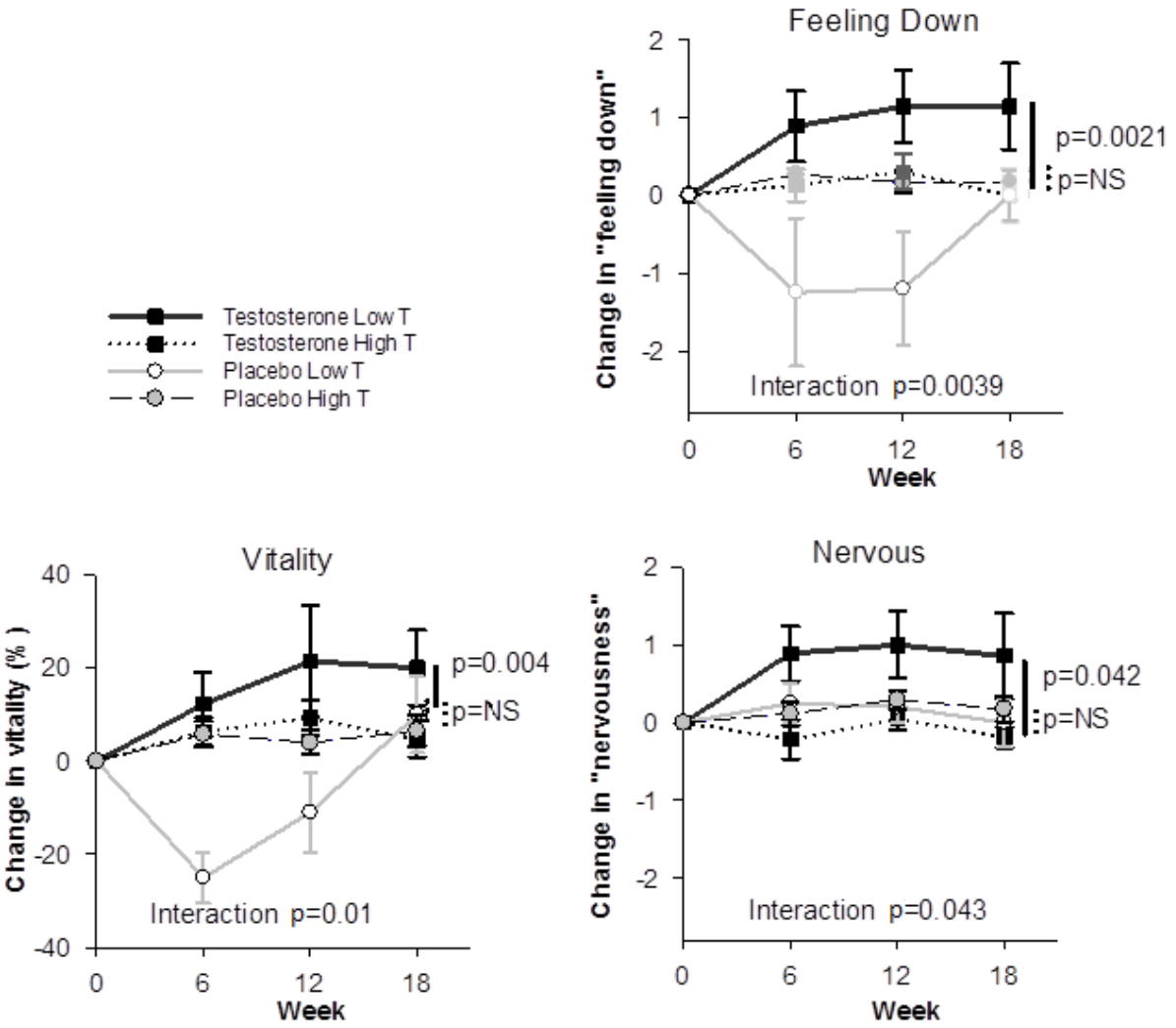


Figure 2.5 Quality of life changes with testosterone stratified by baseline testosterone

Note: Low T defined as <8nmol/L, high T defined as >8 nmol/L. These graphs show changes from baseline for testosterone and placebo for low and high initial testosterone levels for SF-36 questions for vitality, nervousness and feeling down. The overall interaction term is shown at the bottom of the graph, and those at the side show between group differences. The solid bar indicates significant differences between testosterone and placebo in those with low testosterone. The dotted lines indicate no significant difference between testosterone and placebo in the higher baseline testosterone group.

2.4.4 Neurocognitive Function

Testosterone treatment did not change any parameter of neurocognitive function as measured by the Stroop, Tower of London and PVT compared to placebo (**Table 2.3).** Adding baseline blood testosterone concentrations as a continuous covariant, or via stratification, did not alter the significance of any of the between-group associations in mixed model analyses.

Table 2.3 Effect of testosterone on neurocognitive tasks

	Testosterone (n = 33)		Placebo (n = 34)				
	Baseline	Mean change from baseline	Baseline	Mean change from baseline	Mean differences (95% CI)	Effect size (d)	p-value
Tower of London							
Number of errors	0.2 ± 0.1	-0.1	0.3 ± 0.2	-0.1	0.0(-0.1 to 0.1)	0.00	0.98
Number of missed goals	4.0 ± 3.0	-1.3	4.8 ± 4.0	-1.4	0.1(-1.6 to 1.7)	0.03	0.92
Execution time (μsec)	22592.0 ± 7881.9	-1573.1	23543.2 ± 8399.2	-3761.3	2188.1 (-1369.6 to 5745.8)	0.26	0.22
Planning Time (μsec)	12678.6 ± 5113.1	159.5	14547.9 ± 6910.6	-2024.2	2183.6 (-700.7 to 5068.0)	0.32	0.13
Psychomotor Vigilance Task							
Reaction Time (msec)	276.9 ± 7.7	-12.7	271.2 ± 9.2	-9.0	-3.7(-23.2 to 15.8)	-0.40	0.70
Reciprocal reaction time (msec)	3.9 ± 0.5	0.1	3.9 ± 0.1	0.1	0.1(-0.1 to 0.3)	1.00	0.35
Number of Lapses	2.0 ± 0.5	-0.9	2.3 ± 1.3	-0.3	-0.7(-1.9 to 0.6)	-0.54	0.29
Fastest Reaction Time (msec)	206.6 ± 4.7	-6.5	204.7 ± 4.6	-2.9	-3.6(-14.6 to 7.4)	-0.78	0.51
Slowest Reaction Time (msec)	43.4 ± 26.2	-34.0	41.50 ± 18.2	-13.5	-20.6(-83.24 to 42.15)	-1.13	0.51
Stroop Test							
Number of Text correct	97.2 ± 10.3	0.1	94.2 ± 19.4	5.6	-5.5(-14.8 to 3.8)	-0.28	0.24
Number of Colour correct	95.2 ± 16.8	-4.1	98.3 ± 3.5	-11.5	7.4(-5.7 to 20.6)	2.11	0.26
Text Reaction Time	1.0 ± 0.2	0.0	1.1 ± 0.3	-0.1	0.1(-0.1 to 0.2)	0.33	0.53
Colour Reaction Time	1.0 ± 0.3	0.1	1.2 ± 0.4	0.0	0.1(-0.1 to 0.2)	0.25	0.34

Note: p-values of the change from baseline were calculated by mixed model analysis. Effect size (Cohen's d) calculated by dividing difference between testosterone and placebo by the standard deviation of placebo standard deviation at baseline.

2.5 DISCUSSION

This is the first randomised controlled trial to examine the effect of testosterone on sexual function, quality of life and neurocognitive performance in untreated OSA. These findings show that in this population, testosterone administration, compared to placebo, increased sexual desire independent of baseline testosterone levels but had no effect on erectile function, neurocognitive function or overall quality of life. Furthermore vitality, downheartedness, and nervousness were improved in OSA patients with testosterone in the hypogondal ranges.

2.5.1 Hormone Profile

Although the definition of low testosterone is unclear, there is general agreement that levels above 12 nmol/L are normative, and below 8 nmol/L are low [189]. Inclusion into the study was not on the basis of testosterone levels, rather the degree of obesity and obstructive sleep apnoea, both known to reduce testosterone levels. The mean testosterone level classifies this group as eugonadal, however, there were men found to be in the hypogonadal range. This supports previous work which also found normative testosterone levels in a sleep clinic population [396]. One small study found that 60% of men with OSA were eugonadal, compared to 100 % of the age-matched non-OSA controls. Furthermore, an additional study found eugonadal testosterone concentration even in patients with more severe OSA (minimum oxygen saturation less than 70%) [398]. This is despite several authors finding an independent association between the presence of OSA and a reduced level of total testosterone, after other potential factors such as age and obesity have been accounted for [287, 384, 389, 394, 395, 469].

2.5.2 Sexual Function

Testosterone administration increased sexual desire in this eugonadal group of men. This improvement occurred after only one dose of testosterone undeconate, and remained for the duration of the study. The effect remained when only those with levels above previously defined cut points were analysed proving unequivocally that this effect was independent of baseline testosterone levels. Similarly, in a previous study on eugonadal (>20 nmol/L) men with chronic obstructive pulmonary disease, testosterone administration increased overall quality of sexual life with 6 months of treatment, however the effects on sexual desire was not reported [230]. Previous randomised placebo-controlled studies which have specifically recruited eugonandal men, using varying definitions to determine eugonadism, have generally not reported any change in sexual function after the addition of exogenous testosterone levels [205, 214]. Only one study of eugonandal men has found a similar result, when supraphysiological doses were investigated as a contraception, in which there was an increase in sexual desire without a corresponding change in sexual encounters, however this increase was attributed to one individual, without whom the result was no longer significant [214]. A meta-analysis of randomised controlled studies with androgen therapy showed no difference between testosterone and placebo on erectile function, sexual desire or any other sexual function in men with normal testosterone levels [213]. A later meta-analysis found a non-significant increase in libido due to testosterone administration which was not different across categories of testosterone level [196]. A similar result was found in a group of men with diabetes, with baseline testosterone level of between 8 to 12nmol/L, in which all sexual function parameters improved with testosterone administration, which was no different than the response of those with testosterone of less than 8nmol/L, suggesting baseline levels had little influence on response [503]. A potential reason the current study

shows an increase in sexual desire, but not in other studies on eugonadal men may be that the baseline testosterone level was in the lower end of eugonadal range (13nmol/L), whereas other studies of eugonadal men have been in the range of 17-19nmol/L [212, 214]. In the meta-analyses mentioned, all studies were on men with higher baseline testosterone than the present study [212, 214, 215, 472]. Indeed one early study reported that sexual function parameters may be influenced at the lower range of normal [511]. Other authors have previously reported similar positive treatment response in regard to erectile function and libido, but only for those with low baseline testosterone levels, rather than overall [206, 213]. The current study was unable to replicate this finding, with the change in sexual desire seen in the overall population, but not when data was stratified using predefined thresholds of 8, 11 and 13 nmol/L [183]. Potentially, this may be explained by the increasingly documented phenomena of different symptom appearance and reduction at differing levels of serum testosterone in different populations [183]. On the other hand, the difference in this study may be due to the population in this current study had severe OSA, and there may be an alternate mechanism or testosterone threshold at which testosterone administration increases sexual desire, which differs from those with normal breathing during sleep.

Despite an increase in sexual desire, no increase in sexual activity was seen in this population. There was no requirement for participants to have a regular partner during the study which may have an influence on the number of sexual attempts; however, there was also no change in masturbation frequency. Habit, as well no change in social and relationship factors concordant with the increase in libido may contribute to this finding. In this study, the rating of sexual satisfaction did not change with testosterone administration. This supports the findings of a previous meta-analysis of clinical trials in men with either low

or normative levels of serum testosterone having no increase in sexual satisfaction, and extends the finding to men with severe OSA [196].

2.5.3 Quality of Life

Testosterone not only mediates sexual function in males, it also contributes to aspects regarding quality of life such as vitality and strength. Our results do not show, overall, any increase in quality of life parameters of the SF-36 questionnaire with testosterone compared to placebo. Similarly, there were no improvements in any SF-36 parameter with testosterone compared to placebo in a study of men of older men (age 60-80 years) with low (11 nmol/L) serum testosterone [512]. In contrast, in a non-placebo controlled study comparing efficacy of injectable versus implantable testosterone in men with similar levels of testosterone (13.8 nmol/L), improvements in quality of life as measured by the SF-36 questionnaire were seen in the domains of vitality, physical function and social function with both treatment modalities [187]. Lack of placebo control, however, limits the interpretation of these improvements seen.

Previous investigations have found improvements in individual questions of the SF-36 (fatigue, vigor, ability to walk more than more than 1 kilometre, bending, kneeling or stooping and of feeling down) with testosterone supplementation, but only for those with a the lowest baseline threshold tested, that of 8nmol/L [183]. This study also analysed these individual questions of interest, and similarly, found a threshold of 8nmol/L to be below which, testosterone therapy is able to improve the parameter of feeling down, however, was unable to replicate the other findings. However, other domains on the SF-36 were found to have a threshold influence, that of vitality and of nervousness. Vitality has been shown to increase with testosterone supplementation, when performed in men with very

similar basal testosterone levels to the current study (13.8nmol/L) [187]. This difference may be due to a differing population, that of men with OSA, who may have a differing threshold at which treatment is effective.

There was no change with the level of sleepiness, nor functional outcomes of sleep questionnaire with testosterone compared to placebo, a finding which supports that of the only other study reporting this outcome, which used higher doses of testosterone than the present study [260].

2.5.4 Neurocognitive Function

Men with OSA are more likely to have mild detriments in some aspects of memory than the general population, which may be due to a reduction in alertness [494, 496], while the reduction in executive and psychomotor tasks, such as reaction time also seen in men with OSA, may be due to repetitive hypoxia [492]. Thus, this group of men with OSA may have some neurocognitive impairment prior to study entry. Given the inconsistency of results regarding the impact of supplemental testosterone in neurocognitive function, this study provides an opportunity to examine, in a population more likely to have impairment, the effects of testosterone. Our results show that in this population of men with OSA, neurocognitive function, including memory, executive function, and reaction time, does not change with testosterone administration. Recent work in older men, with OSA status unspecified, also found no change in executive function, memory and spatial cognition using large doses of testosterone [242]. Several small studies have reported improvements in memory and spatial cognition for older men but generally only those who had an initial lower level of testosterone [246, 247, 497]. Stratification of the current data by baseline testosterone levels of 8, 11 & 13nmol was unable to show any changes in neurocognitive

outcomes at any threshold. In the non-OSA population there is no clear conclusion that testosterone therapy enhances, impairs or has little effect on neurocognition [205, 231, 242, 245, 246]. The current results suggest that in an OSA population, testosterone therapy has no effect on memory, executive function, or reaction time.

2.5.5 Strengths and Limitations

This study provides a randomised placebo controlled study of the subjective effects of testosterone in regards to sexual function. Being a purely subjective measurement, placebo control is imperative to assess the impact of therapy. Defining sexual desire and describing its manifestation is difficult [8]. Various aspects of sexual function such as arousal, desire, and behaviour, intertwine and influence each other. These different facets are driven by a complex mix of neurochemical, neuroanatomical, psychological and social factors, and sexual desire can be difficult to report in a quantitative research [5]. Subjective measurement via questionnaire is an easy to administer method in clinical research; however, the limitations in this technique must be recognised. A visual analogue scale (VAS), previously been used to assess sexual function in testosterone therapy has been used in this study [187]. An alternative subjective questionnaire, the International index of Erectile Function, has been validated and is more widely used than the VAS used in this study, and may have been a useful measurement tool to allow comparisons between this and other studies [89, 90]. There is no objective measurement of sexual desire, resulting in a reliance on subjective assessment. Erectile function can be quantified using penile tumescence monitoring under nocturnal or provocative conditions [513, 514]. Other studies have shown an increase in erection quality with testosterone using this technique [515]. Analysis of erectile function in this manner may have given a greater insight into testosterone effects on physiologically measured erections. Nevertheless, this study, being

placebo controlled overcomes some of the limitations of subjective measurements, and thus provides valid outcomes for this population.

Consideration should be given to the concept that the sexual function effects of testosterone administration in OSA may only be relevant in patients with symptoms. There is no reference value available for a normal level of sexual desire. As a result it is unclear if this group of men had reduced or normal libido at baseline. This study did not specifically target those with such symptoms, nor was a reduced level of testosterone a study entry requirement. The population in this study, having severe obstructive sleep apnoea, differs from that in the majority of previous research in androgen administration. Sleep apnoea has not been listed as an exclusion criterion in previous studies, and has not been routinely excluded in the majority of these studies, despite the recommendations not to give testosterone to men with OSA. Given the prevalence rates of undiagnosed or untreated sleep apnoea, there may well be some men in these studies which do have sleep apnoea; however, this is not able to be determined.

2.6 CONCLUSION

Testosterone therapy improved sexual desire in obese men with OSA regardless of baseline serum testosterone in this 18 week study. Neither erectile function, nor any other parameter of sexual health improved with testosterone. There were no overall changes in neurocognition or quality of life; however, those with lower levels of baseline serum testosterone were shown to improve in the genres of vitality, feeling down and nervousness only, as measured by the SF-36. These positive effects on quality of life measurements for men with OSA and a baseline testosterone of less than 8 nmol/L, are similar to those seen in the non-OSA population. Although testosterone therapy can be safely prescribed to men with OSA, its efficacy is limited to an increase in libido for all men and some quality of life parameters for those with low baseline levels.

3 Methodology: 2x2 Factorial designed study - the effect of CPAP and Vardenafil on Sexual Function in men with Obstructive Sleep Apnoea and Erectile Dysfunction.

3.1 CHAPTER SUMMARY

This National Health and Medical Research Council (NHMRC) funded study was a 2 x 2 factorial design randomised 'sham' & placebo controlled protocol investigating the effect of both CPAP and Vardenafil, in men with OSA and ED. Sixty-one men were recruited into the study at one of two sites – Sydney and Melbourne. Participants were randomised to receive 12 weeks of either CPAP or sham CPAP, as well as 12 weeks of 10mg daily Vardenafil, a PDE-5 inhibitor or placebo.

This chapter describes methods used to both acquire and analyse the data, including study design, inclusion criteria, polysomnographic methods, subjective and objective assessments of sexual function, as well as subjective measures of quality of life, and the statistical analysis of the factorial design.

Factorial studies provide a cost and resource effective tool to evaluate two separate interventions, in which the efficacy of one treatment does not affect the efficacy of the other. This assumption was tested, with analysis of the interaction between treatments provided here. No interactions were found; therefore the factorial study can be treated as two separate trials which are reported in Chapters 4 and 5.

3.2 METHODS

3.2.1 Study Design

This 2x2 factorial designed study, assessing the efficacy of both CPAP and Vardenafil in men with obstructive sleep apnoea (OSA) and erectile dysfunction (ED) was performed in Sydney at the Woolcock Institute of Medical Research, Glebe, New South Wales and in Melbourne at the Department at Respiratory and Sleep Medicine, Monash Medical Centre, Clayton, Victoria. After screening to ensure all inclusion and exclusion criteria were met, a baseline visit was conducted to determine initial levels of sleep disordered breathing, objective erectile function, hormonal analysis, subjective measurements of sexual functioning and quality of life. After baseline data collection, eligible participants at each site (Sydney and Melbourne) were randomised using two separate computer generated randomization list in blocks of four to one of four groups, as follows –

1. CPAP & Vardenafil;
2. CPAP & Placebo;
3. Sham CPAP & Vardenafil;
4. Sham CPAP & Placebo.

Short visits at week 4 and week 8 were undertaken, during which subjective measurements were conducted, as well as CPAP / sham CPAP machine download to assess adherence to treatment, and a manual count of returned medication in order to assess medication adherence. At these visits, routine clinical observations were also taken (blood pressure, pulse rate), and participants were asked about any adverse events which may have occurred. At 12 weeks, all measurements which were taken at baseline were again performed while using the allocated treatments (see **figure 3.1**).

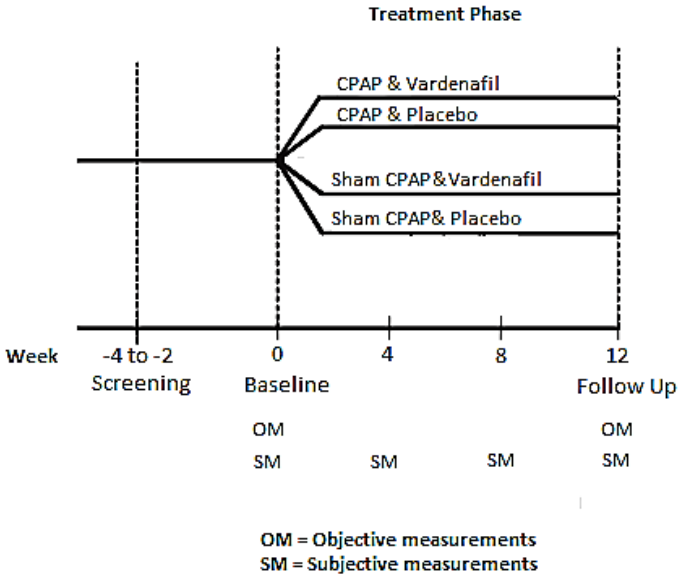


Figure 3.1 Study Design

3.2.2 Participants

Sixty-one men aged between 18-65 years who had both obstructive sleep apnoea, and reported erectile dysfunction were recruited into the study from sleep clinics at Royal Prince Alfred Hospital, Sydney, the Woolcock Institute of Medical Research, Sydney, and Monash Medical Centre, Melbourne, or via community advertising in print and radio.

This study protocol was approved by Human Research Ethics Committee, Concord Repatriation General Hospital for the Sydney site, and Southern Health Human Research Ethics Committee for Melbourne. Site specific ethics approval was obtained through Human Research Ethics Committee, Royal Prince Alfred Hospital, and the Research Governor, Woolcock Institute of Medical Research. All participants provided written consent. Protocol development, electronic source note provision and records, analysis and overall supervision of the study was conducted at the Woolcock Institute of Medical Research.

Participants were required to have at least moderate OSA, defined as an AHI of greater than 20 events per hour, with an oxygen desaturation index of 3% or greater (ODI3) of at least 15 events per hour, as well as erectile dysfunction, defined as a score of less than 26 in the erectile function domain of the International Index of Erectile Function (IIEF) questionnaire since a score of 26 or more indicates no erectile dysfunction. To be included in the study, participants must have been in a stable relationship for at least six months. Excluded from the study were those who had irreversible erectile dysfunction, concurrent treatment with nitrates or nitric oxide donors, treatment of ED within the last month, severe renal or hepatic impairment, uncontrolled diabetes or hypertension, were current smokers, night shift workers, were unable to read the information sheet due to language barrier, or had any chronic medical condition that may limit participation. Those men who were unwilling to use CPAP or whose condition required immediate treatment due to severity or occupation were also excluded. Current medications taken by participants were documented, and the possibility of drug interaction was avoided by careful screening. No medications, apart from the investigational drug, Vardenafil, were changed or initiated by the investigators during the study.

3.2.3 Interventions

Continuous Positive Airway Pressure (CPAP), the first line therapy for obstructive sleep apnoea, was used to maintain upper airway patency during sleep. An established method of a placebo control, an inactive CPAP, "sham CPAP" [516], was used to ensure blinding of participant and study co-ordinator (further explained **in section 4.3.3**).

A PDE-5 inhibitor, the first line therapy for erectile function was also used. A low (10 milligrams) daily dose of Vardenafil hydrochloride trihydrate (product name Levitra) or

placebo (Bayer Schering, Berlin, Germany) was administered. Participants were instructed to take one tablet daily 60 minutes before attempting to fall asleep, regardless of their intention to attempt sexual activity (further explained in **section 5.3.2**)

3.2.4 Statistical Analysis

Statistical analysis was performed using SAS statistical package version 9.2 (SAS Institute, Cary, North Carolina, USA). The sample size was determined on the basis of previously published data of a non-placebo controlled study, in which 3 months of CPAP increased the IIEF-ED domain from 7.0 ± 2.1 to 9.3 ± 3.3 [484]. Assuming conservatively that vardenafil exerts an effect at least as great as CPAP, a sample size of 100 (n=20 withdrawal allowance. Total subjects = 120) will have 80% power to detect both a CPAP vs sham and a vardenafil vs placebo effect. The randomisation code was broken only after all data were collected, data was cleaned and locked, and data was analysed using intention-to-treat principles. This study was analysed as per established guidelines on factorial randomised controlled trials [517, 518]. By performing a 2x2 factorial study, two interventions, which do not have an effect on each other, can be evaluated in the same patients in parallel, allowing a cost-effective method of research [517]. This assumption was tested prior to the two treatments being considered individually. Firstly, a mixed model analysis was used to test the 3 way interaction between the two treatments as well as time. Following this, if no significance was found, the interaction between the two treatments was tested, removing time from the analysis, in order to ensure no interaction between the two treatments.

3.2.5 Subjective Assessments

Subjective measurements of sexual function, relationship quality and quality of life were assessed at baseline and after 4, 8 and 12 weeks of treatment using self-administered computerized or paper based questionnaires, the administration method of which was consistent for individual patients. The session required approximately 1 hour of patient time. Sexual function was assessed primarily using the International Index of Erectile Function, which comprises 16 items related to various facets of erectile and sexual function [89]. This questionnaire is now the gold standard patient reported outcome which is accepted by the US Food and Drug Administration and other regulatory authorities for registration of new therapies for erectile dysfunction [89]. From this questionnaire, an overall score is obtained, as well as scores for the domains of erectile function, intercourse satisfaction, orgasmic function, overall satisfaction and sexual desire. Additional measures of sexual function were obtained from the European Male Aging Study (EMAS) questionnaire, which is of particular relevance for the aging male, with questions relating to changes in and distress caused by sexual dysfunction, as well as overall sexual functioning [84, 85]. An insight into confidence, self-esteem and relationship functioning was gained through the use of the Self-Esteem And Relationship (SERS) questionnaire [519]. Quality of life was assessed using questionnaires designed for general and sleep specific applications. To assess overall health, the generic Short-Form Medical Outcomes Survey (SF-36) was used. This 36 item questionnaire consists of eight domains – physical functioning, role limitations because of health or emotional problems, body pain, general health, vitality, social function and mental health, as well as 2 summary measures of physical and mental health [333, 334, 520]. To assess mood, the 21 item Depression Anxiety Stress Scale was used [521-523]. The Functional Outcomes of Sleep Questionnaire has been developed for

use in patients with sleep disorders to assess the impact of sleepiness on quality of life and was used to provide an overall score, as well as scores for the domains of activity, vigilance, intimacy, productivity and social factors [339]. Levels of sleepiness were assessed using the Epworth Sleepiness Score (ESS), a questionnaire in which 8 scenarios are presented for participants to rate their likelihood of falling asleep or dozing [324, 524].

Satisfaction of the treatment used in regards to its effect on erectile function was assessed at Week 4, Week 8 and Week 12 using the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire [93]. All items on the EDITS were scored from zero (no satisfaction or dissatisfaction) to four (high satisfaction). The mean satisfaction score for each patient was calculated. Each mean score was multiplied by 25 giving a range between 0 (extremely low treatment satisfaction) to 100 (extremely high treatment satisfaction). A score over 50 deemed the participant to be satisfied with treatment [525]. Treatment satisfaction, as determined via this questionnaire, has been found to be pivotal in regards to successful long term therapy for ED [526].

3.2.6 Measurement of Sleep Related Erections

Sleep Related Erections (SRE's) were measured via Nocturnal Penile Tumescence (NPT) monitoring prior to treatment and at study completion using a Rigiscan Plus monitor (Timm Medical Technologies, Minnesota, USA). This device records the frequency and duration of tumescence (circumference) and rigidity (hardness) of the base and tip of the penis during sleep. The recording device is strapped to the participant's thigh using a commercially available strap with a customised pocket to hold the device for the duration of the sleep period. Two small tension cables extend from the device to the penis, which move freely through a conduit and disposable loop covers. These loops are placed around the base and tip of the penis which gently tighten and release every 15 seconds at a force of 114 grams. After the dilatation of the loop, the penile tissue rebounds to the pre-intervention state. During this rebound, a measurement of the erectile tissue engorgement is taken. If an increase in tumescence is detected, compared to previous results, and has shown at least a 6mm increase, a second measurement is taken every 30 seconds. This second measurement records rigidity by tightening the loops to a linear force of 283.5grams and determines the cross sectional response to radial compression [102].

Parameters recorded for each session included number of erections (defined as a 20% increase in tumescence from baseline lasting at least 3 minutes), erection duration in both time and percent of recording, percentage rigidity (compared to 100% being a hard-rubber cylinder), rigidity activation units (a product of minutes spent at a given rigidity level in decimal form, summated for the duration of the erectile event) of both the base and the tip, as well as tumescence activation units (the duration of an erectile event multiplied by the percentage increase in circumference, as a decimal, over the baseline tumescence) of both base and tip [103].

Criteria used to distinguish between the traditional categorisations of organic and psychological origin of ED was as described in commercial documentation of the Rigiscan [527]. To fulfil the criteria of ED due to organic causes, three of the following were required during one night of recording:

1. Less than 3 erections recorded.
2. Less than 10 minutes of erection recorded
3. Less than 10 minutes of erection at greater than 60% rigidity at the base or tip
4. Less than 3cm increase in tumescence at the base of the penis
5. Less than 2cm increase in tumescence at the tip of the penis

As penile tumescence monitoring may be viewed as unacceptable by some participants, a choice was given to opt out of having this test performed. If participants did agree to be monitored, a short fifteen minute characterisation session was performed in the laboratory. This was used for both patient orientation to the device and for measurement of a baseline recording of tumescence. After watching an instructional DVD (Timm Medical Technologies, Minnesota, USA), the participant self-applied the Rigiscan and a baseline recording of at least 5 minutes duration was performed while the penis was in the flaccid state. After ensuring the participant was able to correctly use the Rigiscan, two consecutive nights of data were collected while the participant slept at home, as acclimatization nights. A third recording was performed concurrently with polysomnography in the sleep laboratory.

A unique calibration tool was developed in-house to ensure intra- and inter-reliability of the recordings. Cylindrical cross sectional areas of differing diameters representative of varying penile size were lathed into a solid pipe, providing a known circumference to measure

against. Regular testing of the Rigiscan using this device was undertaken, particularly at times of instability and after annual servicing.

3.2.7 Polysomnography

Overnight polysomnography was performed prior to commencement of study treatment, as well as after 3 months of treatment, in an attended laboratory setting and analysed using a Sandman Elite system and software (Sandman Elite v9.2, Tyco Healthcare, Denver, Colorado) at the Woolcock Institute of Medical Research, Glebe, New South Wales (Sydney site), or Compumedics Profusion 2 (Melbourne, Australia) at the Department of Respiratory and Sleep Medicine, Monash Medical Centre, Clayton, Victoria (Melbourne site).

Standard sensors and measurement techniques were used as per contemporary guidelines for clinical polysomnography [528]. Sleep stage was recorded via electroencephalography (EEG) using the conventional 10-20 system [529] at four sites – C3, C4, O1, & O2 which were each referenced to their opposing mastoid - M1 & M2. Eye movements were recorded using electrooculography for left and right eyes, referenced to M2 and M1 respectively. Sub-mental chin electromyography via differential surface electrodes provided an indication of muscle tone. At the baseline visit, respiratory flow was measured using pressure transduced airflow obtained via nasal cannula, as well as via thermistor to obtain oral respiration. The degree of thoracic and abdominal movement was monitored via respiratory inductive plethysmography using specialised belts around the chest and abdomen. Peripheral oxygen saturation (SaO_2) was obtained as a continuous measurement using either inbuilt (Sydney site) or external finger pulse oximetry entrained into the polysomnograph (Melbourne site). Other routine polysomnographic variables were also recorded as per standard practice [528]. These comprised a single channel

electrocardiograph, anterior tibialis electromyography (leg EMG), body position and digital video.

Manual sleep staging and scoring of these recordings was performed by the same blinded sleep technologist at each site using American Academy of Sleep Medicine guidelines for sleep staging and respiratory scoring [528]. Each 30 second epoch was designated as being either wake, Stage N1, Stage N2, Stage N3 or REM sleep. Stages 1 through 3 were summated and reported as NREM. From this analysis, calculation of sleep parameters was performed, including time spent in each sleep stage, total sleep time, sleep latency (time to fall asleep), and sleep efficiency (percentage of time in bed spent asleep).

Arousals from sleep were identified as being a significant shift to a faster frequency for at least 3 seconds after at least 10 seconds of sleep had occurred. Those arousals which occurred in REM sleep also required an increase in muscle tone [528]. The number of arousals per hour of sleep recorded was reported as the arousal index.

Respiratory events were identified and scored manually on the basis of airflow, oxygen saturation and EEG. Apnoeas were defined as being a cessation of airflow for a minimum of 10 seconds and classified as being obstructive if respiratory effort was seen on the abdominal or thoracic trace, central if there was an absence of such effort, or mixed if there was a combination of the two. Hypopnoeas were defined as a reduction of airflow for more than 10 seconds, followed by an arousal or at least 3 per cent oxygen desaturation. All of these events were reported in terms of events per hour of sleep as the apnoea hypopnoea index (AHI). Oxygen desaturation index was automatically determined via the acquisition / analysis software, through identification of decrease in oxygen saturation by at least 3 per

cent during periods of sleep, expressed as the number of these events per hour of sleep (ODI3).

At the week 12 visit, CPAP or sham CPAP was used for the duration of the sleep period. Polysomnography was repeated using the same methodology as baseline, however, oxygen tubing was attached to the CPAP mask to obtain respiration measurements through a pressure transducer, rather than via nasal cannula and a thermistor was not used. All other methodologies remained the same between visits. The CPAP or sham CPAP device was set to the pressure settings used during the study period.

3.3 RESULTS

The flow of participants through the study is shown in **figure 3.2.** Sixty-one men were randomized into the study, of these, 49 were from the Sydney site and 12 were from Melbourne. There were no significant differences in any of the primary outcome variables, between the participants from Sydney & Melbourne however, participants from Sydney reported a higher masturbation frequency (data not shown). Six participants withdrew from the study after randomisation. Four participants were from the Sydney site, while two were from Melbourne. Of these, two withdrew from the study due to being unhappy with the CPAP/sham CPAP and four withdrew due to personal reasons. Four of the six withdrawals were randomised to receive placebo medication, and four of the six withdrawals were randomised to receive sham CPAP. There was no difference in any demographic, sleep or erectile function parameter between those who withdrew and those who completed the study (data not shown). Fifty five men completed the study.

Twenty participants were adherent to CPAP/sham CPAP, as defined by at least 4 hours per night usage. Of these, 12 were allocated to CPAP, 8 to sham CPAP, further explained in **section 4.4.6.**

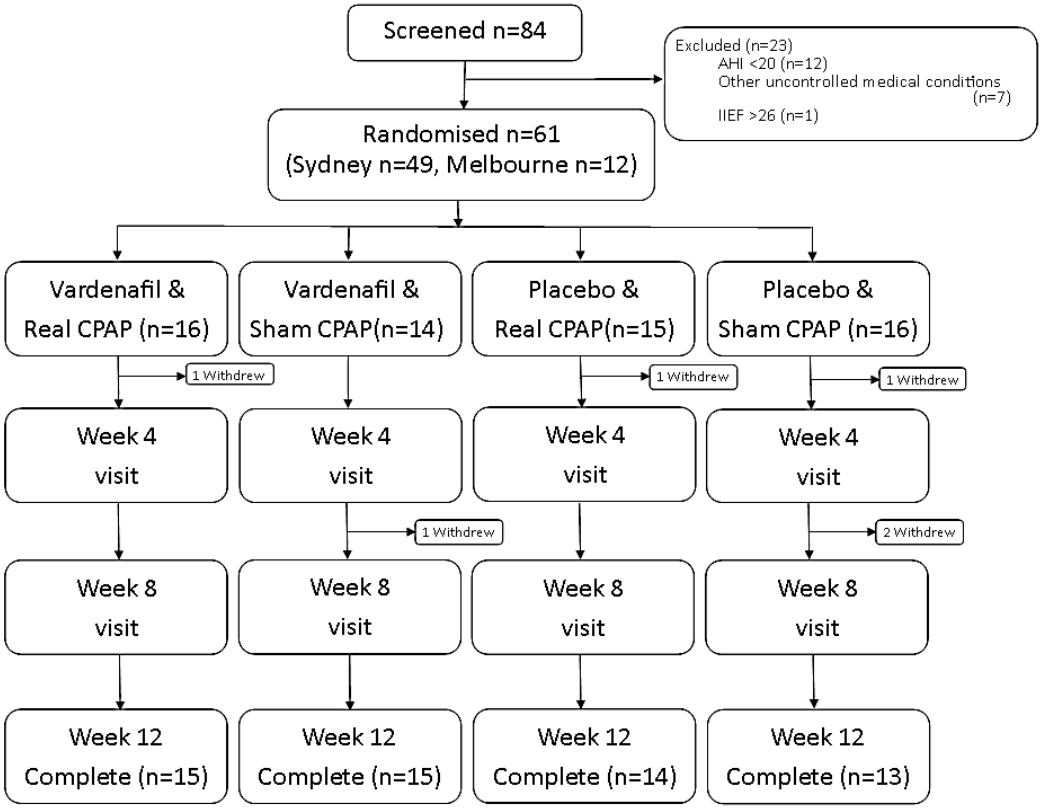


Figure 3.2: Study Flow

3.3.1 Interactions between Treatments

No interactions were found between the two treatments in either a three way or two way analysis. Subjective outcomes, that of questionnaire data, are presented in **table 3.1**, for both 3 way (CPAP/sham*Vardenafil/Placebo*time) and, since none were significant, a 2 way (CPAP/sham*Vardenafil/Placebo) analysis, also shown in **table 3.1**. One objective outcome, the measurement of sleep related erections, is presented in a 2 way interaction only (CPAP/sham CPAP*Vardenafil/Placebo), since this was performed only at the baseline & final visits (**table 3.2**). There were no interactions between the two treatments in either a 3-way or 2-way analysis for any objective or subjective parameter measured. The factorial design assumption, that CPAP does not affect the efficacy of Vardenafil, and vice versa, was confirmed to be upheld.

Table 3.1: Interaction terms for subjective parameters

	3-way p-value	2-way p-value
International Index of Erectile Function (IIEF)		
IIEF - Overall Score	0.7647	0.5641
IIEF - Erectile Function	0.6274	0.6287
IIEF - Intercourse Satisfaction	0.7840	0.5118
IIEF - Orgasmic Function	0.8124	0.4229
IIEF - Overall Satisfaction	0.4974	0.8174
IIEF - Sexual Desire	0.2194	0.8201
European Male Aging Study questionnnaire (EMAS)		
EMAS - Overall Score	0.7413	0.7081
EMAS - Sexual Function Distress	0.7609	0.8238
EMAS - Change in Sexual Function	0.9543	0.9340
EMAS - Overall Sexual Function	0.5679	0.9187
EMAS - Masturbation	0.4843	0.9496
Self-Esteem and Relationship Satisfaction (SERS)		
SERS - Overall Score	0.9381	0.6539
SERS - Sexual Relationship Satisfaction	0.8324	0.5662
SERS - Confidence	0.9764	0.9573
SERS - Self Esteem	0.4464	0.8250
SERS - Overall Relationship Satisfaction	0.2087	0.4835
Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS)	0.7692	0.0552
Functional Outcomes of Sleep (FOSQ)		
FOSQ - Activity	0.1802	0.5258
FOSQ - Vigilance	0.1541	0.8248
FOSQ - Intimacy	0.5258	0.1757
FOSQ - Productivity	0.3789	0.7839
FOSQ - Social Outcomes	0.683	0.5422
Short-form 36 (SF-36)		
SF-36 Physical Function	0.8658	0.4801
SF-36 Role Physical	0.3894	0.3732
SF -36 Body Pain	0.1139	0.2254
SF-36 General Health	0.9690	0.1648
SF-36 Vitality	0.4036	0.7082
SF-36 Social Function	0.4396	0.4267
SF-36 Role Emotional	0.2568	0.4513
SF-36 Mental Health Scale	0.0717	0.6157
SF-36 Physical Health	0.3559	0.1364
SF36 Mental Health Dimension	0.1128	0.4213
Depression Anxiety Stress Scale (DASS)		
DASS Depression	0.9421	0.2350
DASS Anxiety	0.538	0.4421
DASS Stress	0.8581	0.5940
Epworth Sleepiness Score (ESS)	0.1697	0.7379

Note: p-value determined via mixed model analysis.

Table 3.2: Interaction terms for sleep related erections

Sleep Related Erections	2-way p-value
Total Number of Erections	0.7216
Tip Rigidity Activation Units	0.1550
Tip Tumescence Activation Units	0.3073
Base Rigidity Activation Units	0.4923
Base Tumescence Activation Units	0.2739

Note: p-value determined via mixed model analysis.

3.4 DISCUSSION & CONCLUSION

The efficacy of CPAP treatment was not affected by Vardenafil and vice versa for any of the outcomes of this study. In a systematic review regarding the reporting of factorial studies, recommendations were made that interactions from a 2x2 factorial study should be reported, which has been presented here, and that factorial trials are an efficient means of testing two treatments [518]. According to this review, performed in 2003, 82% of the 44 factorial studies found were performed in order to be an efficient manner of testing two treatments in the same population, with the remaining studies testing cumulative effects of two treatments. All trials, except one, reported outcomes for each treatment individually (that is, treatment A versus treatment B, and Treatment C versus Treatment D), 59% reported interactions between the two treatments, and only 6% found any such interaction [518]. The current trial fulfils the requirements of reporting results of interaction analysis, with no such interactions present. The two trials are able to be analysed separately with confidence that the other treatment did not influence efficacy. These two trials are presented in **Chapters 4 and 5** respectively.

4 Effect of CPAP treatment on sexual function, relationship quality, mood and quality of life in men with obstructive sleep apnoea and erectile dysfunction

4.1 CHAPTER SUMMARY

Background: Erectile dysfunction and obstructive sleep apnoea often coexist. Treatment of OSA using CPAP has been reported to improve erectile function; however previous studies have not been performed using the best available placebo (sham) control. The effects of CPAP on other parameters of sexual function have been conflicting. This study aims to assess the effect of CPAP, using a sham CPAP control, on sexual function and quality of life.

Methods: Sixty-one men with severe OSA (AHI 46.1 ± 25.8), who were naïve to CPAP were randomised to either CPAP or sham CPAP as part of a 2x2 factorial study also investigating the efficacy of a PDE-5 inhibitor, Vardenafil, for a period of 12 weeks. Subjective measures of sexual function, mood, relationship factors and quality of life were assessed prior to, and after 4, 8 and 12 weeks of allocated treatment. Objective measurement of erectile function was assessed at baseline and at study completion with nocturnal penile tumescence monitoring.

Results: CPAP, overall, improved overall sexual satisfaction but did not improve subjective erectile function. By week 12, both subjective erectile function and sexual desire improved but only in those men who used CPAP more than 4 hours per night during the treatment period. The number of erections during sleep increased with CPAP compared to sham CPAP (from 2.7±1.9 to 4.1±2.0, p=0.0006), but these did not change in quality. CPAP, compared to sham CPAP, when used more than 4 hours, reduced distress due to sexual dysfunction, and improved mental health, depression, stress, anxiety, sexual relationship satisfaction and participants were satisfied with treatment efficacy.

Conclusion: CPAP, when used as prescribed, is effective in improving sexual health and function in men with erectile difficulties, as well as improving mental health and quality of life. However, effective treatment was tolerated by less than half of study participants.

4.2 INTRODUCTION

Erectile dysfunction (ED) is associated with untreated obstructive sleep apnoea (OSA) [30, 396, 409, 415, 422, 425]. An apnoea hypopnoea index (AHI) of greater than 15 has been found in a large population study to have an odds ratio of having ED as 2.75 [57], with prevalence rates of ED reported in men with OSA ranging from 29-69% [409, 414, 422]. The association between the two conditions is often not addressed in clinical practice and is unknown to many patients undergoing Continuous Positive Airway Pressure (CPAP) treatment for OSA [414, 487].

Quality of life for both men with OSA and men with ED is known to be reduced [338, 530-532] However, for those men who have both conditions, there can be further decrements in quality of life and mood than with OSA alone [414]. Erectile dysfunction impacts on the ability to maintain a healthy sexual relationship, and the social impacts of loud snoring and disrupted sleep for the bed partner can result in a reduction of relationship quality and increase marital conflict [369, 533, 534].

Treatment of OSA using CPAP has long been established as an effective treatment to reduce airway obstruction during sleep [466]. In addition to improvements in hypertension [365], cardiovascular disease [535], sleepiness [536], and quality of life [330], CPAP has also been shown, to a lesser extent, to improve some aspects of sexual function and relationship quality [412, 474]. Erectile function, measured using the International Index of Erectile Function (IIEF) questionnaire, the gold standard of measurement of ED, has shown to increase with CPAP use in uncontrolled trials [484]. Objective measurements of erectile function through the use of nocturnal penile tumescence monitoring have also shown improvements due to CPAP [433, 438, 537]. To date, however, studies investigating the effects of CPAP on sexual function have been limited to observational or non-CPAP placebo

or alternate treatment trials. Randomised sham-controlled CPAP studies have not been performed.

This study aims to investigate the efficacy of CPAP as a treatment for ED using a sham control, while assessing sexual function, mood, and quality of life parameters. Since sexual function is a self-reported subjective outcome, sham control is paramount to ensure adequate blinding.

4.3 METHODS

This was a multisite study, performed in Sydney at the Woolcock Institute of Medical Research, Glebe, New South Wales and in Melbourne at the Department at Respiratory and Sleep Medicine, Monash Medical Centre, Clayton, Victoria, as described in **section 3.2.**

4.3.1 Study Design

This study was performed as part of a 2x2 factoral study, investigating the effects of CPAP and Vardenafil in men with OSA and ED. Sample size was determined as described in section 3.2.4. After baseline data collection, eligible participants at each site (Sydney and Melbourne) were randomised, using two separate computer generated randomization list in blocks of four, to either CPAP or sham CPAP, to be used for 12 weeks at home. Clinical assessments and subjective measurements were assessed before, as well as after 4, 8 and 12 weeks of treatment. Objective measurements were performed at baseline, and at Week 12 whilst using their allocated treatment (see **section 3.2.1**).

4.3.2 Participants

Sixty-one men aged between 18-65 years who had both OSA, and reported ED were recruited into the study as described in **section 3.2.2**. Briefly, participants were required to have at least moderate OSA, defined as an apnoea-hypopnoea index (AHI) measured by polysomnogram, of greater than 20 events per hour, with an oxygen desaturation of 3 % or greater (ODI3) of at least 15 events per hour, as well as ED, defined as a score of less than 26

in the erectile function domain of the International Index of Erectile Function (IIEF) questionnaire.

4.3.3 CPAP Treatment and Sham CPAP Control

CPAP is the first line therapy for obstructive sleep apnoea. Participants were randomly allocated to receive either active CPAP or inactive CPAP therapy – "sham CPAP"- for the duration of the study. Sham CPAP comprised an adapted machine and mask which ensured that the patient received sub-therapeutic (less than 1 cmH2O) therapy, but experienced all other facets of CPAP use. The CPAP motor was set to deliver 10 cmH2O, which was displayed on the patient interface screen. A setting of 10cmH2O is a valid setting for real CPAP, and would not unblind the staff member to the treatment allocation. A restrictor within the device limited the flow output, considerably reducing the pressure delivered. In addition, the usual mask elbow was replaced with a sham mask variant, which had a larger than normal expiratory port [538] . This method of sham control has been successfully used in several other studies [364, 539-542], and analysis of patient perception shows that when used in CPAP naïve patients, adequate blinding is maintained [516].

Prior to commencing on therapy, all participants received an individual education session on obstructive sleep apnoea and CPAP, lasting 1-1.5 hours, delivered by the same staff member in each location, using methods shown to increase adherence to CPAP therapy [543]. Following the education session, each participant chose the most appropriate mask out of those provided to him, which was then tested for suitability regarding correct seal and comfort. The mask was applied with low pressure for about 15 minutes for the participant to become familiar with the sensation, and any questions or concerns allayed. Correct application of the mask and usage of the CPAP machine was reinforced.

Individual pressure requirements for each participant allocated to receive real CPAP were determined via a minimum three night home auto-titration using a Respironics Remstar Pro

CPAP machine (Pittsburgh, USA). A minimum of 4 hours use on any one night was required for the titration to be acceptable. The internal algorithm was used to determine a pressure sufficient to maintain airway patency in each subject. The pressure listed as the 95th percentile was then used to set the machine in a fixed mode for the remainder of the 12 week treatment period. Those participants allocated to receive sham CPAP completed the same procedure, using a sham version of the Respironics Remstar Pro (Pittsburgh, USA).

Double blinding of CPAP settings was strictly maintained via complete separation of machine and mask preparatory procedures from those who had interaction with the participant. All patients, regardless of randomization, completed the home titration procedures. Due to the possibility of unblinding by observation of the CPAP mask, all participants were instructed to speak with an alternate staff member, other than the study co-ordinator, concerning any difficulties they may have with CPAP. This staff member was not involved in any data analysis. CPAP mask choice was limited to those which had a sham version available. This limited the range of masks which could be used to contemporary Respironics nasal masks, namely, Comfort Fusion, Comfort Select, Comfort Gel, Comfort Classic and Profile Lite. Neither full face masks nor nasal pillows were used.

Adherence to CPAP therapy was monitored via product specific memory cards, which were downloaded every 4 weeks of the study. To aid adherence, after 4 weeks of usage all participants watched an 8 minute short film of 4 individuals whom had overcome initial difficulties using CPAP but had persevered to become successful CPAP users. During the study, all efforts were made to encourage participants to use the device whenever they slept. CPAP therapy was commenced without humidification, however, if the participant expressed any concerns regarding nasal stuffiness or dryness, a humidifier was supplied. Appropriate education regarding correct and safe usage of the humidifier was provided prior to initiation.

4.3.4 Subjective Assessments

Subjective measurements of sexual function, relationship quality and quality of life were assessed at baseline and after 4, 8 and 12 weeks of treatment using self-administered computerized or paper based questionnaires as described in **section 3.2.5.**

4.3.5 Measurement of Sleep Related Erections

Sleep Related Erections (SRE's) were measured via Nocturnal Penile Tumescence (NPT) monitoring prior to treatment and at study completion, during polysomnography, using a Rigiscan Plus monitor (Timm Medical Technologies, Minnesota, USA) as per **section 3.2.6**.

4.3.6 Blood Parameters

Fasting blood samples were collected in the morning after the overnight sleep study at baseline and at Week 12. Parameters assessed included reproductive hormones and routine full blood examination.

4.3.7 Polysomnography

Overnight polysomnography was performed prior to commencement of study treatment, as well as after 12 weeks of treatment, in an attended laboratory setting and analysed using a Sandman Elite system and software (Sandman Elite v9.2, Tyco Healthcare, Denver, Colorado) as per **section 3.2.7.**

At the week 12 visit, CPAP or sham CPAP was used for the duration of the sleep period. Polysomnography was repeated using the same methodology as baseline, however, no thermistor was used and oxygen tubing was attached to the CPAP mask to obtain respiration measurements through a pressure transducer, rather than via nasal cannula. All other methodologies remained the same between visits. The CPAP or sham CPAP device was set to the pressure settings used during the study period.

4.3.8 Statistical analysis

Statistical analysis was performed using SAS statistical package version 9.2 (SAS Institute, Cary, North Carolina, USA), as described in section 3.2.5. Student t-tests and Fishers exact test were first used, as appropriate, to establish differences in groups at baseline. Mixed model analysis was first used to ensure there was no interaction between the two concurrent study protocols, as described in **section 3.2.4.** Since this hypothesis was upheld, (see **section 3.3.1**), the effect of each treatment was assessed in separate models. Data was analysed using intention-to-treat principles and the outcome variables were the mean values at weeks 4, 8 and 12 weeks as appropriate. A mixed model analysis compared CPAP with sham CPAP, taking baseline data into consideration. The raw mean, standard deviation, and between-group difference at each time point was reported, with the Week 12 time point being the outcome of interest. Normality of residuals of the final model was confirmed. Per-protocol analysis was then undertaken using the same mixed model analyses in order to examine the influence of CPAP adherence on the effect of treatment. The between CPAP and sham group difference were reportedly separately in the adherent participants.

4.4 RESULTS

The flow of participants through the study is shown in **figure 4.1**. Sixty-one men were randomized into the study. Of these participants, 31 were allocated to receive real CPAP, and 30 to sham CPAP. Six participants withdrew from the study after commencing treatment. Of these, two withdrew from the study due to being unhappy with treatment (both from the sham CPAP group), and four (2 on sham, 2 on real) withdrew due to personal reasons. There was no difference in any demographic, sleep or erectile function parameter between those who withdrew and those who completed the study (data not shown). Fifty five men completed the study. Baseline characteristics of demographic, medical history, sleep and breathing, and sexual function parameters between those who were randomised to CPAP or sham CPAP as shown in **table 4.1.** Despite randomisation, a significant difference was noted in the primary outcome, namely the IIEF questionnaire overall. Additionally, the IIEF domains of intercourse satisfaction, orgasmic function, and overall satisfaction, as well as the FOSQ domain of intimacy were also found to be different at baseline.

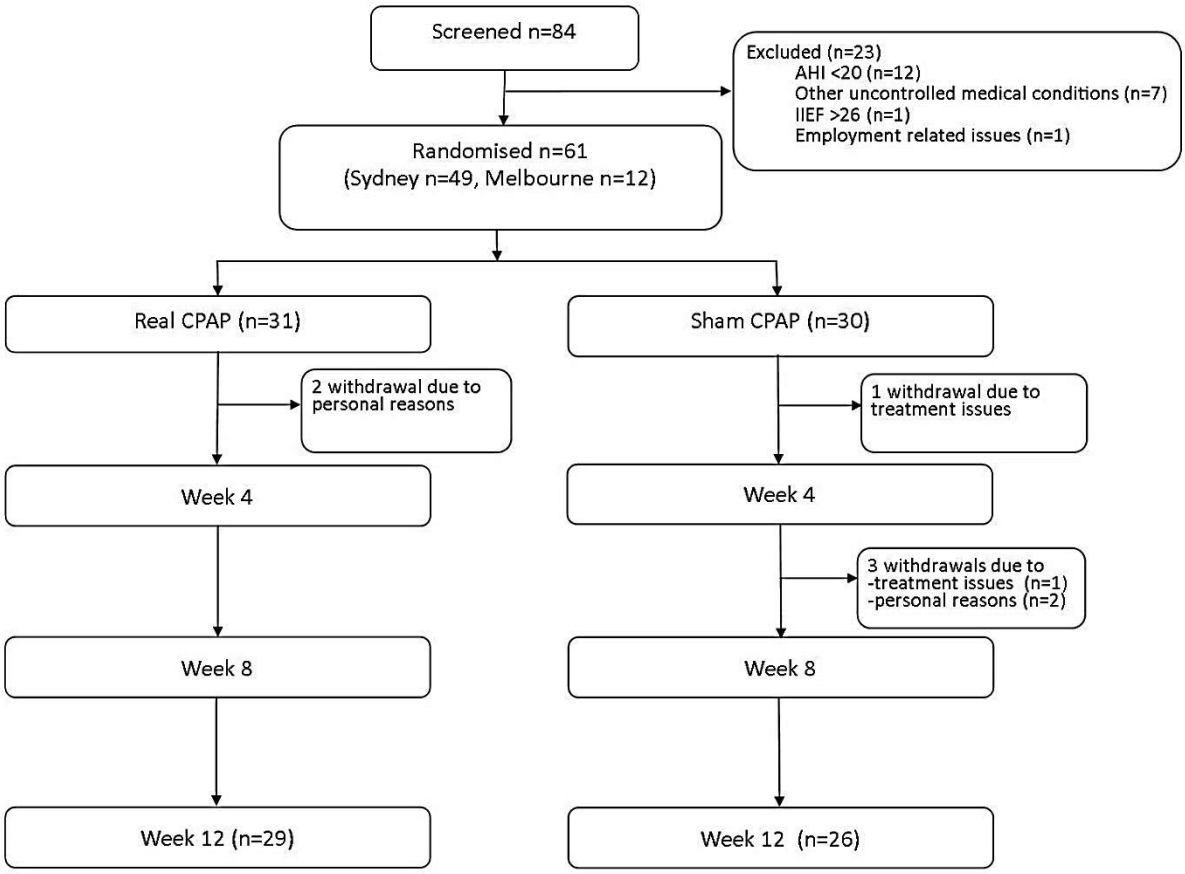


Figure 4.1 Study Flow

Table 4.1 Baseline Characteristics

	CPAP (n=31)	Sham CPAP (n=30)	p-value
Age (years)	55.7 ± 7.7	52.6 ± 10.4	0.178
Medical History			
Hypertension n (%)^	18 (58)	14 (47)	0.401
Using antihypertensives n (%)	15 (48)	10 (33)	0.192
Hypercholesterolemia n (%)^	8 (26)	8 (26)	0.999
Using statins n (%)	6 (19)	5 (17)	0.802
Diabetes n (%)^	7 (23)	4 (13)	0.187
Using diabetic medications (%)	7 (23)	4 (13)	0.188
Lifestyle Factors			
Number of drinks per week	9.1 ± 9.8	10.6 ± 15.6	0.659
Drink more than 10 drinks/week n(%)	11 (36)	10 (33)	0.782
Past smokers n(%)	25 (81)	25 (83)	0.903
Anthropometry			
Weight (kg)	101.0 ± 14.0	100.1 ± 18.0	0.827
Body Mass Index (kg/m^2)	32.9 ± 4.2	32.7 ± 5.5	0.881
Neck circumference (cm)	42.9 ± 3.3	42.9 ± 2.9	0.946
Mid-arm circumference (cm)	32.8 ± 2.5	33.7 ± 3.5	0.250
Waist circumference (cm)	112.0 ± 11.6	109.7 ± 13.3	0.481
Hip circumference (cm)	108.7 ± 10.1	109.5 ± 11.6	0.790
Mid-Thigh circumference (cm)	51.9 ± 4.6	52.8 ± 7.9	0.602

Values are mean ± standard deviation or number (percentage). p-value calculated by Students t-test or Fishers exact test. ^as diagnosed prior entry into the study.

(Continued over)

Table 4.1 Baseline Characteristics (continued)

	CPAP (n=31)	Sham CPAP (n=30)	p-value
Sleep and Breathing			
Total Sleep Time (minutes)	364.9 ± 54.8	330.6 ± 93.4	0.084
Sleep Efficiency (%)	80.4 ± 11.1	75.3 ± 20.9	0.236
REM (% of total sleep time)	16.9 ± 6.4	16.2 ± 7.8	0.700
Arousal index (/hour)	34.1 ± 20.9	34.1 ± 19.6	0.999
Apnoea Hypopnoea Index (AHI)	48.2 ± 26.9	44.0 ± 24.9	0.527
NREM AHI	50.0 ± 28.5	44.6 ± 26.3	0.453
REM AHI	50.9 ± 24.3	45.2 ± 26.4	0.399
Minimum SpO2	77.3 ± 10.1	74.6 ± 11.2	0.336
Time SaO2 below 90% (min)	11.9 ± 15.7	12.9 ± 14.7	0.815
Oxygen Desaturation (3%) Index	43.7 ± 30.9	44.5 ± 27.7	0.919
Sexual Function & Relationship Parameters			
Relationship duration (years)	17.3 ± 13.5	17.2 ± 14.0	0.984
Fathers n (%)	22 (71)	23 (77)	0.712
Duration of erectile dysfunction (years)	6.0 ± 4.6	6.2 ± 5.5	0.857
International Index of Erectile Function (IIEF)	39.0 ± 14.9	30.0 ± 16.3	**0.029**
IIEF - Erectile Function	14.3 ± 7.3	10.7 ± 7.4	0.062
IIEF - Intercourse Satisfaction	6.8 ± 3.7	4.8 ± 4.0	**0.045**
IIEF - Orgasmic Function	6.8 ± 2.9	4.6 ± 3.5	**0.011**
IIEF - Overall Satisfaction	4.9 ± 2.3	3.8 ± 2.0	**0.045**
IIEF - Sexual Desire	6.2 ± 1.6	6.1 ± 2.4	0.909
European Male Aging Study Questionnaire (EMAS)	33.1 ± 8.2	34.3 ± 7.2	0.531
EMAS - Sexual Function related distress	9.3 ± 3.9	11.6 ± 5.7	0.069
EMAS - Change in Sexual Functioning	-3.3 ± 2.9	-3.1 ± 3.5	0.812
EMAS - Overall Sexual Functioning	15.8 ± 5.2	15.0 ± 6.7	0.605
EMAS - Masturbation	2.3 ± 1.8	2.2 ± 1.6	0.839
Self Esteem and Relationship Questionnaire (SERS)	39.5 ± 11.0	37.4 ± 12.0	0.482
SERS - Sexual Relationship Satisfaction	19.9 ± 6.8	17.8 ± 8.1	0.278
SERS - Confidence	19.6 ± 5.6	19.2 ± 5.3	0.793
SERS - Self Esteem	12.6 ± 4.1	12.1 ± 4.6	0.675
SERS - Overall Relationship Satisfaction	7.0 ± 2.0	7.0 ± 2.0	0.898
Nocturnal Penile Tumescence (n=43)			
Total number of erections	2.7 ± 1.9	2.5 ± 2.3	0.762
Tip Rigidity Activation Units	26.5 ± 31.3	20.7 ± 17.8	0.473
Tip Tumescence Activation Units	18.6 ± 20.1	20.6 ± 34.9	0.832
Base Rigidity Activation Units	32.3 ± 35.6	34.2 ± 32.9	0.868
Base Tumescence Activation Units	19.9 ± 21.8	27.7 ± 32.8	0.369
Organic Erectile Dysfunction (%)*	13 (59)	14 (67)	0.754

Note: Values are mean ± standard deviation. p-value calculated by Students t-test. * As defined in **section 3.2.6**

(Continued over)

Table 4.1 Baseline Characteristics (continued)

	CPAP (n=31)	Sham CPAP (n=30)	p-value
Quality of Life			
Subjective Sleepiness (ESS)	10.3 ± 5.1	10.3 ± 4.4	0.987
Functional Outcomes of Sleep Questionnaire (FOSQ)			
FOSQ - Overall score	15.9 ± 3.0	14.9 ± 3.2	0.183
FOSQ - Activity	3.1 ± 0.7	3.0 ± 0.7	0.569
FOSQ - Vigilance	3.2 ± 0.6	3.1 ± 0.6	0.731
FOSQ - Intimacy	2.8 ± 0.7	2.3 ± 1.0	**0.041**
FOSQ - General Productivity	3.5 ± 0.5	3.4 ± 0.6	0.458
FOSQ - Social Outcome	3.5 ± 0.8	3.6 ± 0.7	0.786
Depression Anxiety Stress Scale (DASS)			
DASS - Depression	7.4 ± 7.3	11.4 ± 9.9	0.074
DASS - Anxiety	6.6 ± 5.8	7.0 ± 5.8	0.763
DASS - Stress	12.4 ± 7.1	13.2 ± 7.8	0.659
Short Form 36 (SF-36)			
SF-36 - Physical Function	72.3 ± 21.8	72.0 ± 26.4	0.967
SF-36 - Role - Physical	75.8 ± 29.2	67.2 ± 37.3	0.22
SF-36 - Body Pain	74.9 ± 16.6	72.7 ± 25.9	0.701
SF-36 - General Health	63.4 ± 18.3	59.6 ± 19.9	0.437
SF-36 - Vitality	53.5 ± 21.8	49.8 ± 21.8	0.509
SF-36 - Social Function	82.0 ± 23.8	77.6 ± 27.3	0.511
SF-36 - Role Emotional	72.1 ± 34.6	66.7 ± 36.8	0.562
SF-36 - Mental Health	75.0 ± 16.3	68.3 ± 20.0	0.157
SF-36 - Physical Health	67.9 ± 15.1	64.8 ± 20.4	0.510
SF-36 - Mental Health Dimension	76.4 ± 21.1	72.1 ± 23.3	0.462

Note: Values are mean ± standard deviation. p-value calculated by Students t-test. ESS = Epworth Sleepiness Score

4.4.1 Sleep and breathing

At study entry, there were no differences between the CPAP and sham CPAP groups in terms of sleep and breathing parameters. The baseline AHI was 46.1±25.8 with a minimum SaO2 of 76.0±10.6%. Treatment with CPAP did not change total sleep time or REM percentage from baseline or between groups. CPAP therapy, but not sham CPAP, reduced the severity of OSA (**table 4.2**). CPAP reduced the AHI by 43.1 events per hour ($p<0.001$) to a mean of 7.3±6.6, while sham CPAP did not change AHI. Similarly, the oxygen desaturation index (ODI) was reduced by 38.7 events per hour with CPAP to 7.2±8.7 and did not change for sham CPAP (**table 4.2**).

4.4.2 Subjective Sexual functioning

At baseline, of the 61 study participants, 11.4% had mild ED (IIEF-ED score 22-25), 21.3% had mild-moderate ED (IIEF-ED score 17-21), 26.2% had moderate ED (IIEF-ED score 11-16) and 41% had severe ED (IIEF-ED score 6-10) [430, 544]. CPAP treatment improved overall satisfaction, as measured by the IIEF compared to sham CPAP, and trended toward an improvement in in both overall score and the overall sexual relationship satisfaction domain of the SERS questionnaire ($p=0.06$ and $p=0.07$ respectively). CPAP did not improve any other domain in the IIEF, EMAS or SERS questionnaires compared to sham CPAP (**table 4.3**).

Table 4.2 Effect of CPAP on sleep disordered breathing

	CPAP (n=31)			Sham CPAP (n=30)			Difference between groups (95% CI)	
	Baseline	Week 12	p-value	Baseline	Week 12	p-value		p-value
TST (minutes)	364.9 ± 54.8	371.8 ± 50.1	.616	330.6 ± 93.4	352.5 ± 76.0	.358	-0.9 (-37.1 to 35.2)	.959
REM (% of TST)	16.9 ± 6.4	20.9 ± 10.2	.076	16.2 ± 7.8	17.7 ± 8.6	.502	3.2 (-2.0 to 8.4)	.223
Arousal Index	34.1 ± 20.9	14.4 ± 6.9	**<.001**	34.1 ± 19.6	38.2 ± 23.6	.484	-24.2 (-35.6 to -12.7)	**<.001**
AHI	48.2 ± 26.9	7.3 ± 6.6	**<.001**	44.0 ± 24.9	42.4 ± 27.1	.831	-41.6 (-54.7 to -28.4)	**<.001**
NREM AHI	50.0 ± 28.5	7.6 ± 7.2	**<.001**	44.6 ± 26.3	41.7 ± 29.3	.706	-39.9 (-54.1 to -25.7)	**<.001**
REM AHI	50.9 ± 24.3	10.0 ± 7.3	**<.001**	45.2 ± 26.4	45.3 ± 26.6	.997	-45.2 (-56.7 to -33.8)	**<.001**
Minimum SaO2	77.3 ± 10.1	89.2 ± 5.0	**<.001**	74.6 ± 11.2	77.4 ± 8.7	.332	8.9 (2.8 to 15.0)	**.005**
Time SaO2 below 90% (min)	11.9 ± 15.7	1.7 ± 2.1	**0.001**	12.9 ± 14.7	11.6 ± 12.0	.730	-8.0 (-15.9 to 0.2)	**.046**
ODI	43.7 ± 30.9	7.2 ± 8.7	**<.001**	44.5 ± 27.7	43.6 ± 28.4	.911	-37.4 (-52.4 to -22.4)	**<.001**

Note: Values are mean ± standard deviation. p-value calculated by Students t-test. Abbreviations: AHI = Apnoea Hypopnea Index, NREM: Non Rapid Eye Movement sleep, ODI = Oxygen Desaturation (3%) Index, REM=Rapid Eye Movement Sleep, SaO2 = Oxygen saturation, TST = Total Sleep Time.

Table 4.3 Effect of CPAP versus Sham CPAP on Sexual Function

Variable	Visit	CPAP (n=31)	Sham CPAP (n=30)	Difference Mean (95% CI)	Effect size (d)	p-value
International Index of Erectile Function (IIEF)						
Overall Score	Week 4	43.00 ± 18.29	38.48 ± 19.38	4.52 (-5.67 to 14.71)	0.28	0.842
	Week 8	42.78 ± 17.23	36.96 ± 22.18	5.82 (-5.34 to 16.97)	0.36	0.843
	Week 12	43.31 ± 20.01	33.46 ± 20.08	9.85 (-1.01 to 20.71)	0.61	0.342
Erectile Function	Week 4	16.79 ± 8.68	14.96 ± 9.23	1.82 (-3.02 to 6.67)	0.24	0.866
	Week 8	16.30 ± 8.45	14.60 ± 10.46	1.70 (-3.64 to 7.03)	0.23	0.982
	Week 12	16.28 ± 9.45	13.35 ± 9.43	2.93 (-2.18 to 8.04)	0.39	0.680
Intercourse Satisfaction	Week 4	7.36 ± 4.59	5.96 ± 4.65	1.39 (-1.08 to 3.87)	0.36	0.852
	Week 8	7.07 ± 4.52	6.40 ± 5.22	0.67 (-2.01 to 3.36)	0.17	0.778
	Week 12	7.52 ± 4.93	5.12 ± 4.67	2.40 (-0.20 to 5.01)	0.61	0.281
Orgasmic Function	Week 4	7.07 ± 3.11	5.93 ± 3.92	1.15 (-0.77 to 3.06)	0.34	0.839
	Week 8	6.93 ± 3.22	5.32 ± 3.77	1.61 (-0.32 to 3.54)	0.47	0.543
	Week 12	6.76 ± 3.40	4.69 ± 3.71	2.07 (0.14 to 3.99)	0.61	0.286
Overall Satisfaction	Week 4	5.57 ± 2.33	4.67 ± 2.34	0.90 (-0.36 to 2.17)	0.40	0.531
	Week 8	5.93 ± 2.18	4.52 ± 2.86	1.41 (-0.01 to 2.83)	0.63	0.106
	Week 12	6.17 ± 2.65	4.35 ± 2.53	1.83 (0.42 to 3.23)	0.82	**0.038**
Sexual Desire	Week 4	6.21 ± 1.71	6.74 ± 2.10	-0.53 (-1.56 to 0.51)	-0.26	0.397
	Week 8	6.39 ± 1.91	6.12 ± 2.15	0.27 (-0.85 to 1.39)	0.13	0.716
	Week 12	6.59 ± 2.08	5.96 ± 2.37	0.62 (-0.58 to 1.83)	0.31	0.284

Note: Values are mean ± standard deviation. p-value calculated by mixed model analysis. Effect size (Cohen's d) calculated by dividing difference between CPAP and sham by the standard deviation at baseline.

(Continued over)

Table 4.3 Effect of CPAP versus Sham CPAP on Sexual Function (continued)

Variable	Visit	CPAP Mean ± SD	Sham CPAP Mean ± SD	Difference Mean (95% CI)	Effect size (d)	p-value
European Male Aging Study questionnaire (EMAS)						
Overall Score	Week 4	34.29 ± 8.89	33.96 ± 9.26	0.33 (-4.79 to 5.45)	0.04	0.227
	Week 8	35.89 ± 7.84	35.57 ± 7.71	0.32 (-4.12 to 4.76)	0.04	0.331
	Week 12	35.83 ± 8.73	34.83 ± 7.70	0.99 (-3.60 to 5.58)	0.13	0.226
Sexual	Week 4	7.14 ± 4.42	8.78 ± 5.60	-1.63 (-4.36 to 1.09)	-0.33	0.895
Function	Week 8	7.21 ± 4.27	10.32 ± 7.23	-3.11 (-6.46 to 0.25)	-0.63	0.201
Distress	Week 12	6.45 ± 4.82	8.80 ± 6.26	-2.35 (-5.38 to 0.68)	-0.47	0.384
Change in	Week 4	-1.43 ± 4.31	-1.69 ± 5.18	0.26 (-2.27 to 2.79)	0.08	0.790
Sexual	Week 8	-0.96 ± 3.99	-1.85 ± 5.51	0.88 (-1.73 to 3.49)	0.28	0.304
Function	Week 12	-0.62 ± 4.36	-1.62 ± 4.46	0.99 (-1.39 to 3.38)	0.31	0.443
Overall	Week 4	17.11 ± 5.67	15.77 ± 6.62	1.34 (-2.02 to 4.70)	0.23	0.393
Sexual	Week 8	17.89 ± 5.35	16.52 ± 6.58	1.37 (-2.07 to 4.81)	0.23	0.075
Function	Week 12	18.34 ± 5.91	16.83 ± 7.46	1.51 (-2.17 to 5.20)	0.26	0.147
Masturbation	Week 4	2.46 ± 1.57	2.15 ± 1.61	0.32 (-0.55 to 1.18)	0.18	0.301
	Week 8	2.54 ± 1.71	2.12 ± 1.72	0.42 (-0.53 to 1.36)	0.25	0.372
	Week 12	2.41 ± 1.74	2.24 ± 1.74	0.17 (-0.78 to 1.13)	0.10	0.876
Self-Esteem and Relationship Satisfaction (SERS)						
Overall Score	Week 4	44.11 ± 10.40	39.31 ± 14.31	4.80 (-2.00 to 11.6)	0.42	0.186
	Week 8	44.07 ± 9.59	40.59 ± 16.29	3.48 (-4.5 to 11.46)	0.30	0.480
	Week 12	46.79 ± 12.60	40.04 ± 14.18	6.75 (-0.64 to 14.14)	0.59	0.066
Sexual	Week 4	22.75 ± 6.58	19.81 ± 8.93	2.94 (-1.29 to 7.16)	0.40	0.405
Relationship	Week 8	22.79 ± 6.61	19.67 ± 10.02	3.12 (-1.73 to 7.97)	0.42	0.443
Satisfaction	Week 12	24.66 ± 8.43	19.40 ± 9.00	5.26 (0.49 to 10.02)	0.71	0.059
Confidence	Week 4	21.36 ± 5.26	19.23 ± 6.33	2.13 (-1.05 to 5.30)	0.39	0.101
	Week 8	21.29 ± 4.77	20.57 ± 6.65	0.72 (-2.62 to 4.06)	0.13	0.637
	Week 12	22.14 ± 5.15	20.33 ± 6.91	1.80 (-1.52 to 5.13)	0.33	0.186
Self Esteem	Week 4	13.68 ± 4.17	12.26 ± 4.76	1.42 (-1.00 to 3.84)	0.33	0.230
	Week 8	14.25 ± 3.04	12.96 ± 5.66	1.29 (-1.33 to 3.91)	0.30	0.301
	Week 12	14.69 ± 3.66	12.68 ± 5.33	2.01 (-0.54 to 4.56)	0.46	0.090
Overall	Week 4	7.68 ± 2.13	6.63 ± 2.48	1.05 (-0.20 to 2.30)	0.53	0.077
Relationship	Week 8	7.04 ± 2.46	7.26 ± 2.20	-0.23 (-1.55 to 1.10)	-0.11	0.524
Satisfaction	Week 12	7.45 ± 2.13	7.33 ± 2.37	0.11 (-1.13 to 1.36)	0.06	0.818

Note: Values are mean ± standard deviation. p-value calculated by mixed model analysis. Effect size (Cohen's d) calculated by dividing difference between CPAP and sham by the standard deviation at baseline.

4.4.3 Hormonal Analysis

At study commencement, testosterone levels spanned the lower part of the normal young adult reference range (10.2±3.7 nmol/L). CPAP therapy did not increase testosterone levels. There was an increase in testosterone from baseline to week 12 in those allocated to sham CPAP (12.4±4.3, p=0.04) which was not different than CPAP. There was no change in luteinizing hormone, follicular stimulating hormone, or sex hormone binding globulin.

4.4.4 Nocturnal Penile Tumescence

Twenty eight participants (46%) were agreeable to undertake, and completed nocturnal penile tumescence (NPT) monitoring both prior treatment and study completion. Of these, 15 were on CPAP, 13 were on sham CPAP. Participants who agreed to take part in this monitoring did not differ from those who declined in terms of age, severity of ED, sleepiness, testosterone or weight. However, those who did NPT monitoring had less severe OSA compared to those who did not (AHI: 41.5±22.7 vs 56.9±29.9, p=0.033; Minimum SaO2: 78.5±9.0% vs 70.1±12.0, p=0.004; Oxygen Desaturation Index 37.9±25.1 vs 58.4±33.4, p=0.011). Results for NPT monitoring are given in **table 4.4**. Data shown is from one night, that of the night of polysomnography at each visit. At baseline, there were no differences in any NPT parameter between the CPAP and sham groups (**table 4.1**). At Week 12, those who were allocated to CPAP had an increased number of erections compared to sham CPAP but did not show any improvement in any other parameter of NPT (**table 4.4**). Nocturnal erections recorded occurred during periods of REM sleep, as well as some periods either side of those epochs designated as REM sleep. An example of an individual NPT recording with concurrent sleep staging and pulse oximetry is shown for Baseline and Week 12 for a participant allocated to CPAP treatment (**figure 4.2**).

Table 4.4 Effect of CPAP on Sleep Related Erections

	Baseline	Week 12			
	All (n=38)	CPAP (n=15)	Sham CPAP (n=13)	Effect size (d)	p-value
Number of erections per night	2.6 ± 2.1	4.1 ± 2.0	2.4 ± 1.8	0.81	**<0.001**
Tip Rigidity Activation Units	24.0 ± 24.3	45.7 ± 45.2	47.0 ± 54.7	-0.05	0.713
Tip Tumescence Activation Units	19.6 ± 19.4	33.6 ± 34.3	36.4 ± 47.0	-0.14	0.395
Base Rigidity Activation Units	39.7 ± 48.2	68.2 ± 58.5	57.0 ± 58.6	0.23	0.974
Base Tumescence Activation Units	30.9 ± 36.9	41.6 ± 39.9	49.2 ± 67.8	-0.21	0.101

Note: Values are mean ± standard deviation. p-value calculated by mixed model analysis. Effect size (Cohen's d) calculated by dividing difference between CPAP and sham by the standard deviation at baseline.

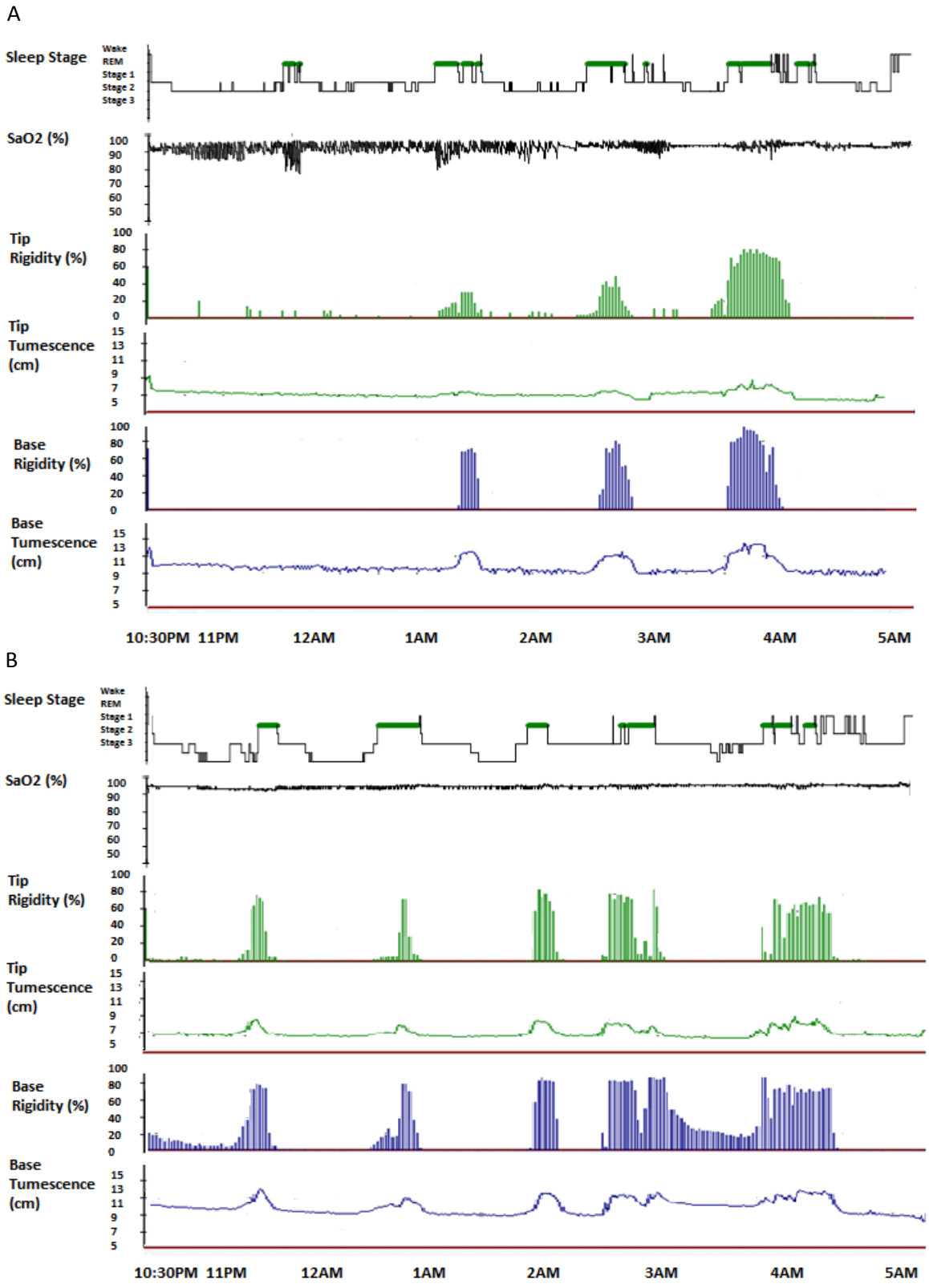


Figure 4.2: Sleep staging, pulse oximetry & NPT recording for a patient allocated to CPAP

Note: (A) Baseline recording with no treatment. Several erectile episodes are seen during some but not all of the REM sleep periods. (B) Recording at Week 12 for the same participant, using CPAP. Erectile episodes are seen during all REM sleep periods. The number of episodes of erection increased however there has not been a change in quality.

4.4.5 Quality of Life

Allocation to CPAP therapy, compared to sham CPAP, did not change levels of sleepiness, depression, anxiety or stress (data not shown). Improvements were seen only in the domains of Vitality, in the SF-36 questionnaire, and in Vigilence in the FOSQ questionnaire, for those randomised to CPAP versus sham CPAP (mean difference, 95% CI: 11.05(-0.49 to 22.60), p=0.03, and 0.36(-0.05 to 0.77), p=0.01 respectively) at the Week 12 timepoint.

4.4.6 CPAP adherence

Adherence rates to CPAP therapy are listed in **Table 4.5**. During the treatment period there was no significant difference between the usage of CPAP and sham CPAP, as measured by average hours used per intended days of use. The average usage was 3.7 ± 2.5 hours and 2.6 ±2.2 hours per night for CPAP and sham CPAP groups respectively (p=0.092). Adherence to therapy, defined by CPAP usage for more than 4 hours per night, was achieved by 46% of those randomised to real CPAP and 29% of those allocated to sham CPAP. There appeared to be a bimodal distribution of low usage and high usage in the CPAP group, split at the commonly used definition of adherence, 4 hours per night minimum usage, but not in the placebo group (**figure 4.3**).

Those participants adherent to treatment used the device for 6.2±0.9 hours per night for the CPAP group and 5.1±1.2 hours per night for the sham CPAP group (p=0.146). Apart from relationship duration and a trend toward erectile dysfunction duration and pre-exisiting hypercholesterolemia, there was no other identifiable difference between those who did and did not adhere to CPAP therapy (t**able 4.6**).

Hereafter those participants who used CPAP or sham CPAP for more or less than 4 hours per night are referred to as “adherers” and “non-adherers” respectively. The baseline characteristics of these two groups are described in **table 4.7**. Apart from prevalence of a

diagnosis of diabetes, the treatment two groups exhibited no differences at baseline. There were a higher percentage of those with diabetes in the adherent CPAP group, compared to the adherent sham CPAP group (p=0.02).

Table 4.5 CPAP Adherence (hours of use per night) for study completers

	CPAP (n=26)[#]	Sham (n=28)^	p-value
Hours / intended days of use (mean ± SD)	3.7 ± 2.5	2.6 ±2.2	0.092
Hours / days used (mean ± SD)	4.5 ± 2.0	4.0 ± 1.9	0.422
Adherent to therapy (>4hours) n (%)	12 (46)	8 (29)	0.683

Values are mean ± standard deviation. p-value calculated using students t-test

NOTE: [#]Although 31 participants were allocated to CPAP, data is only available for 26. Data missing for 3 participants due to technical failure of CPAP recording cards and 2 withdrew before treatment commenced. ^Although 30 participants were allocated to sham CPAP, data is only available for 28. Data missing for 1 participant due to technical failure of CPAP recording card and 1 withdrew before treatment commenced.

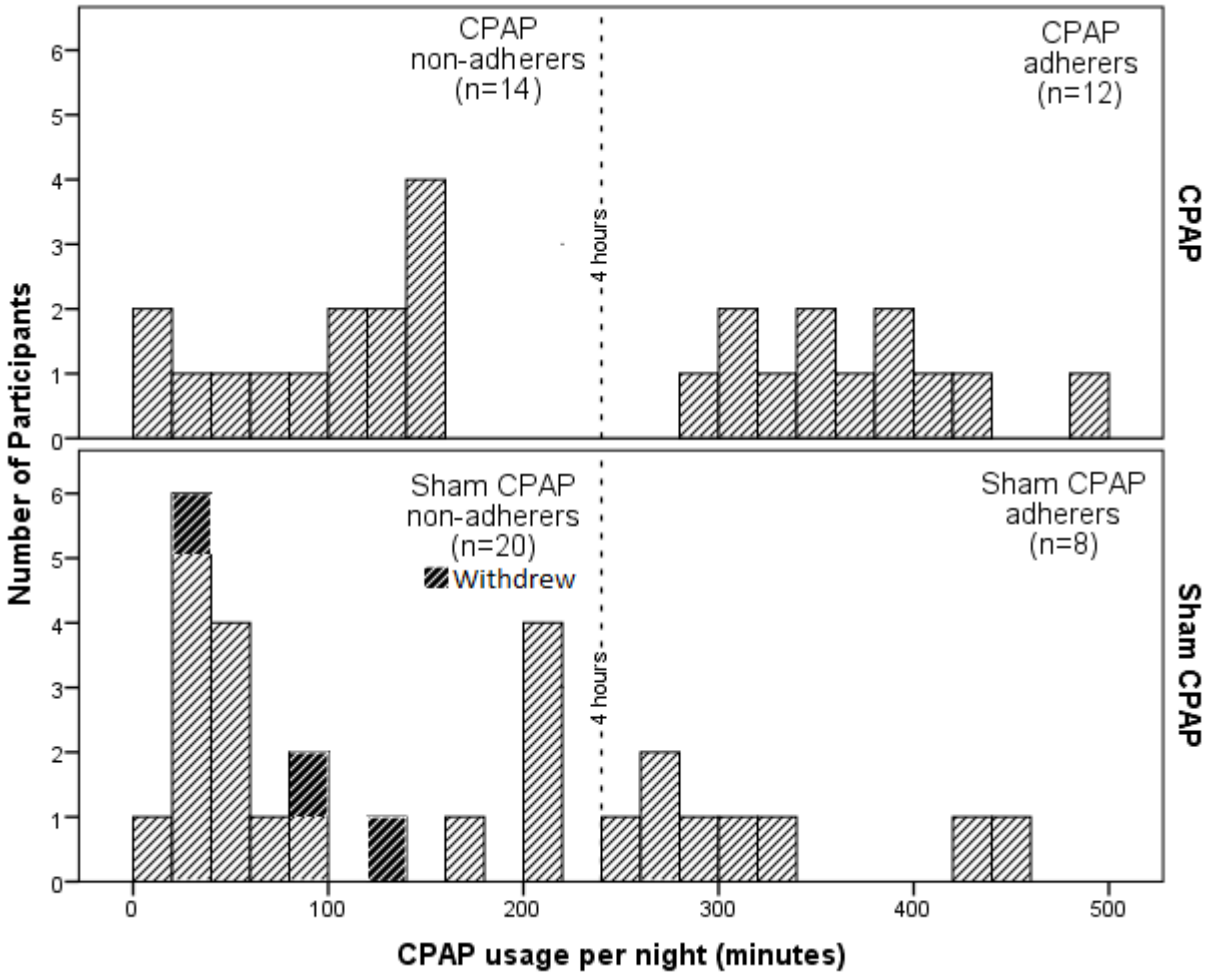


Figure 4.3: CPAP and Sham CPAP usage per night for all participants.

Note: Histogram data shows the average usage of CPAP / sham CPAP in terms of number of participants who used CPAP (top row) or sham CPAP (bottom row) device in 20 minute epochs from no usage to 8 hours. The dashed vertical line represents the cut off mark of 4 hours per night, allocating patients to the adherent and non-adherent groups. Participants who withdrew after commencing treatment are indicated by the darker dashed squares.

Table 4.6 Characteristics of participants adherent and not adherent to CPAP treatment

	Non adherers (<4 hrs CPAP usage) (n=34)	Adherers (>4 hrs CPAP usage) (n=20)	p value
General Health			
Hypertension n (%)	20 (59)	10 (50)	0.581
Hypercholesterolemia n (%)	6 (18)	9 (45)	0.056
Diabetes n (%)	6 (18)	4 (20)	0.998
Body Mass Index (kg/m2)	33.7 ± 5.2	31.6 ± 4.7	0.143
Erectile function			
Duration of Erectile Dysfunction (years)	7.4 ± 5.7	4.2 ± 3.9	0.059
International Index of Erectile Function	33.9 ± 16.2	33.2 ± 17.5	0.885
IIEF Erectile Dysfunction	11.9 ± 7.7	12.3 ± 8.0	0.857
IIEF Intercourse Satisfaction	5.6 ± 4.2	5.7 ± 4.1	0.964
IIEF Orgasmic Function	5.8 ± 3.5	5.3 ± 3.6	0.643
IIEF Overall Satisfaction	4.3 ± 2.2	4.0 ± 2.1	0.630
IIEF Sexual Desire	6.3 ± 2.4	6.0 ± 1.6	0.490
Testosterone (nmol/L)	9.3 ± 3.0	10.4 ± 4.2	0.545
Sleep and Breathing parameters			
Total Sleep Time	348.6 ± 91.6	337.8 ± 52.9	0.631
Sleep Efficiency	78.8 ± 20.0	76.0 ± 12.2	0.576
REM proportion (%)	17.5 ± 6.9	15.1 ± 8.0	0.261
Arousal Index (per hour)	33.3 ± 20.0	38.5 ± 22.2	0.381
Apnoea Hypopnoea Index (AHI)	47.0 ± 25.7	50.6 ± 27.7	0.636
REM AHI	48.1 ± 27.8	52.5 ± 28.7	0.590
NREM AHI	51.6 ± 23.9	48.1 ± 26.8	0.626
Minimum SaO2	73.3 ± 10.0	78.0 ± 11.5	0.122
Time below SaO2 90%	13.0 ± 13.1	14.1 ± 19.7	0.798
Oxygen desaturation Index (per hour)	45.3 ± 28.0	48.4 ± 33.1	0.716
Social & Lifestyle Factors			
Alcoholic drinks per week	10.9 ± 15.1	8.3 ± 10.0	0.496
Age (years)	52.7 ± 9.5	56.1 ± 9.1	0.208
Relationship length (years)	12.3 ± 12.3	21.6 ± 13.6	**0.013**
Fathers n (%)	24.0 (71)	14.0 (70)	0.990
Site: Sydney based (versus Melbourne) n	29.0 (85)	16.0 (80)	0.179
Past smoker	28.0 (83)	16.0 (80)	0.990

Characteristics of those who did and did not adhere to CPAP/sham therapy, according to adherence definition of 4 hours minimum per night. Values are mean ± standard deviation. p-value calculated using students t-test. CPAP adherence data missing for 4 participants due to technical difficulties (3 from CPAP group, 1 from sham CPAP). No CPAP adherence data for 3 participants who withdrew before CPAP treatment commenced (2 from CPAP group, 1 from sham)

Table 4.7 Baseline Characteristics of participants adherent to CPAP / Sham CPAP

	CPAP (n=12)	Sham CPAP (n=8)	p-value
Age (years)	56.9 ± 6.7	54.9 ± 12.3	0.636
Medical History			
Hypertension n (%)^	4 (33)	2 (25)	0.999
Using antihypertensives n (%)	4 (33)	1 (4)	0.603
Hypercholesterolemia n (%)^	7 (58)	3 (38)	0.650
Using statins n (%)	7 (58)	1 (13)	0.070
Diabetes n (%)^	9 (75)	1 (13)	**0.020**
Using diabetic medications (%)	9 (75)	1 (13)	**0.020**
Lifestyle Factors			
Number of drinks per week	8.0 ± 11.1	8.8 ± 8.6	0.871
Past smokers n(%)	9 (75)	7 (88)	0.619
Anthropometry			
Weight (kg)	99.7 ± 16.2	88.4 ± 16.6	0.148
Body Mass Index (kg/m^2)	32.9 ± 4.4	29.7 ± 4.6	0.132
Neck circumference (cm)	42.7 ± 3.4	41.4 ± 3.3	0.418
Mid-arm circumference (cm)	32.1 ± 2.1	31.9 ± 2.8	0.897
Waist circumference (cm)	111.4 ± 12.3	101.3 ± 9.9	0.069
Hip circumference (cm)	109.7 ± 10.3	103.4 ± 6.9	0.148
Mid-Thigh circumference (cm)	51.0 ± 5.3	51.2 ± 5.7	0.954

Note: Values are mean ± standard deviation or number (percentage). p-value calculated by Students t-test or Fishers exact test. ^as diagnosed prior entry into the study.

(Continued over)

Table 4.7 Baseline Characteristics of participants' adherent to CPAP/Sham CPAP (continued)

	CPAP (n=20)	Sham CPAP (n=8)	p-value
Sleep and Breathing			
Total Sleep Time (minutes)	341.0 ± 37.6	333.0 ± 73.1	0.783
Sleep Efficiency (%)	77.6 ± 9.0	73.5 ± 16.4	0.478
REM (% of total sleep time)	13.6 ± 7.3	17.4 ± 8.9	0.305
Arousal index (/hour)	43.6 ± 25.2	30.9 ± 15.1	0.216
Apnoea Hypopnoea Index (AHI)	59.1 ± 28.5	37.8 ± 22.4	0.093
NREM AHI	61.7 ± 29.1	38.6 ± 23.2	0.076
REM AHI	55.5 ± 22.9	37.8 ± 29.9	0.162
Minimum SpO2	77.1 ± 10.8	79.4 ± 13.1	0.675
Time SaO2 below 90% (min)	17.9 ± 21.6	8.5 ± 16.0	0.306
Oxygen Desaturation (3%) Index	53.0 ± 36.4	41.7 ± 28.5	0.469
Sexual Function & Relationship Parameters			
Relationship duration (years)	21.6 ± 12.3	21.6 ± 16.3	0.995
Duration of erectile dysfunction (years)	5.1 ± 4.7	3.1 ± 2.4	0.330
International Index of Erectile Function (IIEF)			
IIEF – Overall Score	38.4 ± 15.0	25.4 ± 18.9	0.103
IIEF - Erectile Function	14.3 ± 7.5	9.1 ± 8.1	0.157
IIEF - Intercourse Satisfaction	7.0 ± 3.5	3.8 ± 4.2	0.078
IIEF - Orgasmic Function	6.5 ± 2.9	3.5 ± 3.9	0.062
IIEF - Overall Satisfaction	4.2 ± 2.1	3.8 ± 2.3	0.680
IIEF - Sexual Desire	6.4 ± 1.2	5.3 ± 1.8	0.105
European Male Aging Study Questionnaire (EMAS)			
EMAS – Overall Score	33.4 ± 8.4	30.3 ± 3.9	0.344
EMAS - Sexual Function related distress	9.0 ± 3.2	10.9 ± 5.6	0.355
EMAS - Change in Sexual Functioning	-3.6 ± 3.2	-2.6 ± 3.2	0.521
EMAS - Overall Sexual Functioning	15.8 ± 5.0	12.0 ± 6.7	0.157
EMAS - Masturbation	2.6 ± 1.7	1.5 ± 1.7	0.183
Self Esteem and Relationship Questionnaire (SERS)			
SERS – Overall Score	38.7 ± 10.9	36.4 ± 14.5	0.707
SERS - Sexual Relationship Satisfaction	19.6 ± 6.7	17.0 ± 9.4	0.494
SERS - Confidence	19.1 ± 5.0	18.1 ± 7.2	0.730
SERS - Self Esteem	12.1 ± 3.5	11.3 ± 6.1	0.735
SERS - Overall Relationship Satisfaction	7.0 ± 2.0	6.9 ± 2.2	0.895

Note: Values are mean ± standard deviation. p-value calculated using students t-test.

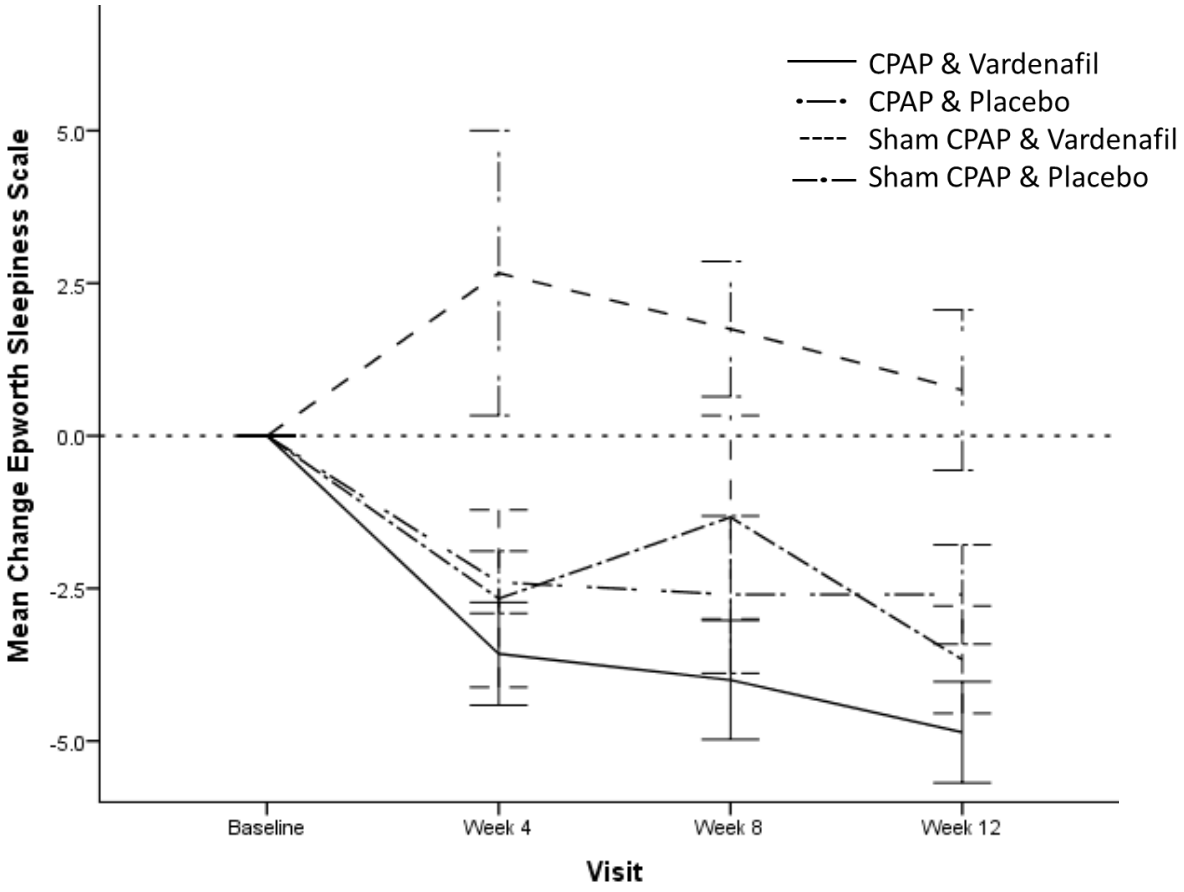
4.4.7 Interactions between treatments for adherers

In order to assess any treatment interactions with Vardenafil in those participants adherent to CPAP or sham CPAP, interactions were tested in this sub-analysis, in the same manner as described in **section 3.2.4,** and presented in **table 4.8.** No 3 way interactions between treatments were found in any parameter. Since no interactions were seen in the 3 way analysis, a 2 way analysis of interactions was performed. When analysed in a 2-way interaction, having removing visit from the model, there were no interactions found in any sexual function parameter. However, four quality of life parameters were found to have an interaction – the Epworth Sleepiness Scale, and in the SF-36 questionnaire domains of Role Physical, General Health and Physical Health. These parameters are presented in **figure 4.4,** presented by visit**.** No synergistic effects were found in any of these parameters.

Table 4.8: Interaction between treatments for adherent CPAP/sham CPAP users.

	3 way p-value	2 way p-value
International Index of Erectile Function (IIEF)		
IIEF - Overall Score	0.7667	0.8673
IIEF - Erectile Function	0.6414	0.5361
IIEF - Intercourse Satisfaction	0.6018	0.6629
IIEF - Orgasmic Function	0.1862	0.8600
IIEF - Overall Satisfaction	0.3365	0.6296
IIEF - Sexual Desire	0.9637	0.1507
European Male Aging Study questionnnaire (EMAS)		
EMAS - Overall Score	0.3574	0.7761
EMAS - Sexual Function Distress	0.5092	0.7518
EMAS - Change in Sexual Function	0.9576	0.4318
EMAS - Overall Sexual Function	0.7031	0.3858
EMAS - Masturbation	0.9091	0.7384
Self-Esteem and Relationship Satisfaction (SERS)		
SERS - Overall Score	0.9496	0.2741
SERS - Sexual Relationship Satisfaction	0.7008	0.8099
SERS - Confidence	0.7995	0.0787
SERS - Self Esteem	0.9913	0.1625
SERS - Overall Relationship Satisfaction	0.2571	0.2844
Epworth Sleepiness Score (ESS)		
ESS - Overall Score	0.3062	**0.0029**
Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS)		
EDITS - Overall Score	0.3165	0.9239
Functional Outcomes of Sleep (FOSQ)		
FOSQ - Activity	0.9102	0.7010
FOSQ - Vigilance	0.5846	0.0611
FOSQ - Intimacy	0.8148	0.4865
FOSQ - Productivity	0.8071	0.6796
FOSQ - Social Outcomes	0.2179	0.2389
Short-form 36 (SF-36)		
SF-36 Physical Function	0.5608	0.3733
SF-36 Role Physical	0.3804	**0.0124**
SF -36 Body Pain	0.0506	0.0660
SF-36 General Health	0.5941	**0.0188**
SF-36 Vitality	0.5068	0.8819
SF-36 Social Function	0.4115	0.3719
SF-36 Role Emotional	0.1655	0.1395
SF-36 Mental Health Scale	0.6753	0.7350
SF-36 Physical Health	0.2216	**0.0100**
SF36 Mental Health Dimension	0.1253	0.3042
Depression Anxiety Stress Scale (DASS)		
DASS Depression	0.0742	0.6527
DASS Anxiety	0.4511	0.0694
DASS Stress	0.7453	0.7871

Note: Interaction terms presented as 3 way (CPAP/shamCPAP*Vardenafil/Placebo*time) and 2 way analysis (CPAP/sham CPAP*Vardenafil/Placebo). p-value determine via mixed model analysis.



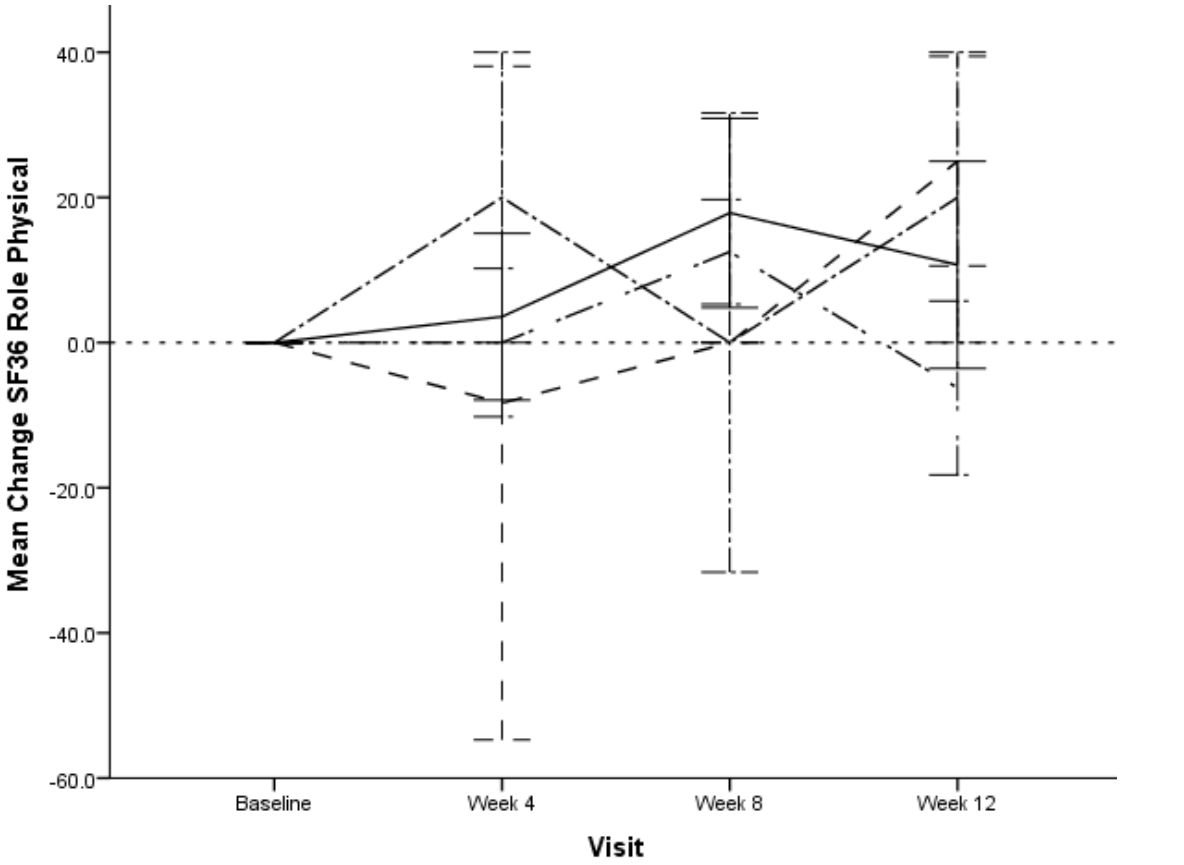


Figure 4.4 Change from baseline for variables with treatment interactions

NOTE: Values shown are mean change from baseline, shown with standard error, for variables shown to have a statistical interaction between the two treatments.

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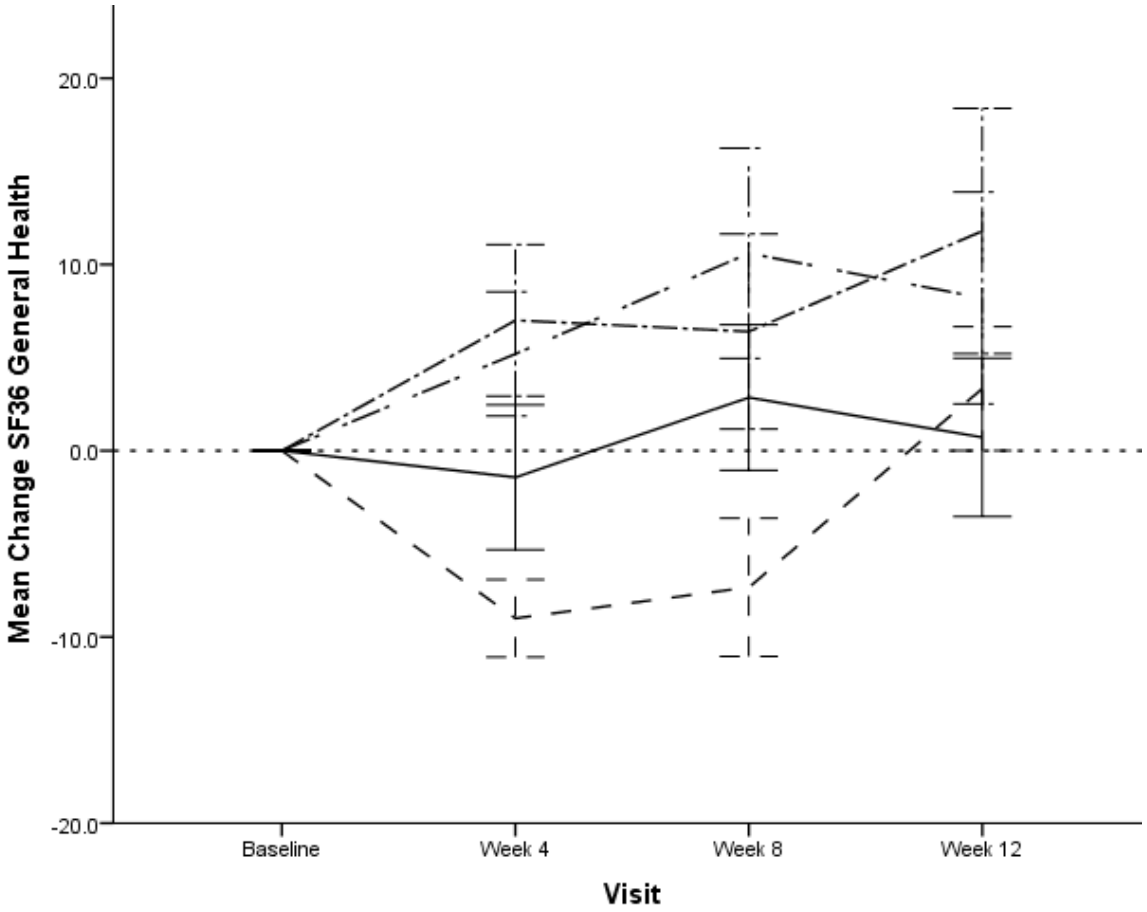


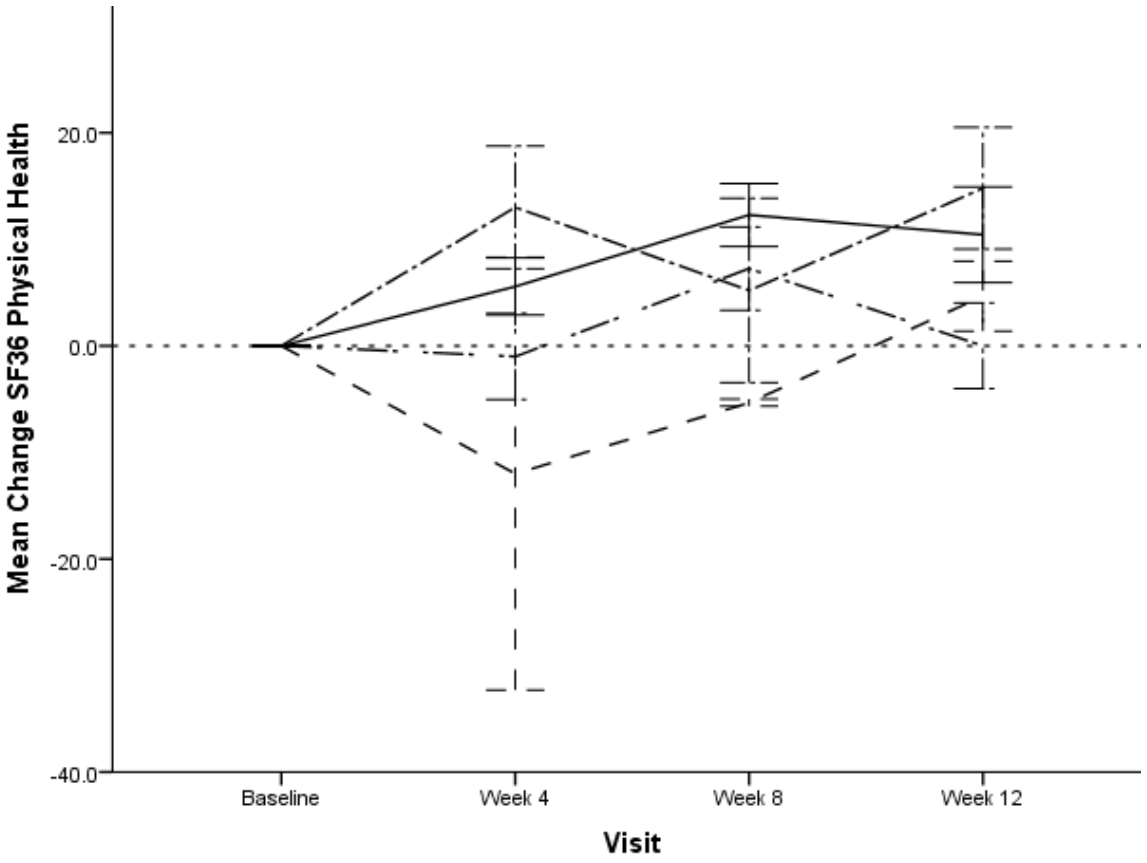


Figure 4.4 Change from baseline for variables with treatment interactions (Continued)

NOTE: Values shown are mean change from baseline, shown with standard error, for variables shown to have a statistical interaction between the two treatments.

4.4.8 Effect of adherence to CPAP therapy

Due to the disparity regards adherence to therapy between participants, results were stratified into two groups: adherent and non-adherent users. Baseline characteristics of these participants are shown in **table 4.6**. Participants adherent to therapy comprise the per-protocol analysis. Whereas only overall satisfaction was seen to occur in the intend-to-treat analysis of those allocated to CPAP versus sham CPAP, several more changes were found in the per-protocol analysis. At Week 4, no improvements were seen in any parameter. At week 8, overall satisfaction, as measured by the IIEF, had improved with CPAP compared to sham CPAP. At week 12, CPAP improved erectile function, sexual desire, distress due to sexual dysfunction, overall sexual function, self-esteem, sexual relationship satisfaction and overall score in the SERS questionnaire compared to sham CPAP (**table 4.9**). Clinical improvement in erectile function, as defined as an improvement by more than 4 points in the IIEF-ED domain was seen in 7 participants (58%), whereas no participants adherent to sham CPAP improved by more than 4 points. Graphic representations of the effects of CPAP therapy compared to sham CPAP for some of the parameters of sexual function and relationship over the 12 week treatment period for adherent users are shown in **figure 4.5** and **figure 4.6**.

Several quality of life measurements in the ESS, DASS, SF-36 and FOSQ questionnaires showed improvements with CPAP compared to sham CPAP for adherent users. CPAP usage, compared to sham CPAP decreased levels of sleepiness, stress and depression (**table 4.10**). Improvements in several parameters of mental health were seen with CPAP compared to sham CPAP (**figure 4.7**). Quality of life domains of Vigilance in the FOSQ, and Social Function and Physical Function of the SF-36 questionnaire also improved with CPAP compared to sham CPAP (**figure 4.8**).

Nocturnal penile tumescence was performed on the night of Week 12 polysomnography. On this night, all patients, regardless of adherence to therapy throughout the study, used CPAP/sham CPAP. Per-protocol analysis for this data did not differ from the original intention to treat analysis.

Table 4.9 Effect of adherent CPAP use on sexual function and relationship parameters

Variable	Visit	CPAP (n=12)			Sham CPAP (n=8)			Difference Mean (95% CI)	Effect size (d)	p-value
International Index of Erectile Function (IIEF)										
Overall Score	Week 4	47.50	±	14.85	37.50	±	23.87	10.00	(-9.24 to 29.24)	0.57	0.827
	Week 8	47.83	±	14.26	30.00	±	24.28	17.83	(-0.66 to 36.33)	1.02	0.264
	Week 12	48.58	±	19.44	24.25	±	17.28	24.33	(6.47 to 42.20)	1.39	**0.031**
Erectile Function	Week 4	19.00	±	6.61	14.33	±	10.31	4.67	(-3.76 to 13.09)	0.59	0.640
	Week 8	19.17	±	7.12	11.14	±	11.13	8.02	(-0.75 to 16.80)	1.01	0.182
	Week 12	18.67	±	9.00	8.50	±	8.26	10.17	(1.80 to 18.53)	1.28	**0.037**
Intercourse Satisfaction	Week 4	8.75	±	3.67	5.57	±	5.44	3.18	(-1.22 to 7.57)	0.78	0.633
	Week 8	8.33	±	3.82	6.00	±	5.63	2.33	(-2.22 to 6.89)	0.57	0.999
	Week 12	9.00	±	4.31	3.63	±	3.58	5.38	(1.50 to 9.25)	1.32	0.068
Orgasmic Function	Week 4	7.67	±	2.93	5.17	±	4.71	2.50	(-2.47 to 7.47)	0.70	0.775
	Week 8	7.42	±	2.71	3.86	±	4.10	3.56	(0.28 to 6.84)	1.00	0.325
	Week 12	7.58	±	3.34	3.63	±	3.70	3.96	(0.62 to 7.30)	1.11	0.144
Overall Satisfaction	Week 4	5.33	±	2.06	4.83	±	2.99	0.50	(-2.03 to 3.03)	0.24	0.626
	Week 8	6.17	±	1.90	3.71	±	2.93	2.45	(0.13 to 4.78)	1.16	**0.020**
	Week 12	6.25	±	2.70	3.38	±	2.07	2.88	(0.50 to 5.25)	1.35	**0.006**
Sexual Desire	Week 4	6.75	±	1.29	6.67	±	1.37	0.08	(-1.31 to 1.48)	0.05	0.882
	Week 8	6.75	±	1.54	5.29	±	2.06	1.46	(-0.29 to 3.21)	0.93	0.146
	Week 12	7.08	±	1.62	5.13	±	1.96	1.96	(0.27 to 3.65)	1.24	**0.031**

Note: Values are mean ± standard deviation. p-value calculated using mixed model analysis. Effect size (Cohen's d) calculated by dividing difference between CPAP and sham by the standard deviation at baseline.

(Continued over)

Table 4.9 Effect of adherent CPAP use on sexual function and relationship parameters (continued)

Variable	Visit	CPAP (n=12)	Sham CPAP (n=8)	Difference Mean (95% CI)	Effect size (d)	p-value
European Male Aging Study questionnaire (EMAS)						
Overall Score	Week 4	34.58 ± 8.12	30.17 ± 9.13	4.42 (-4.54 to 13.37)	0.64	0.314
	Week 8	36.82 ± 7.49	31.50 ± 5.61	5.32 (-2.17 to 12.81)	0.77	0.336
	Week 12	36.67 ± 8.91	30.43 ± 4.12	6.24 (-1.36 to 13.83)	0.91	0.158
Sexual	Week 4	6.67 ± 4.52	9.00 ± 5.03	-2.33 (-7.06 to 2.39)	-0.54	0.798
Distress	Week 8	5.75 ± 3.44	10.29 ± 7.11	-4.54 (-11.19 to 2.12)	-1.05	0.114
	Week 12	4.67 ± 2.42	10.00 ± 5.78	-5.33 (-10.25 to -0.42)	-1.24	**0.017**
Change in	Week 4	-0.42 ± 5.45	-1.75 ± 4.23	1.33 (-3.47 to 6.14)	0.42	0.469
Function	Week 8	0.08 ± 5.02	-2.13 ± 4.22	2.21 (-2.32 to 6.74)	0.70	0.265
	Week 12	0.25 ± 5.46	-2.00 ± 1.77	2.25 (-1.98 to 6.48)	0.71	0.257
Overall Sexual	Week 4	17.17 ± 5.11	14.29 ± 5.85	2.88 (-2.52 to 8.29)	0.49	0.655
Function	Week 8	18.58 ± 4.83	14.00 ± 6.78	4.58 (-1.26 to 10.43)	0.78	0.118
	Week 12	19.50 ± 5.96	12.57 ± 6.27	6.93 (0.84 to 13.02)	1.18	**0.024**
Masturbation	Week 4	2.67 ± 1.67	1.43 ± 1.40	1.24 (-0.35 to 2.82)	0.71	0.220
	Week 8	2.75 ± 1.66	1.88 ± 1.46	0.88 (-0.64 to 2.39)	0.50	0.705
	Week 12	2.58 ± 1.24	1.50 ± 1.69	1.08 (-0.29 to 2.46)	0.62	0.442
Self-Esteem and Relationship Satisfaction (SERS)						
Overall Score	Week 4	42.75 ± 13.18	41.67 ± 16.15	1.08 (-13.94 to 16.11)	0.09	0.655
	Week 8	45.92 ± 10.41	37.29 ± 17.33	8.63 (-4.68 to 21.94)	0.72	0.118
	Week 12	48.50 ± 12.50	37.29 ± 14.19	11.21 (-1.95 to 24.38)	0.93	**0.033**
Sexual	Week 4	22.25 ± 7.57	21.83 ± 9.97	0.42 (-8.48 to 9.31)	0.05	0.957
Relationship	Week 8	24.50 ± 6.02	17.71 ± 11.76	6.79 (-4.25 to 17.82)	0.89	0.089
Satisfaction	Week 12	25.83 ± 7.02	18.14 ± 8.63	7.69 (0.04 to 15.34)	1.00	**0.045**
Confidence	Week 4	20.50 ± 6.71	19.83 ± 8.21	0.67 (-6.98 to 8.31)	0.11	0.260
	Week 8	21.42 ± 5.05	19.57 ± 6.48	1.85 (-3.77 to 7.46)	0.32	0.270
	Week 12	22.67 ± 5.69	19.14 ± 7.73	3.52 (-2.99 to 10.03)	0.60	0.055
Self Esteem	Week 4	13.00 ± 4.84	11.57 ± 6.35	1.43 (-4.01 to 6.87)	0.31	0.281
	Week 8	14.25 ± 3.25	12.00 ± 5.83	2.25 (-2.80 to 7.30)	0.49	0.257
	Week 12	15.08 ± 3.85	11.50 ± 6.05	3.58 (-1.73 to 8.90)	0.78	**0.039**
Overall	Week 4	7.50 ± 2.20	7.00 ± 2.53	0.50 (-1.94 to 2.94)	0.25	0.322
Relationship	Week 8	7.17 ± 2.37	6.57 ± 2.30	0.60 (-1.76 to 2.95)	0.30	0.371
Satisfaction	Week 12	7.58 ± 2.27	6.71 ± 2.36	0.87 (-1.44 to 3.18)	0.44	0.218

Note: Values are mean ± standard deviation. p-value calculated using mixed model analysis. Effect size (Cohen's d) calculated by dividing difference between CPAP and sham by the standard deviation at baseline.

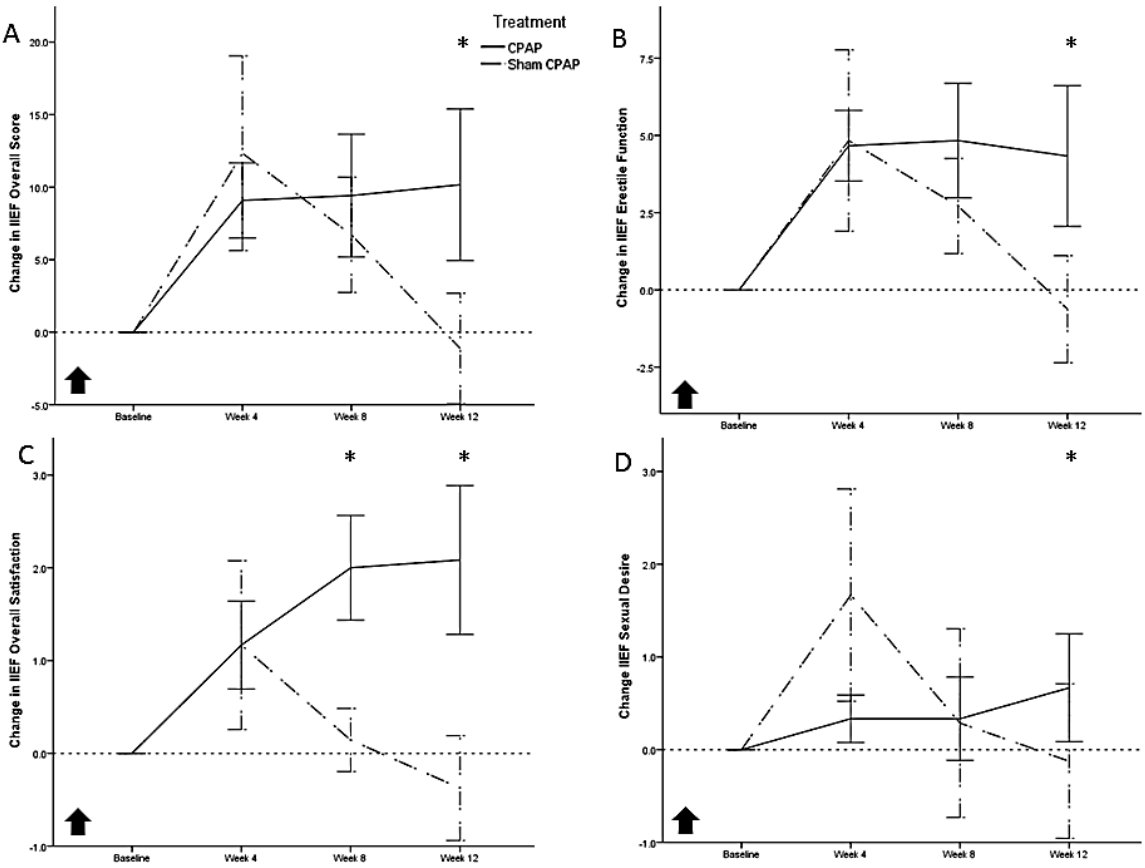


Figure 4.5 Effect of CPAP on sexual function, as measured by the IIEF in adherers

Note: Adherence defined as greater than 4hours use per night. All values shown are change from baseline. Data are mean and standard error of the mean of the change from baseline. (A) IIEF Overall score (B) IIEF Erectile Function (C) Overall Satisfaction (D) Sexual Desire

⬆⬇ Arrow indicates direction of improvement. *p<0.05 as determined by mixed model analysis.

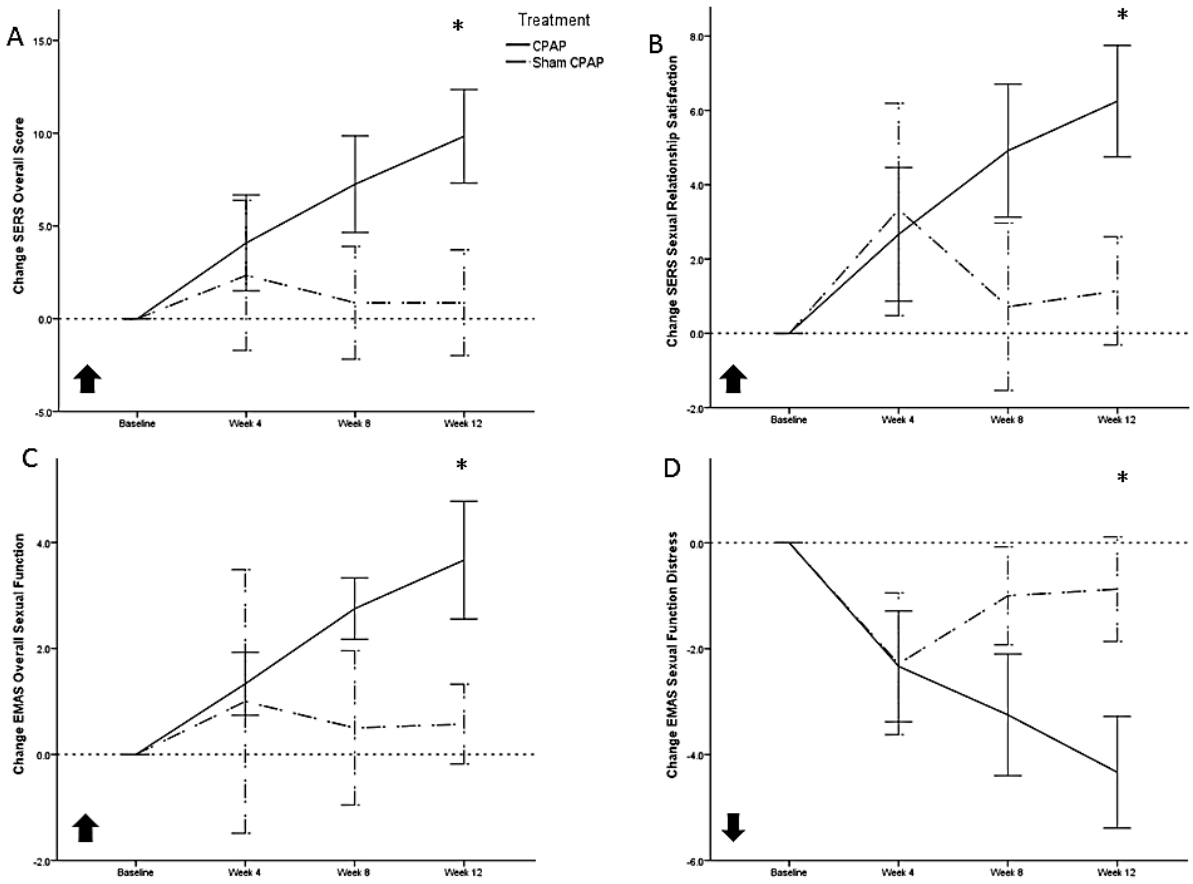


Figure 4.6. Effect of CPAP on sexual function & relationship satisfaction in adherers

Note: Adherence defined as greater than 4hours use per night. (A) SERS Overall Score (B) SERS Sexual Relationship Satisfaction (C), EMAS Overall Sexual Function (D) EMAS Sexual Function Distress. All measurements are mean change from baseline and one standard error of the mean.

⬆⬇ Arrows represent direction of improvement. *p<0.05 as determined by mixed model analysis

Table 4.10 Effect of adherent CPAP use on quality of life parameters

Variable	Visit	CPAP (n=12)	Sham CPAP (n=8)	Difference Mean (95% CI)	Effect size (d)	p-value
Epworth	Week 4	5.75 ± 3.67	10.57 ± 6.02	-4.82 (-9.48 to -0.17)	-1.08	**0.001**
Sleepiness	Week 8	5.42 ± 2.84	11.00 ± 4.24	-5.58 (-9.00 to -2.17)	-1.24	**<0.001**
Scale	Week 12	4.92 ± 3.26	8.75 ± 5.73	-3.83 (-8.80 to 1.14)	-0.86	**0.004**
Functional Outcomes of Sleep (FOSQ)						
Activity	Week 4	3.58 ± 0.41	3.20 ± 0.61	0.38 (-0.11 to 0.87)	0.64	0.101
	Week 8	3.67 ± 0.32	3.18 ± 0.40	0.49 (0.15 to 0.83)	0.83	0.102
	Week 12	3.67 ± 0.44	3.26 ± 0.60	0.40 (-0.09 to 0.89)	0.69	0.209
Vigilance	Week 4	3.73 ± 0.31	3.00 ± 0.79	0.73 (0.06 to 1.39)	1.59	**0.003**
	Week 8	3.71 ± 0.29	3.29 ± 0.35	0.42 (0.12 to 0.72)	0.92	0.211
	Week 12	3.78 ± 0.30	3.10 ± 0.92	0.68 (-0.10 to 1.46)	1.48	**0.006**
Intimacy	Week 4	3.57 ± 0.52	2.92 ± 0.83	0.65 (-0.05 to 1.35)	0.83	0.245
	Week 8	3.69 ± 0.54	2.74 ± 0.99	0.95 (0.22 to 1.68)	1.21	0.083
	Week 12	3.59 ± 0.64	2.90 ± 1.00	0.69 (-0.12 to 1.51)	0.88	0.099
Productivity	Week 4	3.85 ± 0.26	3.44 ± 0.54	0.41 (-0.05 to 0.88)	0.88	0.064
	Week 8	3.88 ± 0.20	3.59 ± 0.27	0.29 (0.07 to 0.51)	0.63	0.243
	Week 12	3.78 ± 0.37	3.57 ± 0.46	0.21 (-0.22 to 0.63)	0.45	0.448
Social	Week 4	3.88 ± 0.31	3.56 ± 0.62	0.31 (-0.22 to 0.85)	0.60	0.412
Outcomes	Week 8	3.96 ± 0.14	3.75 ± 0.46	0.21 (-0.18 to 0.60)	0.39	0.940
	Week 12	3.92 ± 0.29	3.50 ± 0.53	0.42 (-0.05 to 0.88)	0.79	0.122
Depression Anxiety Stress Scale (DASS)						
Depression	Week 4	3.17 ± 14.50	14.50 ± 16.41	-11.33 (-25.11 to 2.45)	-0.99	**0.014**
	Week 8	4.50 ± 15.50	15.50 ± 20.33	-11.00 (-28.12 to 6.12)	-0.96	**0.019**
	Week 12	4.00 ± 14.50	14.50 ± 15.70	-10.50 (-23.89 to 2.89)	-0.91	**0.028**
Anxiety	Week 4	1.83 ± 8.29	8.29 ± 7.43	-6.45 (-13.33 to 0.43)	-1.19	**0.049**
	Week 8	2.83 ± 7.75	7.75 ± 11.39	-4.92 (-14.51 to 4.68)	-0.90	0.079
	Week 12	2.73 ± 5.75	5.75 ± 6.54	-3.02 (-7.86 to 1.81)	-0.55	0.341
Stress	Week 4	5.33 ± 15.75	15.75 ± 12.85	-10.42 (-21.33 to 0.49)	-1.22	**0.007**
	Week 8	7.00 ± 15.75	15.75 ± 13.75	-8.75 (-20.47 to 2.97)	-1.02	**0.032**
	Week 12	8.73 ± 17.25	17.25 ± 10.02	-8.52 (-16.95 to -0.09)	- 1.00	**0.031**

Note: Values are mean ± standard deviation. p-value calculated using mixed model analysis. Effect size (Cohen's d) calculated by dividing difference between CPAP and sham by the standard deviation at baseline.

(Continued over)

Table 4.10 Effect of adherent CPAP use on quality of life parameters (continued)

Variable	Visit	CPAP (n=12)	Sham CPAP (n=8)	Difference Mean (95% CI)	Effect size (d)	p-value
Short-form 36 (SF-36)						
Physical	Week 4	85.83 ± 12.40	62.14 ± 34.62	23.69 (-8.48 to 55.86)	1.25	**0.006**
Function	Week 8	86.67 ± 11.35	79.29 ± 22.25	7.38 (-13.50 to 28.26)	0.39	0.414
	Week 12	89.17 ± 9.73	76.88 ± 23.59	12.29 (-7.76 to 32.34)	0.65	0.083
Body Pain	Week 4	79.17 ± 16.70	72.00 ± 32.74	7.17 (-16.07 to 30.41)	0.35	0.198
	Week 8	76.67 ± 21.04	76.50 ± 24.61	0.17 (-21.40 to 21.74)	0.01	0.850
	Week 12	79.33 ± 20.07	78.00 ± 25.29	1.33 (-20.00 to 22.66)	0.06	0.708
General	Week 4	66.92 ± 16.26	63.00 ± 32.79	3.92 (-24.23 to 32.06)	0.19	0.680
Health	Week 8	69.17 ± 16.57	67.00 ± 31.10	2.17 (-24.67 to 29.00)	0.11	0.929
	Week 12	70.17 ± 19.17	69.50 ± 27.46	0.67 (-21.16 to 22.49)	0.03	0.851
Vitality	Week 4	68.75 ± 14.79	52.50 ± 29.88	16.25 (-9.39 to 41.89)	0.67	**0.031**
	Week 8	71.67 ± 9.61	44.38 ± 24.41	27.29 (6.58 to 48.00)	1.13	**<0.001**
	Week 12	75.42 ± 16.02	46.88 ± 24.34	28.54 (9.67 to 47.41)	1.18	**<0.0001**
Social	Week 4	90.75 ± 15.02	65.75 ± 31.86	25.00 (-2.25 to 52.25)	1.04	**0.003**
Function	Week 8	87.67 ± 14.93	84.50 ± 25.68	3.17 (-15.83 to 22.17)	0.13	0.519
	Week 12	89.67 ± 17.47	72.00 ± 30.39	17.67 (-8.74 to 44.08)	0.73	**0.027**
Role	Week 4	86.08 ± 26.53	52.43 ± 50.41	33.65 (-13.72 to 81.03)	1.00	**0.014**
Emotional	Week 8	94.50 ± 12.85	87.50 ± 35.36	7.00 (-16.23 to 30.23)	0.21	0.502
	Week 12	86.08 ± 26.53	66.63 ± 39.92	19.46 (-11.61 to 50.53)	0.58	0.127
Mental	Week 4	82.67 ± 17.25	64.57 ± 33.97	18.10 (-13.78 to 49.97)	0.82	**0.044**
Health	Week 8	82.00 ± 17.10	61.00 ± 28.59	21.00 (-0.37 to 42.37)	0.95	**0.012**
Scale	Week 12	81.67 ± 17.76	59.50 ± 27.42	22.17 (1.05 to 43.29)	1.00	**0.006**
Physical	Week 4	77.50 ± 11.02	62.00 ± 27.26	15.50 (-3.03 to 34.03)	1.11	0.155
Health	Week 8	78.17 ± 12.26	66.29 ± 24.67	11.88 (-5.84 to 29.61)	0.85	0.423
	Week 12	81.08 ± 12.24	69.88 ± 20.84	11.21 (-4.26 to 26.68)	0.80	0.265
Mental	Week 4	86.42 ± 18.44	64.17 ± 36.99	22.25 (-16.52 to 61.02)	0.99	**0.007**
Health	Week 8	88.17 ± 11.72	77.63 ± 28.24	10.54 (-8.49 to 29.58)	0.47	0.190
Dimension	Week 12	85.83 ± 19.54	66.13 ± 30.27	19.71 (-3.58 to 42.99)	0.88	**0.021**

Note: Values are mean ± standard deviation. p-value calculated using mixed model analysis. Effect size (Cohen's d) calculated by dividing difference between CPAP and sham by the standard deviation at baseline.

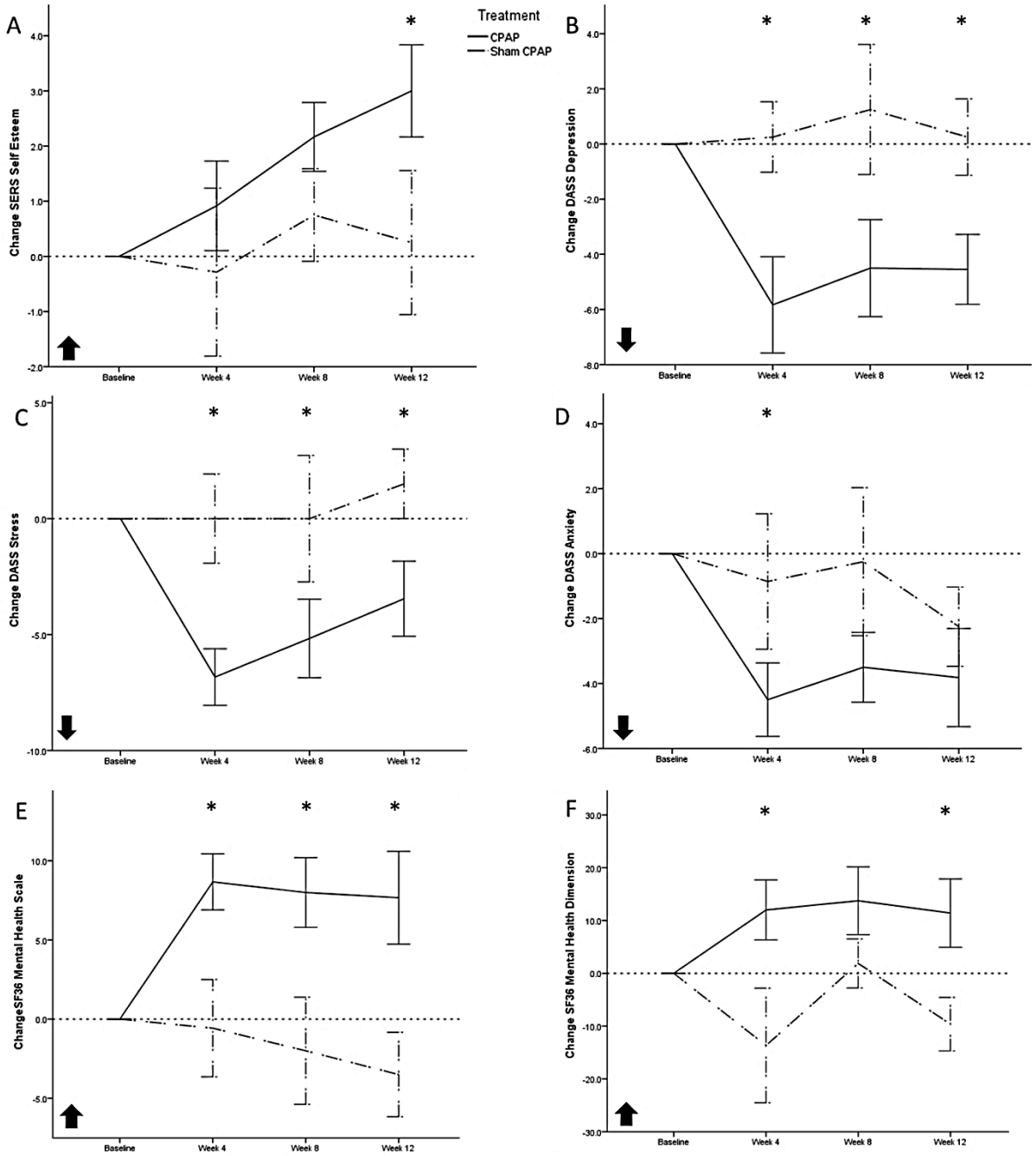


Figure 4.7 Effect of CPAP on mental health in adherers

Note: Adherence defined as greater than 4 hours use per night. (A) Self Esteem (B) Depression (C), Stress (D), Anxiety and (E) SF-36 Mental Health Scale and (F) Mental Health Dimension. All measurements are change of scores from baseline and one standard error of the mean for the change from baseline

⬆⬇ Arrows indicates direction of an improvement. * $p<0.05$ as determined by mixed model analysis.

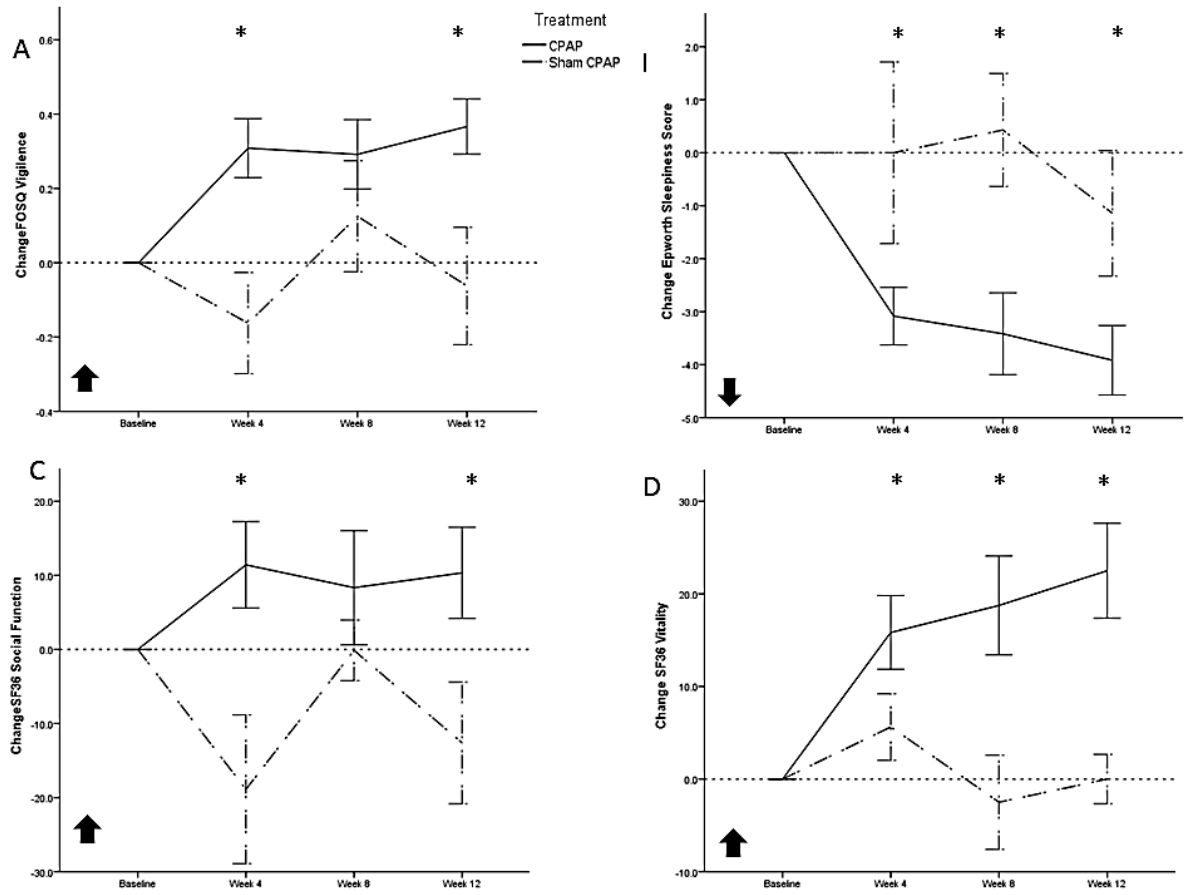


Figure 4.8 Effect of CPAP on quality of life in adherers

Note: Adherence defined as greater than 4 hours use per night. (A) FOSQ Vigilance domain (B), Epworth Sleepiness Score, SF-36 domains of (C) Social Function and (D) Vitality. All measurements are change of scores from baseline for only those who used CPAP or sham CPAP for more than 4 hours per night. Data are mean and standard error of the mean for the change from baseline.

↑↓ Arrows indicates direction of an improvement. * $p<0.05$ as determined by mixed model analysis.

4.4.9 Non-sexual relationships

Adherence to sham CPAP, compared to CPAP appeared to impair non-sexual relationships, as measured by the single EMAS question related to Non-Sexual Relationship satisfaction at all time points (**figure 4.9**). Three other measured parameters included aspects of non-sexual relationship, that of Social Function domain in the SF-36, the SERS Overall Relationship Satisfaction domain and the EMAS Overall Relationship Satisfaction single question. Overall Relationship satisfaction in the EMAS questionnaire showed both an increase with CPAP, and a decrease with sham CPAP, which was significantly different at week 12 ($p=0.005$). In the SERS questionnaire, all scores decreased for sham CPAP and increased for CPAP, however, there was no significance difference (**figure 4.9**). Similarly social function in the SF-36 both increased with CPAP and decreased with sham CPAP, leading to a significant difference at Weeks 4 & 12 (**figure 4.8C**).

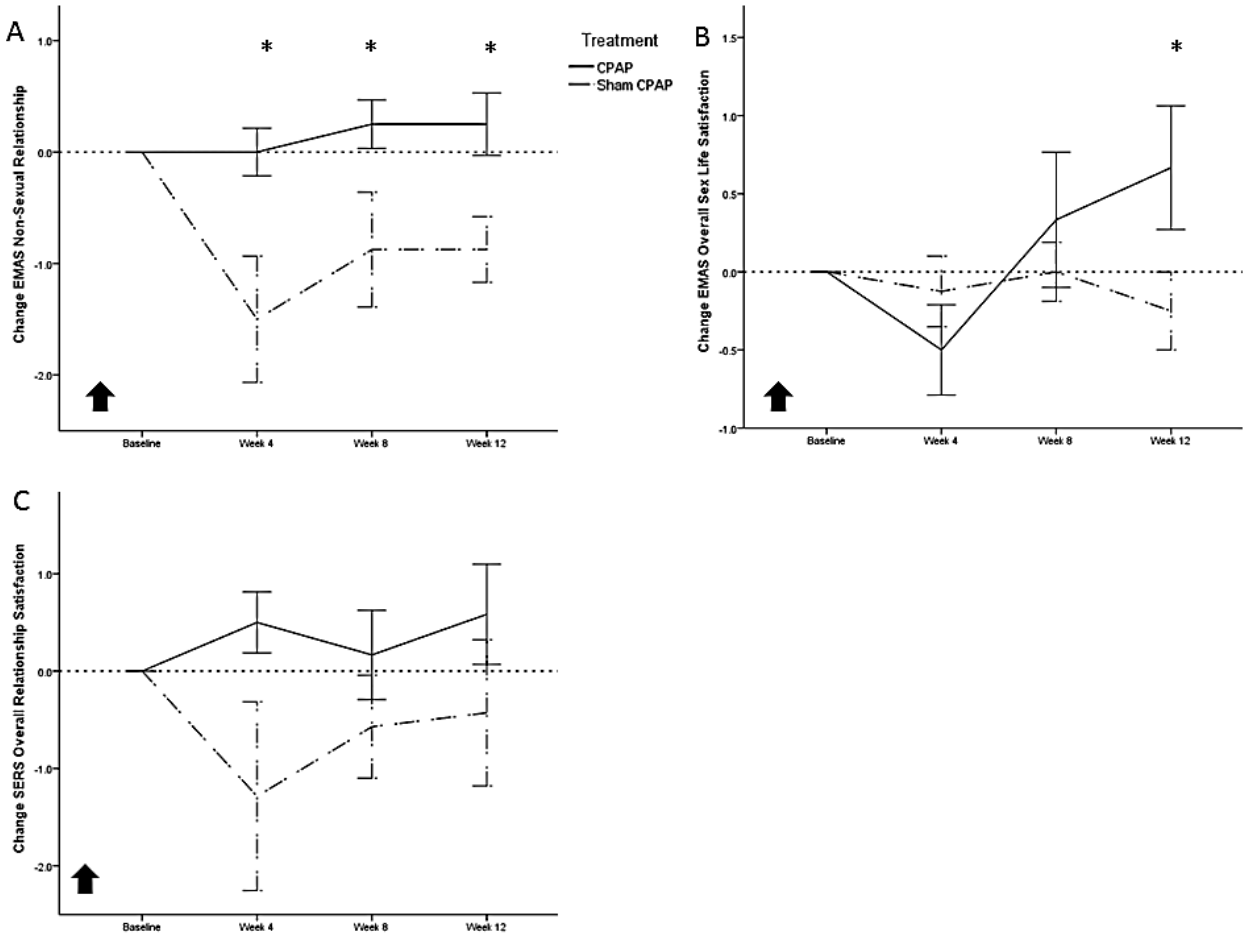


Figure 4.9 Effect of sham CPAP on relationship factors in adherers

Note: Adherence defined as greater than 4 hours use per night. (A) Change in non-sexual relationship question of the European Male Aging Study questionnaire. Non-sexual relationship declined for sham CPAP users compared to no change or a slight improvement in this domain for CPAP users. All time points differed between sham CPAP and CPAP. (B) Change in Overall Sex Life Satisfaction: An increase was seen at Week 12 with CPAP, accompanied by a slight decrease with sham CPAP, leading to a statistical difference. (C) Change in overall relationship satisfaction in the Self-Esteem and Relationship Satisfaction questionnaire. Sham CPAP showed a decline at all time points compared to no change or a slight improvement in CPAP users, however, no there was no statistical difference.

⬆⬇ Arrows indicate direction of improvement. * $p<0.05$

4.4.10 Non-adherence to therapy

In participants not adherent to CPAP / sham CPAP, those who used the device less than 4 hours per night or not at all, several differences were noted between the CPAP (n=14) and sham CPAP (n=20) groups at Week 12. All differences were due to decrements in CPAP group and improvements in sham CPAP group, opposite to that of participants' adherent to therapy. There was a worsening in the CPAP group, compared to improvements with sham CPAP, in the depression domain of the DASS (change from baseline: CPAP 2.14±3.46, sham CPAP -4.35±6.17, p=0.002), the SF36 Role Emotional domain (CPAP -16.64±33.93, sham CPAP 13.77±29.06, p=0.012) and the SF36 Mental Health Dimension (CPAP -6.38±18.46, sham CPAP 8.94±17.81, p=0.026).

4.4.11 Treatment Satisfaction

After 4, 8 and 12 weeks of CPAP/sham CPAP, participants were asked about their satisfaction with treatment as it referred to erectile function using the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire. Participants allocated to CPAP were more satisfied with treatment, as it related to erectile function, than those allocated to sham CPAP at the week 12 time point (**table 4.10A**). This difference became more apparent for adherent users of CPAP treatment (**table 4.10B**). At all time points, over 70% of those allocated to CPAP were satisfied with treatment, as defined by a score greater than 50, compared to less than 60% of those allocated to sham CPAP. For adherent users, 100% of participants allocated to CPAP were satisfied with treatment at Week 12 compared with 37% of adherent sham CPAP users (p=0.005) (**figure 4.10**). Given the factorial nature of the study, the effects of Vardenafil may influence this result. Satisfaction rates with Vardenafil versus placebo (Vardenafil 67-72% vs placebo 46-51%) were very similar to that of CPAP versus sham CPAP. In the assessment of those men who had received placebo medication,

55-60% were satisfied with CPAP versus 39-40% of men allocated to sham CPAP. This was significantly different at weeks 8 & 12 (p=0.016 and p =0.041 respectively)

Table 4.11 Treatment satisfaction scores for CPAP

A

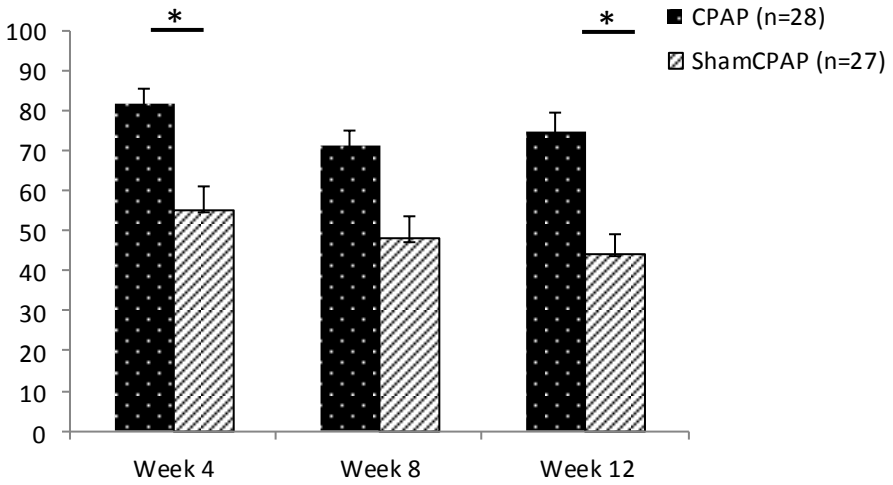
	CPAP (n=28)	Sham CPAP (n=27)	p-value
Week 4	65.4 ± 19.4	56.6 ± 24.7	0.190
Week 8	64.1 ± 20.2	55.3 ± 26.0	0.199
Week 12	67.4 ± 22.8	53.6 ± 24.5	**0.041**

B

	Adherent CPAP (n=12)	Adherent Sham CPAP (n=8)	p-value
Week 4	68.4 ± 18.7	71.8 ± 20.1	0.711
Week 8	76.3 ± 13.6	52.0 ± 26.6	**0.016**
Week 12	78.8 ± 14.5	54.4 ± 19.4	**0.012**

Note: (A) All participants; (B) CPAP Adherers only. Values are mean ± standard deviation. p-value calculated using mixed model analysis.

A



B

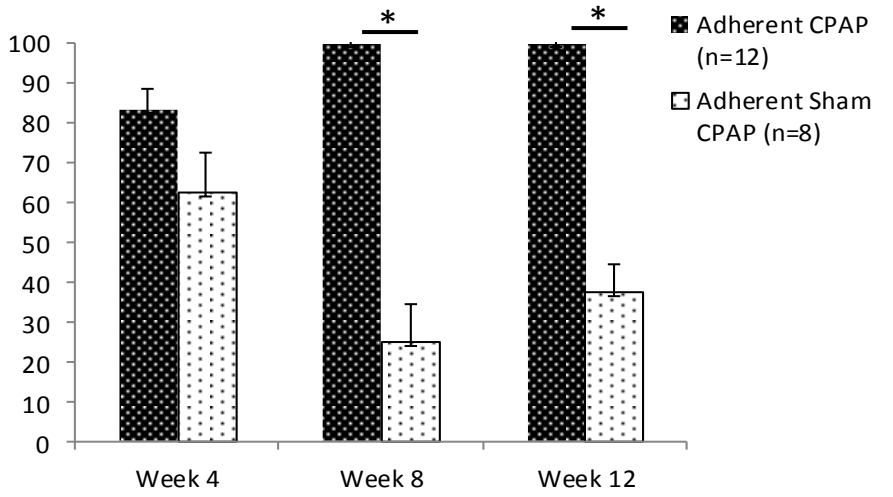


Figure 4.10 Percentage of participants satisfied with treatment for erectile function

Note: Satisfaction defined as a score of more than 50 in the EDITS questionnaire (A) CPAP versus sham CPAP, (B) Adherent users of CPAP versus adherent users of sham CPAP. * $p<0.05$

4.5 DISCUSSION

This is the first randomised sham controlled study to investigate the effect of CPAP on sexual function. Using a factorial 2x2 randomised controlled trial, this study confirms that CPAP improves sexual satisfaction and increases the number of sleep related erections, without increases in tumescence or rigidity, but does not improve subjective erectile function on an intention-to-treat basis. However, for those men who adhered to treatment, (per-protocol analysis) both erectile function and sexual desire improved. There were significant improvements in several aspects of sexual functioning and relationship parameters. Additionally, those participants who were adherent to CPAP also had reduced sleepiness, improved levels of mood and several parameters related to quality of life, and were satisfied with treatment compared to sham treatment.

4.5.1 Subjective Erectile Function

This study has demonstrated that CPAP treatment, under an intention to treat basis does not improve subjective erectile function compared to that of sham CPAP. However, for those men who are adherent to CPAP, there was a statistical ($p=0.037$) and clinically meaningful improvement in erectile function (IIEF-ED increase by at least 4 points) [545] compared to those adherent to sham CPAP. Response to CPAP treatment differed between participants. A little over half of men adherent to CPAP treatment had clinically significant improvements in erectile function. This finding is in contrast to previous uncontrolled studies which have found little improvement in erectile function when OSA is treated. In one such study, no improvement from baseline was found in erectile function in 16 men with OSA who had used CPAP for 7 months, as measured via the Korean version of the IIEF [483]. Similarly, another study also found no improvement in erectile dysfunction in 27 men with 10 weeks of adequate CPAP usage respectively [408]. Two studies have reported that 4

in 5 patients with OSA and ED did not report an improvement in erectile function with 3 months and 1 year of CPAP usage [484, 546]. Likewise, in another study, 2 out of 3 patients did not find an improvement in ED with one year of CPAP usage [474]. A long term (3 year) observational study of CPAP users and non-users found that overall there was no improvement in erectile function, however, only those with moderate-severe ED improved with CPAP therapy [412]. A shorter study of 2-3 months similarly found a greater improvement only in those with significant ED, but not overall [408]. However, like the present study, several others have reported improvements in erectile function overall. In one of the few other studies specifically targeting men with both OSA and ED, a group of 15 men who were all treated with CPAP for 12 weeks in an observational study, an improvement in erectile dysfunction was found, as well as all other domains in the IIEF except sexual desire [473]. A small (n = 27) randomised no-treatment controlled study showed a significant improvement in ED after 1 month of CPAP [481], however this should be interpreted with caution, given the short period of treatment, and the lack of placebo control. A prospective randomised study, using an anti-depressant as a comparator treatment, found that one month of CPAP treatment in those with severe sleep apnoea was sufficient to increase IIEF scores from 15 to 19. Although this study was described as placebo controlled, the placebo was an anti-depressant medication, which may negatively impact on erectile function [417, 482]. An interim report of a longer study not yet completed reported that 23 patients treated with either CPAP, surgery or oral device found an increase in IIEF scores after 3 months of treatment [475]. The increase in sexual function in this study was not accompanied by any changes in testosterone levels, suggesting there may be an alternative mode of action.

The current data found a significant improvement in erectile function with CPAP compared to sham CPAP, but only in those who adhered to treatment. The absence of a placebo control in previous studies has clearly been a limitation. A notable placebo effect was seen in the current study, particularly with those who were adherent to treatment, with participants allocated to sham CPAP reporting an increase in erectile function at week 4, with a decline at week 8, and an eventual return to baseline at Week 12 in the sham control group.

4.5.2 Objective Erectile Function

The number of sleep related erections (SRE's) increased with CPAP treatment. This improvement in the number of erections overnight with CPAP use suggests that by abolishing airway obstruction and thus disruption from sleep, erections in REM sleep were no longer inhibited. The disruption of REM sleep due to OSA may reduce SRE's, which normally occur during each REM sleep period [30]. The first study to report impaired SRE's with patients with OSA was in 1981 which found that 7 of 15 patients in the study with apnoea or hypoventilation showed abnormal NPT determined via visual inspection of the recording [433]. Likewise, a review of 31 patients in 1986 being investigated for ED with NPT, found that 10 of these patients had sleep apnoea, resulting in disturbed nocturnal erections, and concluded that full sleep studies should be performed in conjunction with NPT to ensure that there is not an incorrect diagnosis of an abnormal NPT, namely, OSA [434]. There was no comment that this may be a contributor to ED. In 1989, a small correlation was found between apnoea index and penile rigidity in a study of 285 patients [437]. The earliest study regarding the effect of CPAP on nocturnal erections reported that one night of CPAP usage was sufficient to improve nocturnal erections for some men when measured using mercury strain gauges [438]. Of the 22 OSA patients presenting with ED for

this study, 15 had impaired NPT recordings on a night without CPAP, defined as penile rigidity less than 500 grams and a tip circumference change of less than 16 millimetres. Overall, there was no change in NPT parameters when CPAP was used, however, as with subjective erectile function, there was individual variation. There were 5 individuals who no longer had an impaired reading on the next night using CPAP. This interpretation of this result is limited, however. Depending on the criterion used to assess abnormality of NPT, there can be considerable night-to-night variability [472]. In the only other study assessing the impact of CPAP on nocturnal erections, after 3 months of treatment which included participants using CPAP as well as those who had undergone surgery for OSA, the only parameter reported was of percentage rigidity greater than 80%, which showed an improvement from 13.8% to 40%. Duration of erection, rigidity activation units and tumescence activation units were not reported. In a review of the current methodology using the Rigiscan device parameters of RAU and TAU compared with traditional cut-offs of normal and abnormal recordings, the diagnostic accuracy of the device did not go above 75% in any of the parameters, due to a large overlap in the RAU and TAU in that of men considered to have normal and abnormal erectile function, however, the authors recognised its utility in a research context and in documenting treatment efficacy in a clinical setting [105]. In this regard, changes in NPT are a more useful measurement of treatment efficacy. The current study showed no improvement with CPAP in the quality of nocturnal erections, only the quantity. Since erections occur in REM sleep, it is important to consider the quantity of this sleep stage, which may change due to the treatment of OSA. No such change was seen in this study between the percentage of REM sleep at baseline and Week 12. Visual inspection of NPT recordings shows that while at baseline some participants did not have erections during all episodes of REM sleep, these were more common at the Week

12 visit, as shown in the example given. Unfortunately, in the current study, only 16 participants were both agreeable to NPT monitoring and adherent to CPAP (n=10) /sham CPAP (n=6), which limits full investigation of the effect of CPAP on NPT in this population.

Although NPT measurements may be able to distinguish the cause of ED as being either physiological or psychological in origin, there is controversy regarding the distinct bimodal categorization of aetiology, as well as the accuracy of device itself. However, to fully investigate the current data using previously defined criteria was considered useful. By analysing baseline data for the subset of patients, whom were agreeable to NPT monitoring, approximately one third would be considered to have a psychological basis of their erectile dysfunction using traditional criteria. If these men do have purely psychological erectile dysfunction, the additional of physical treatments such as CPAP, may not address the underlying issue. Given the association of OSA with depression [547], and the bidirectional relationship between ED and negative mood, self-esteem and life satisfaction [37], this complex relationship may play an important role in response to treatment. Prior to the 1990's, ED was thought to be completely psychological in origin [101], and in a complete turnaround, it has now been suggested that sexual dysfunction has been increasingly attributed to medical causes and overlooks the contribution of psychological and social factors [11]. Indeed none of the studies aforementioned in regards to the association between OSA & ED have mentioned the possibility of a psychological influence. In the present study, at baseline, half of all participants scored at least moderate depression on the Depression Anxiety Depression Scores [548]. With the presence of emotional problems or stress increasing the likelihood of ED by 3.5 [1], the possibility that there may be a

psychological influence on ED in this study cannot be ignored, however, the small numbers of participants agreeable to NPT monitoring limits further investigation.

4.5.3 Non-Erectile Sexual Function

The effect of CPAP on sexual function other than erectile function has not previously been studied in a randomised controlled study. In this study, satisfaction with sexual function, as determined by the overall satisfaction domain of the IIEF was found to be improved with CPAP. Likewise, a previous observational study of 1 year of CPAP treatment, in which all participants used CPAP for more than 4 hours, showed improvements in sexual satisfaction in men with OSA [474], however, this was not seen in a shorter 2-3 month study of CPAP in which all participants were included, with adherence self-reported to be over 6 hours per night [408]. Both of these previous studies were in men with OSA, not specifically included on the basis of erectile dysfunction. The improvement in sexual satisfaction seen in the longer term study thus may not necessarily relate to improvements in erectile function. The current study showed improvements in sexual satisfaction occurred in the absence of statistical improvements in erectile function. This suggests there may be other factors, such as sleepiness, mood or relationship factors which improve with CPAP, and contribute to sexual satisfaction.

An increase in sexual desire was seen in this study for participants adherent to CPAP treatment. Only two other studies have reported the influence of CPAP on libido. Unlike the current study, three months of CPAP treatment did not change libido in 15 men with OSA and ED [473]. A long term observation study of 3 years of CPAP use found a change in libido between those who did and did not use CPAP, in that a slight improvement in those who used CPAP, compared to an equal decline in those who did not use CPAP resulted in a

significant difference [412], suggesting that CPAP treatment may prevent a decline in libido with the progression of time, rather than increase it. CPAP did not change orgasmic function in this study. Effects of CPAP on orgasmic function has been previously reported only in one study, and was shown only to decline in those men with OSA who do not use CPAP compared to those who did [412].

4.5.4 Sleepiness and Sexual Function

Studies reporting aspects of sexual function affected by sleepiness, and the effect of CPAP thereof have been limited. The Intimacy and Sexual Relationships domain of the FOSQ questionnaire provides an opportunity to evaluate how sleepiness can affect intimacy and sexual relationships, in regard to sexual desire, ability to become aroused and the ability to have an orgasm. The current study, did not find an improvement in this domain of the FOSQ due to CPAP compared to sham CPAP either when analysed under intend-to-treat or per-protocol analysis. Several other studies have also not found any improvement in this domain with CPAP treatment [366, 549-551]. In contrast, some observational studies have found an improvement. In a large (n=123) study using this questionnaire, at least 3 months of CPAP treatment improved in this domain with an effect size of 0.44 for all subjects compared to baseline ($p<0.001$), however when stratified on the basis of severity of OSA, only those with the most severe apnoea (AHI greater than 60) had significant improvement, with an effect size of 0.77 [410]. Similarly, the FOSQ Intimacy domain improved with CPAP use by 0.57 points in men in a study investigating the efficacy of a hypnotic agent on CPAP adherence [476]. The lack of control group in these studies limits the interpretation of the improvement seen, due to the subjective nature of sexual functioning. In the current study, both CPAP and sham CPAP improved from baseline to week 12 in the per-protocol analysis in this domain but there was no statistical difference between the two.

4.5.5 Relationship Factors

The detriment in non-sexual relationships and social function with adherence to sham CPAP is a novel finding. No other study has reported decrements with adherent use of sham CPAP. Participants, who diligently persevere with treatment, without receiving benefit, may have a decrement in relationship quality for a number of reasons. Potentially, both patient and partner have high expectations and devote energy to successful use of treatment, and experience discomfort from the addition of the sham CPAP mask to the bedroom, without receiving the rewards, thereby creating disappointment and potentially conflict. For the partner, both the snoring and the sound of the sham CPAP machine and mask could also contribute to continuing poor sleep quality.

4.5.6 Quality of Life

For those men adherent to treatment, but not overall, significant improvements were seen in several parameters of psychological wellbeing, including stress, depression in the DASS questionnaire, as well as the mental health domains in the SF-36. Previous studies have shown improvements in depression scores even with low usage of CPAP (<3 hours) compared to an oral placebo [361]. The current study was not able to show such an increase in the intention to treat analysis, which yielded a higher adherence rate (3.7hours), however, there was a significant improvement in depression levels at all timepoints for those who adhered (>4hours) to CPAP treatment. Adherent CPAP users exhibited several improvements in quality of life, specifically in regards to reduced sleepiness, vigilance and vitality. A reduced level of sleepiness may have some impact upon mood, which may also have impacts on quality of life. Of all the sub-scores in the quality of life measurement tool SF-36, that of vitality is said to be the most affected in those with OSA, and has been reported as the only domain sensitive to clinical categories of sleep disordered breathing

[330, 337]. This study did show an improvement in vitality, but only for those who were adherent to treatment. Improvements in other parameters of quality of life have also been noted in CPAP use, particularly for those who experience more symptoms pre-treatment [346]. Improvements in domains of the SF-36 have been shown in several studies, with particular improvements in the field of mental health and vitality, more so with those who adhere to treatment [361, 363, 552]. Improvements in all except one domain (intimacy and social function) of the FOSQ were found in a sham CPAP controlled study of 45 patients [364]. In contrast, in another oral placebo randomised controlled study of those with mild-moderate (AHI 5-30) OSA, no change was seen in any parameter of the SF-35 or FOSQ questionnaire by the use of CPAP [368]. Limitations in interpreting this result include low usage of CPAP (3.5±2.1 hours/night) and a placebo effect was noted in the control arm, [368]. However, a sub analysis of those whom were adherent to CPAP treatment (>4hours) also showed no improvement in any domain of the SF36 or FOSQ questionnaires in this mild OSA group [368]. Potentially this may be due to lower symptomatology in this group.

4.5.7 Adherence to CPAP

CPAP use in this study (mean 3.7 hours, 48% using more than 4 hours per night) is similar to a number of other studies of men with severe OSA [542, 553, 554]. Other studies have found AHI, BMI, and ESS to have effects on CPAP adherence [357, 555, 556], however this study found no such difference. The only statistical difference between the those who adhered and did not adhere to CPAP treatment was that of relationship length, in that those who were adherent had been in a relationship for an average of 21.6 years, compared to those 12.3 years for non-adherent users. Previous studies have also found partner influence to be influential in CPAP usage. One study showed that those patients whom were living with a partner tended to have a higher adherence rate to treatment, with an odds ratio of

1.5 of being adherent (>4hours/night) with CPAP treatment [357]. In a small, 2 week study, the number of nights in which a man with OSA slept in the same bed as his wife was positively correlated with CPAP adherence [195]. In a longer term (6 month) sham controlled study, those who were more adherent to treatment, in both active and placebo arms, were more likely to be married [359]. Indeed having a partner at home has been identified as being a predictor in adherence to treatment [557]. This study required that all participants be in a stable relationship for at least 6 months prior to entry to ensure that there was ample opportunity to assess erectile function. For couples in which erectile dysfunction is present, relationship quality can be detrimentally affected [558]. This relationship quality can have an influence on CPAP adherence, with levels of conflict in the relationship, as well as perceived pressure from partners, having an inverse relationship with hours of CPAP use [355, 356]. In another study, patients whom had sought treatment for OSA due to their spouse rather than being self-referred were less adherent to CPAP treatment [537]. The presence of ED may have effects on CPAP adherence, both detrimental and beneficial, depending on relationship quality. Potentially, there may be a bidirectional relationship regarding relationship quality and CPAP adherence in this population. Trending towards a difference but not reaching statistical significance was the duration of erectile dysfunction with those adherent to treatment having ED for a shorter time ($p=0.059$). In a study of men seeking medical assistance for their erectile function from their GP, the majority were those who had experienced ED for a shorter time frame (<1 year) [559]. These men may be more receptive to treatment options than those who have had the condition for a longer period, and is an important consideration in the clinical setting.

Adherence to CPAP treatment in previous trials in men with OSA and ED has been addressed using differing methodologies. Several studies did not report adherence [438, 484, 485] while in other studies, those not adherent to CPAP were either excluded [414], allocated to surgery as an alternative treatment [354] or used as controls [412]. In a study of CPAP versus an anti-depressant, all patients were reported to use CPAP 7 hours a night every night, and another study comparing oral appliance with CPAP reported CPAP usage of 6.8 hours per night [408, 417]. Neither of these studies report on how such a high adherence rate was achieved or determined.

In men adherent to CPAP treatment in this study, 100% were satisfied with treatment as it pertained to erectile function. In the only other similar study reporting treatment satisfaction with CPAP, only 20% of all participants reported satisfaction with CPAP compared with 53% satisfied with Sildenafil [484]. This study, however, did not report on, nor stratify by adherence to CPAP. Potentially, the perceived positive effects of CPAP may reinforce CPAP use, with those finding benefit from treatment more likely to persist with treatment.

When data was stratified by adherence, there were four parameters in which a significant interaction between CPAP and Vardenafil was found in those who used CPAP greater than 4 hours per night - ESS, SF-36 domains Role Physical, General Health, and Physical Health. When these parameters were investigated further, there were no synergistic effects, that is, receiving both treatments did not produce an effect greater than the sum of the two.

4.5.8 Strengths and Limitations

One of the strengths of this study is the randomised control design. Given the reliance on subjective outcomes in relation to sexual function and quality of life parameters, a placebo component is imperative to correctly verify the impact of treatment. Additionally, the duration of the study being twelve weeks allowed changes which take time to occur to become apparent, as well as extricating a placebo effect for many parameters which declined with time. A longer period of treatment may have further quantified the effect of treatment or a lack of decline in functionality as seen in other long term studies [412, 546]. Limitations to the study include a low adherence to CPAP treatment overall which limits findings, and low patient numbers who adhered to treatment may not have provided sufficient power to clearly document the effect of CPAP on sexual function. The intervention at week 4 to enhance adherence may not have been early enough to be effective. CPAP did not completely eliminate OSA, with participants falling into the mild range (AHI 7) at study completion, which may limit treatment effects seen. Additionally, low overall numbers may have been insufficient to detect interactions between the two treatment arms.

4.6 CONCLUSION

This data provides evidence that CPAP is able to improve sexual function, erectile function and increase sexual desire when used as prescribed. Reduction in scores of rates of depression, stress, anxiety and sleepiness due to CPAP use may contribute to overall satisfaction in sexual relationships, and improve several aspects of quality of life. Sham CPAP may not be an ideal control device due to decrements in relationship quality. CPAP treatment of more than 4 hours per night may be an effective treatment for improving overall sexual health as well as quality of life, however, a little over a third of patients are able to adhere to this treatment.

5 The effects of Vardenafil on sleep disordered breathing, sexual functioning and quality of life in men with OSA

5.1 CHAPTER SUMMARY

Introduction: Erectile dysfunction and obstructive sleep apnoea occur together in approximately 10-15% of community dwelling men. PDE-5 administration, the current treatment of choice for ED, has been shown to improve erectile function and sleep related erections in otherwise healthy men; however uncontrolled studies have reported PDE-5 inhibitors to be less effective in men with OSA than that of other populations. High dose PDE-5 inhibitors when used on-demand have been shown to increase nasal obstruction, making those susceptible to airway collapse at higher risk of obstructed breathing. Men with OSA are reported to have impaired sleep related erections. The efficacy of PDE-5 inhibitors on sleep related erections in men with OSA has not been investigated. This study aims to determine if a low daily dose of 10mg Vardenafil is effective in improving subjective erectile function and sleep related erections, as well as self-esteem, relationship, quality of life and treatment satisfaction without worsening sleep disordered breathing in men with OSA and ED.

Methods: Sixty-one men with erectile dysfunction (ED) and obstructive sleep apnoea (OSA) were randomised to receive either daily 10mg Vardenafil or placebo as part of a 2x2 factorial study also investigating the efficacy of continuous positive airway pressure (CPAP), for a period of 12 weeks. Subjective measures of sexual function, mood, relationship factors and quality of life were assessed prior to, and after 4, 8 and 12 weeks of allocated treatment. Objective measures of sleep, breathing, and sleep related erections were recorded at baseline and after 12 weeks.

Results: Vardenafil did not worsen any parameter of sleep disordered breathing for those allocated to sham CPAP treatment. Subjective erectile function improved initially at Week 4 & Week 8, but was not different than that of placebo at Week 12. Nocturnal erection quality improved with Vardenafil in regards to rigidity and tumescence. Vardenafil reduced distress due to sexual dysfunction and improved self-esteem and relationship satisfaction but had little impact on any other measurement in quality of life. Treatment satisfaction scores were higher for those taking Vardenafil than placebo throughout the study; however, in terms of being satisfied with treatment, this was only apparent at Week 4.

Conclusion: Although an improvement in sleep related erections was seen, a daily dosage of 10mg Vardenafil may not be sufficient to completely improve erectile function in all men with OSA and ED, however, sufficient improvements in self-esteem and relationship satisfaction may warrant clinical application. This dose did not worsen sleep disordered breathing.

5.2 INTRODUCTION

Erectile dysfunction (ED) and obstructive sleep apnoea (OSA) often co-exist. As well as OSA being male predominant, these conditions have common risk factors such as obesity and increasing age, and co-morbidities such as diabetes, hypertension, depression and cardiovascular disease [62, 313, 560-564]. Current literature suggests a high overlap between the two conditions, with rates ranging from 30-70% of OSA clinic based patients having ED [404, 409, 414, 422, 431], with similar rates of ED clinic patients having OSA [415, 424, 434, 437]. Men with OSA and ED thus represent a large population for whom effective treatments exist; however, these treatments have not been fully investigated in the presence of the other condition.

The current treatment of choice for erectile dysfunction is the class of medication known as prosphodiesterase type 5 (PDE-5) inhibitors, used when needed (i.e. on-demand). These act by increasing cyclic quanosine monophosphate (cGMP) in the corpus cavernosum. As a result, there is a relaxation of the previously contracted smooth muscle and an inflow of blood, leading to an erection. This action enhances the normal response to sexual stimulation, which is a release of nitric oxide in the corpus cavernosum. Nitric oxide activates an enzyme, guanylate cyclise, which in turn increases cGMP [565].

PDE-5 administration has been shown to increase nasal obstruction, both subjectively and objectively, in the nasal mucosa [460, 461]. For those susceptible to sleep disordered breathing, this creates a theoretical risk of further impaired airway patency due to engorgement of upper airway tissues, which may result in a reduction of nasal cross-sectional area and increase the tendency for relaxation of the soft tissue in the pharyngeal muscles [460-462] thus increasing the risk of obstructive sleep apnoea. Indeed, a recent randomised placebo-controlled study of

13 men with severe OSA showed that a 50mg dose of Sildenafil prior to sleep increased the apnoea hypopnoea index (AHI) from 32.3±11.3 to 48.1±20.8 (p=0.01), oxygen desaturation index from 18.5±9.1 to 30.3±14.5 (p<0.01), and amount of time hypoxic while asleep from 7.9%±3.3%, to 15.6% ±9.6% (p<0.01) [463, 464]. This small study requires further investigation to determine if a lower dose of PDE-5 inhibitors is safe for those with OSA.

Sleep related erections (SRE's) occur during REM sleep, and have been shown to be impaired in men with OSA, potentially due to sleep fragmentation or hypoxaemia [22, 434]. SRE's have been described in the scientific literature since the 1940's [23, 24]. These were confirmed to be associated with REM sleep some thirteen years after the discovery of this stage of sleep [25, 26]. During the sleep period, approximately 1-2.5 hours are spent in REM sleep [566]. Erections occur during approximately 90% of this time [7]. Although the function of nocturnal erections is unknown, these episodes of penile blood engorgement increase corporeal oxygenation and may function to protect the morphological integrity of the penis [30, 31]. Without regular oxygenation, fibrosis of the smooth muscle may occur leading to atrophy of the corpora cavernosa [567]. PDE-5 administration has been shown to improve sleep related erections in otherwise healthy males [130, 132, 568, 569], however, this has not been investigated in the presence of OSA. Potentially, the administration of PDE-5 inhibitors can assist SRE's and may be useful in the prevention of deterioration in the cavernosal smooth muscle [569]. The efficacy of PDE-5 inhibitors in men with OSA has been reported in one uncontrolled study to be less than that of the general male population [484]. Given this report, together with the lack of placebo controlled studies in men with OSA and the widespread use of this medication, further investigation into the effects of PDE-5 inhibitors on breathing during sleep and its efficacy in this population are required. This study aims to investigate if a low

dose of 10mg Vardenafil, administered daily, is effective in improving subjective erectile function and sleep related erections, without worsening sleep disordered breathing in men with OSA and ED.

5.3 METHODS

This was a multisite study, performed in Sydney at the Woolcock Institute of Medical Research, Glebe, New South Wales and in Melbourne at the Department at Respiratory and Sleep Medicine, Monash Medical Centre, Clayton, Victoria, as described in **section 3.2.**

This study was performed as part of a 2x2 factorial study, investigating the effects of 12 weeks of Vardenafil and CPAP in men with OSA and ED. Sample size was determined as described in section 3.2.4. After baseline data collection, eligible participants at each site (Sydney and Melbourne) were randomised using two separate lists via computer generated random blocks of four to either 10mg Vardenafil or placebo in a 1:1 ratio. Participants were also allocated to either CPAP or sham CPAP concurrently, in equal numbers between the two groups. Subjective measurements were assessed before, as well as after 4, 8 and 12 weeks of treatment. Once treatment was commenced, subjective efficacy of treatment was assessed at all following visits. Objective measurements were performed at baseline, prior treatment and week 12, when the allocated treatment was used.

5.3.1 Participants

Sixty one men aged between 18 and 65 years who had both obstructive sleep apnoea and erectile dysfunction were recruited into the study, as described in **section 3.2.2**. Briefly, participants were required to have at least moderate obstructive sleep apnoea, defined as an apnoea-hypopnoea index (AHI) measured by polysomnogram, of greater than 20 events per hour, with an oxygen desaturation of 3 % or greater (ODI3) of at least 15 events per hour, as

well as erectile dysfunction, defined as a score of less than 26 in the erectile function domain of the International Index of Erectile Function (IIEF) questionnaire.

5.3.2 Vardenafil & Placebo

Participants were randomised to receive either 10 milligrams of Vardenafil hydrochloride trihydrate (product name Levitra) or placebo (Bayer Schering Berlin, Germany). Peak concentration of Vardenafil is reached in around one hour (minimum being around 15 minutes), with a half-life of around 4 hours [570]. Participants were instructed to take one tablet daily one hour before attempting to fall asleep, regardless of their intention to attempt sexual activity. Medication sufficient for a four week period was dispensed at baseline, week 4 and week 8 with any remaining tablets returned at the next visit. Returned tablets were counted manually to assess adherence with treatment.

5.3.3 Statistical Analysis

Statistical analysis was performed using SAS statistical package version 9.2 (SAS Institute, Cary, North Carolina, USA), as described in **section 3.2.4**. Student t-tests, or Fishers exact tests, were first used to compare groups at baseline. The outcome variables were the mean values at weeks 4, 8 and 12 weeks as appropriate, with week 12 being the visit of interest. Data was analysed using intention-to-treat principles, performed as per established methods for factorial studies [517, 518]. Mixed model analysis was first used to test the hypothesis there was no interaction between the treatments used in the 2x2 factorial study. The interaction between the two treatments, as well as time, was assessed. If interaction terms were not significant, a secondary analysis of treatment effects, in the absence of time was assessed. If no interaction was found, the effect of each treatment was assessed in separate models of treatment, time and the interaction term treatment*time, taking baseline values into consideration. The raw mean, standard deviation, and between-group difference at each time point was

reported. Normality of residuals of the final model was confirmed. Where no baseline data was present (ie for treatment efficacy), mixed model analysis was used, in the absence of any baseline considerations. Student t-tests were used to compare the number of participants satisfied with treatment at each time point.

5.3.4 Subjective Assessment of Sexual Function

Subjective measurements of sexual function, relationship quality and quality of life were assessed at baseline and after 4, 8 and 12 weeks of treatment using self-administered computerized or paper based questionnaires, which was consistent for individual patients as described in **section 3.2.5.** Briefly, participants sexual function was primarily assessed using the International Index of Erectile Function (IIEF) questionnaire [89]. Additional measures of sexual function were obtained from the European Male Aging Study (EMAS) [84, 85] and the Self-Esteem And Relationship Satisfaction (SERS) questionnaires [519]. Quality of life was assessed using the Short-Form Medical Outcomes Survey (SF-36) [333, 334, 520], the Depression Anxiety Stress Scale (DASS) [521-523] and the Functional Outcomes of Sleep Questionnaire (FOSQ) [339]. Levels of sleepiness were assessed using the Epworth Sleepiness Score (ESS) [324, 524]. Satisfaction with treatment was assessed at Week 4, Week 8 and Week 12 using the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire [93].

5.3.5 Nocturnal Penile Tumescence (NPT)

Sleep related erections were measured on a subset of participants who agreed to take part, using nocturnal penile tumescence (NPT) monitoring prior to treatment and at study completion using a Rigiscan Plus monitor [102] as described in **section 3.2.6.**

5.3.6 Blood Parameters

A single early morning fasted blood sample was collected after the overnight sleep study at baseline and at Week 12. Parameters assessed included reproductive hormones and routine full blood examination for safety.

5.3.7 Polysomnography

Overnight polysomnography was performed at baseline, prior treatment, and at Week 12 using the allocated treatment, in an attended laboratory setting and analysed using a Sandman Elite system and software (Sandman Elite v9.2, Tyco Healthcare, Denver, Colorado) at the Sydney site, or Compumedics Profusion 2 (Melbourne, Australia) at the Melbourne site. A description of polysomnographic methods and analysis can be found in **section 3.2.7.**

5.4 RESULTS

The flow of participants through the study is shown in **figure 5.1**. Sixty-one men were randomized into the study, of these, 49 were from the Sydney site and 12 were from Melbourne. Of these participants, 30 were allocated to receive Vardenafil, and 31 to placebo. Six participants withdrew from the study after randomisation. Four participants were from the Sydney site, while two were from Melbourne. Of these, two withdrew from the study due to being unhappy with the CPAP/sham treatment and four withdrew due to personal reasons. Four of the six withdrawals were randomised to placebo medication. There was no difference in any demographic, sleep or erectile function parameter between those who withdrew and those who completed the study (data not shown). Fifty five men completed the study.

Participants were aged 54.1±9.1 years, had severe OSA (AHI 46.1±25.8) and moderate ED (IIEF-ED 12.5±7.5). Baseline characteristics of sleep and breathing parameters, medical history and degree of erectile dysfunction between those who were randomised to Vardenafil and placebo are shown in **table 5.1**. There were no differences between the groups in regard to demographic variables or disease severity, with the only exception being duration of sleep and neck circumference, which were longer/larger in the Vardenafil group.

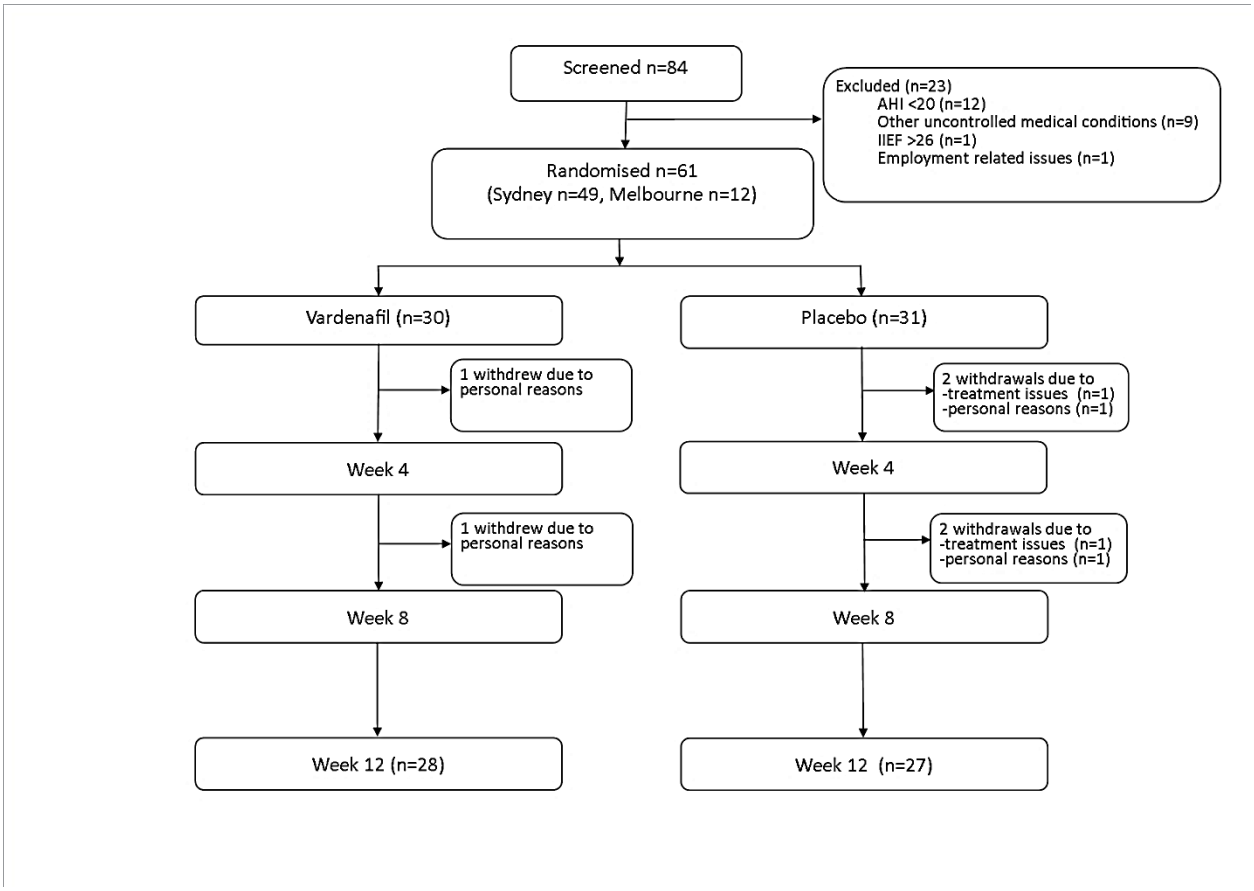


Figure 5.1 Study Flow

Table 5.1 Baseline characteristics

	Vardenafil (n=30)	Placebo (n=31)	p-value
Age (years)	54.5 ± 9.5	53.8 ± 8.9	0.770
Medical History			
Duration of erectile dysfunction (years)	6.0 ± 4.8	6.2 ± 5.4	0.853
Hypertension n (%)^	17 (57)	15 (48)	0.492
Using antihypertensives n (%)	13 (43)	12 (39)	0.731
Hypercholesterolemia n (%)^	9 (30)	7 (23)	0.454
Using statins n (%)	7 (23)	4 (13)	0.187
Diabetes n (%)^	6 (20)	5 (16)	0.523
Lifestyle Factors			
Relationship duration (years)	17.1 ± 14.0	17.4 ± 13.5	0.938
Number of drinks per week	8.4 ± 9.6	11.2 ± 15.5	0.398
Drink more than 10 drinks/week n(%)	10 (33)	11 (36)	0.782
Past smokers n(%)	25 (83)	25 (81)	0.903
Fathers n(%)	24 (80)	21 (68)	0.448
Anthropometry			
Weight (kg)	100.7 ± 15.6	100.4 ± 16.5	0.944
Body Mass Index (kg/m^2)	32.7 ± 4.6	32.9 ± 5.2	0.860
Neck circumference (cm)	43.9 ± 3.0	42.0 ± 2.8	**0.012**
Mid-arm circumference (cm)	33.3 ± 2.7	33.1 ± 3.3	0.817
Waist circumference (cm)	111.6 ± 11.8	110.1 ± 13.1	0.635
Hip circumference (cm)	109.7 ± 9.3	108.5 ± 12.1	0.664
Mid-Thigh circumference (cm)	52.3 ± 6.5	52.5 ± 6.6	0.951

Note: Values are mean ± standard deviation or number (percentage). p-value calculated by Students t-test or Fishers exact test. ^as diagnosed prior entry into the study. kg=kilograms, kg/m^2= kilograms per metre squared. cm=centimetres

(Continued over)

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Table 5.1 Baseline Characteristics (continued)

	Vardenafil (n=30)	Placebo (n=31)	p-value
Sleep and Breathing			
Total Sleep Time (minutes)	369.4 ± 50.8	327.4 ± 93.0	**0.033**
Sleep Efficiency (%)	82.5 ± 9.5	73.4 ± 20.7	**0.031**
REM (% of total sleep time)	16.3 ± 7.7	16.8 ± 6.6	0.797
Arousal index (/hour)	39.0 ± 23.3	29.1 ± 15.1	0.056
Apnoea Hypopnoea Index (AHI)	48.9 ± 26.8	43.4 ± 24.9	0.410
NREM AHI	49.6 ± 28.4	45.1 ± 26.5	0.527
REM AHI	49.3 ± 23.2	46.9 ± 27.6	0.722
Minimum SpO2	74.8 ± 11.0	77.2 ± 10.3	0.387
Time SpO2 below 90% (min)	12.6 ± 15.5	12.2 ± 14.9	0.905
Oxygen Desaturation (3%) Index	47.7 ± 30.6	40.4 ± 27.7	0.341
Subjective Sexual Function & Relationship			
International Index of Erectile Function (IIEF)	34.5 ± 16.2	34.6 ± 16.3	0.978
IIEF - Erectile Function	12.7 ± 7.5	12.3 ± 7.7	0.808
IIEF - Intercourse Satisfaction	6.0 ± 3.8	5.7 ± 4.1	0.786
IIEF - Orgasmic Function	5.7 ± 3.3	5.7 ± 3.5	0.991
IIEF - Overall Satisfaction	4.2 ± 2.2	4.5 ± 2.2	0.545
IIEF - Sexual Desire	5.9 ± 1.9	6.4 ± 2.1	0.317
European Male Aging Study (EMAS)	34.7 ± 6.7	32.8 ± 8.5	0.344
EMAS - Sexual Function related distress	11.2 ± 5.2	9.7 ± 4.7	0.245
EMAS - Change in Sexual Functioning	-3.0 ± 3.0	-3.4 ± 3.5	0.703
EMAS - Overall Sexual Functioning	15.7 ± 5.2	15.2 ± 6.6	0.782
EMAS - Masturbation	2.2 ± 1.6	2.3 ± 1.8	0.839
Self Esteem and Relationship (SERS)	38.1 ± 12.0	38.9 ± 11.1	0.792
SERS - Sexual Relationship Satisfaction	19.2 ± 8.0	18.6 ± 6.9	0.783
SERS - Confidence	18.6 ± 5.5	20.3 ± 5.3	0.237
SERS - Self Esteem	11.7 ± 4.5	13.0 ± 4.1	0.276
SERS - Overall Relationship Satisfaction	6.9 ± 1.9	7.1 ± 2.1	0.608
Nocturnal Penile Tumescence (n=43)			
Tip Rigidity Activation Units	20.4 ± 17.1	26.0 ± 30.2	0.503
Tip Tumescence Activation Units	17.1 ± 15.0	21.3 ± 34.5	0.642
Base Rigidity Activation Units	35.1 ± 34.9	31.9 ± 33.8	0.767
Base Tumescence Activation Units	24.2 ± 25.8	23.3 ± 29.4	0.912
Organic erectile dysfunction# (%)	11 (55%)^	16 (70%)[@]	0.323

Note: Values are mean ± standard deviation. p-value calculated by Students t-test or Fishers exact test. #Organic erectile dysfunction as determined using criteria specified in **section 3.2.6**. ^subset (n=20), [@] Subset (n=23), SpO2= Oxygen saturation

Table 5.1 Baseline Characteristics (continued)

	Vardenafil (n=30)	Placebo (n=31)	p-value
Quality of Life			
Subjective Sleepiness (ESS)	10.4 ± 4.6	10.2 ± 5.0	0.818
Functional Outcomes of Sleep Questionnaire (FOSQ)			
FOSQ - Overall score	15.3 ± 2.8	15.5 ± 3.5	0.873
FOSQ - Activity	3.1 ± 0.6	3.1 ± 0.8	0.646
FOSQ - Vigilance	3.2 ± 0.5	3.1 ± 0.6	0.781
FOSQ - Intimacy	2.6 ± 0.9	2.6 ± 1.0	0.985
FOSQ - General Productivity	3.5 ± 0.5	3.4 ± 0.6	0.689
FOSQ - Social Outcome	3.5 ± 0.7	3.6 ± 0.8	0.557
Depression Anxiety Stress Scale (DASS)			
DASS - Depression	9.5 ± 9.3	9.2 ± 8.5	0.916
DASS - Anxiety	5.9 ± 4.7	7.7 ± 6.6	0.213
DASS - Stress	13.3 ± 7.2	12.3 ± 7.7	0.581
Short Form 36 (SF-36)			
SF-36 - Physical Function	76.7 ± 15.7	67.7 ± 29.5	0.148
SF-36 - Role - Physical	76.7 ± 27.5	66.9 ± 37.9	0.263
SF-36 - Body Pain	75.0 ± 19.6	72.7 ± 23.5	0.677
SF-36 - General Health	63.0 ± 20.8	60.1 ± 17.4	0.551
SF-36 - Vitality	49.5 ± 22.2	53.9 ± 21.4	0.437
SF-36 - Social Function	81.8 ± 22.9	78.0 ± 28.0	0.565
SF-36 - Role Emotional	70.0 ± 34.3	68.9 ± 37.1	0.903
SF-36 - Mental Health	72.9 ± 18.6	70.5 ± 18.4	0.602
SF-36 - Reported Health	67.3 ± 14.9	65.5 ± 20.4	0.694
SF-36 - Mental Health Dimension	74.9 ± 21.3	73.7 ± 23.3	0.836

Note: Values are mean ± standard deviation. p-value calculated by Students t-test . ESS = Epworth Sleepiness Score.

5.4.1 Sleep and breathing

Despite randomization, at baseline, there was a difference in sleep duration, and thus sleep efficiency, by more than 40 minutes between the Vardenafil and placebo groups, however as this was not a primary endpoint, this was not considered detrimental to the analysis. There was no difference in the change of any sleep or breathing parameters between Vardenafil and placebo overall. Half of the study population was allocated to CPAP treatment, who should be effectively treated for their sleep disordered breathing. The other half who received sham CPAP thus had untreated sleep apnoea. In this group of participants (allocated to sham CPAP) there was no difference at baseline between the Vardenafil and placebo groups in regard to sleep and breathing parameters. When measured at 12 weeks, Vardenafil did not change any parameter of sleep or sleep disordered breathing including total sleep time, REM sleep duration, AHI or ODI between baseline and Week 12 (**table 5.2**).

Table 5.2 Effect of Vardenafil on sleep disordered breathing

	Vardenafil (n=14)					Placebo (n=16)						
	Baseline		Week 12		p-value	Baseline		Week 12		p-value	Difference between groups (95% CI)	p-value
TST (minutes)	365.3	± 53.0	375.6	± 78.5	0.694	300.3	± 111.1	329.4	± 68.9	0.432	-2.2 (-48.4 to 44.1)	0.923
REM (% of TST)	15.7	± 9.0	15.7	± 8.0	0.990	16.6	± 6.9	19.8	± 9.0	0.306	-0.5 (-6.3 to 5.3)	0.863
Arousal Index	39.3	± 24.4	42.5	± 29.6	0.768	29.2	± 12.8	34.0	± 15.7	0.385	-8.5 (-24.4 to 7.3)	0.274
AHI	47.1	± 24.5	46.7	± 31.1	0.969	41.0	± 25.8	38.2	± 23.1	0.767	-8.5 (-25.9 to 8.8)	0.317
NREM AHI	47.1	± 26.9	46.6	± 33.8	0.967	42.3	± 26.6	36.8	± 24.4	0.586	-1.4 (-20.3 to 17.5)	0.882
REM AHI	47.5	± 22.1	48.6	± 21.0	0.905	43.1	± 30.6	42.2	± 31.5	0.943	-8.8 (-22.8 to 5.2)	0.203
Minimum SpO2	71.1	± 11.3	74.9	± 10.5	0.390	77.9	± 10.5	79.8	± 6.0	0.570	2.9 (-5.6 to 11.4)	0.487
Time SpO2 below 90% (min)	15.8	± 19.3	15.1	± 15.0	0.917	10.3	± 8.9	8.1	± 7.1	0.481	-4.8 (-24.2 to 14.6)	0.611
ODI	47.5	± 27.7	49.4	± 32.0	0.874	41.6	± 28.3	37.8	± 24.3	0.714	-0.2 (-9.7 to 9.2)	0.958

Note: Only those participants allocated to sham CPAP (ie, untreated OSA) are presented here. Values are mean ± SD. TST = Total Sleep Time, REM = Rapid Eye Movement Sleep, AHI = Apnoea Hypopnea Index, ODI = Oxygen Desaturation (3%) Index, SpO2=Oxygen saturation, min=minutes. p-value determined by students t-test.

5.4.2 Subjective Sexual functioning

At baseline, of the 61 study participants, 11.4% had mild ED (IIEF-ED score 22-25), 21.3% had mild-moderate ED (IIEF-ED score 17-21), 26.2% had moderate ED (IIEF-ED score 11-16) and 41% had severe ED (IIEF-ED score 6-10) [430, 544].

Vardenafil, compared to placebo, improved the overall score of the International Index of Erectile Function (IIEF) at the Week 8 timepoint by 11 points (p=0.024). An increase was seen at Week 4 and Week 12 by 10 and 8 points respectively but this did not reach statistical significance over placebo (p=0.09 and p=0.07 respectively) (**Table 5.3 and Figure 5.2**). Contributing to this overall improvement at week 8 was the improvement seen in the erectile function and intercourse satisfaction domains; however no improvements were seen in the domains of orgasmic function, overall satisfaction, and sexual desire. Increases in the IIEF-ED domain by more than 4 points are considered clinically meaningful [545] which were seen at weeks 4 & 8 (5.3±6.7 and 5.4±7.5 points respectively), while there was only a borderline improvement at week 12 (increase by 4.0±7.7 points) which was not statistically different than placebo. At week 12, 25% of those allocated to Vardenafil reported normal erectile function, compared to 7% of those allocated to placebo, which when analysed using Fishers exact test, was not different (**figure 5.3**). At Week 12, there were no differences in any domain, or the overall score of the IIEF between Vardenafil and placebo.

Significant improvements were seen with Vardenafil compared to placebo in the European Male Aging Study questionnaire (**table 5.4**). At all timepoints there was a reduction in distress caused by sexual dysfunction, and there was also consistent improvement in the domain related to change in sexual function throughout the study (**figure 5.4**). No changes were seen in the overall score, or the domains of overall sexual function or masturbation.

Vardenafil improved the overall score in the Self Esteem and Relationship Satisfaction questionnaire at week 4 and week 12. At week 4, there was an improvement in the Sexual Relationship Satisfaction domain with Vardenafil compared to placebo (**figure 5.4**). No other improvements in other domains were seen (**table 5.4**). Stratification into initial severity groups on the basis of IIEF-ED domain did not show any group to respond to Vardenafil moreso than placebo in any domain measured.

Table 5.3 Effect of Vardenafil on Sexual Function: International Index of Erectile Function

Variable	Visit	Vardenafil (n=30)	Placebo (n=31)	Difference Mean (95% CI)	Effect size (d)	p-value
International Index of Erectile Function (IIEF)						
Overall Score	Week 4	44.39 ± 19.15	37.04 ± 18.01	7.36 (-2.71 to 17.42)	0.46	0.088
	Week 8	45.04 ± 19.76	34.92 ± 18.84	10.12 (-0.64 to 20.87)	0.63	**0.024**
	Week 12	42.89 ± 21.91	34.26 ± 18.23	8.63 (-2.29 to 19.56)	0.53	0.067
Erectile Function	Week 4	18.14 ± 8.84	13.56 ± 8.54	4.59 (-0.12 to 9.29)	0.61	**0.038**
	Week 8	18.12 ± 9.50	12.85 ± 8.73	5.27 (0.19 to 10.35)	0.70	**0.024**
	Week 12	17.11 ± 9.92	12.59 ± 8.56	4.51 (-0.50 to 9.53)	0.60	0.069
Intercourse Satisfaction	Week 4	7.43 ± 4.69	5.89 ± 4.52	1.54 (-0.93 to 4.00)	0.39	0.194
	Week 8	8.31 ± 4.43	5.26 ± 4.80	3.05 (0.50 to 5.60)	0.78	**0.010**
	Week 12	7.46 ± 4.82	5.26 ± 4.85	2.21 (-0.41 to 4.82)	0.56	0.100
Orgasmic Function	Week 4	6.75 ± 3.47	6.26 ± 3.68	0.49 (-1.44 to 2.42)	0.14	0.636
	Week 8	6.35 ± 3.57	6.00 ± 3.59	0.35 (-1.63 to 2.32)	0.10	0.537
	Week 12	6.18 ± 3.72	5.37 ± 3.63	0.81 (-1.18 to 2.80)	0.24	0.291
Overall Satisfaction	Week 4	5.46 ± 2.52	4.78 ± 2.17	0.69 (-0.59 to 1.96)	0.31	0.116
	Week 8	5.81 ± 2.64	4.74 ± 2.49	1.07 (-0.35 to 2.48)	0.48	0.061
	Week 12	5.82 ± 3.16	4.78 ± 2.12	1.04 (-0.42 to 2.51)	0.47	0.074
Sexual Desire	Week 4	6.61 ± 1.91	6.33 ± 1.94	0.27 (-0.77 to 1.32)	0.14	0.296
	Week 8	6.46 ± 1.86	6.07 ± 2.16	0.39 (-0.73 to 1.50)	0.19	0.124
	Week 12	6.32 ± 2.06	6.26 ± 2.43	0.06 (-1.15 to 1.28)	0.03	0.381

Note: Values are mean ± standard deviation. * p-value calculated by mixed model analysis. Effect size (Cohen's d) calculated by dividing difference between CPAP and sham by the standard deviation at baseline.

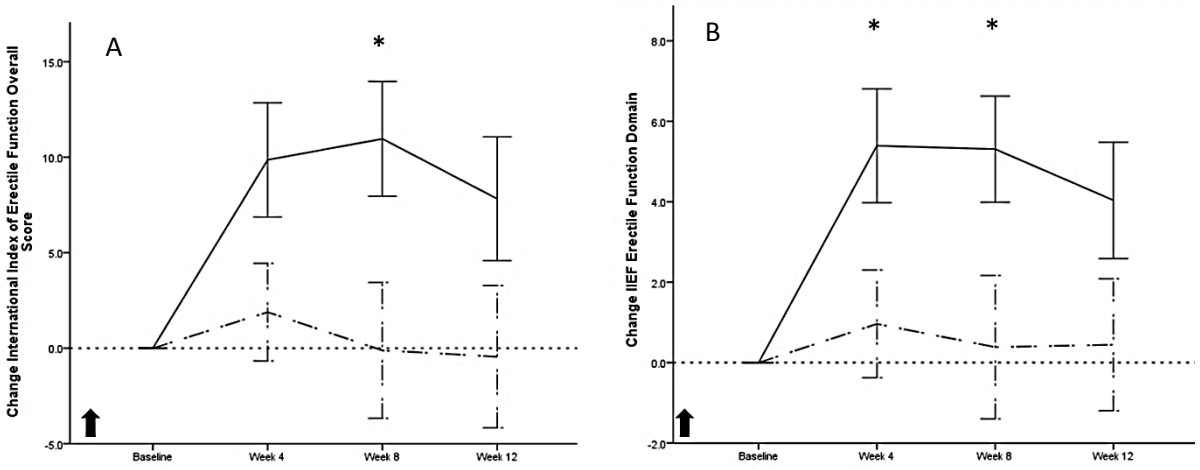

Figure 5.2 Effect of Vardenafil on erectile function over time

Note: (A) IIEF Overall Score, (B) IIEF Erectile Function domain. Values shown are change from baseline means plus standard error. *p<0.05 as calculated by mixed model analysis. Arrows indicate direction of improvement.

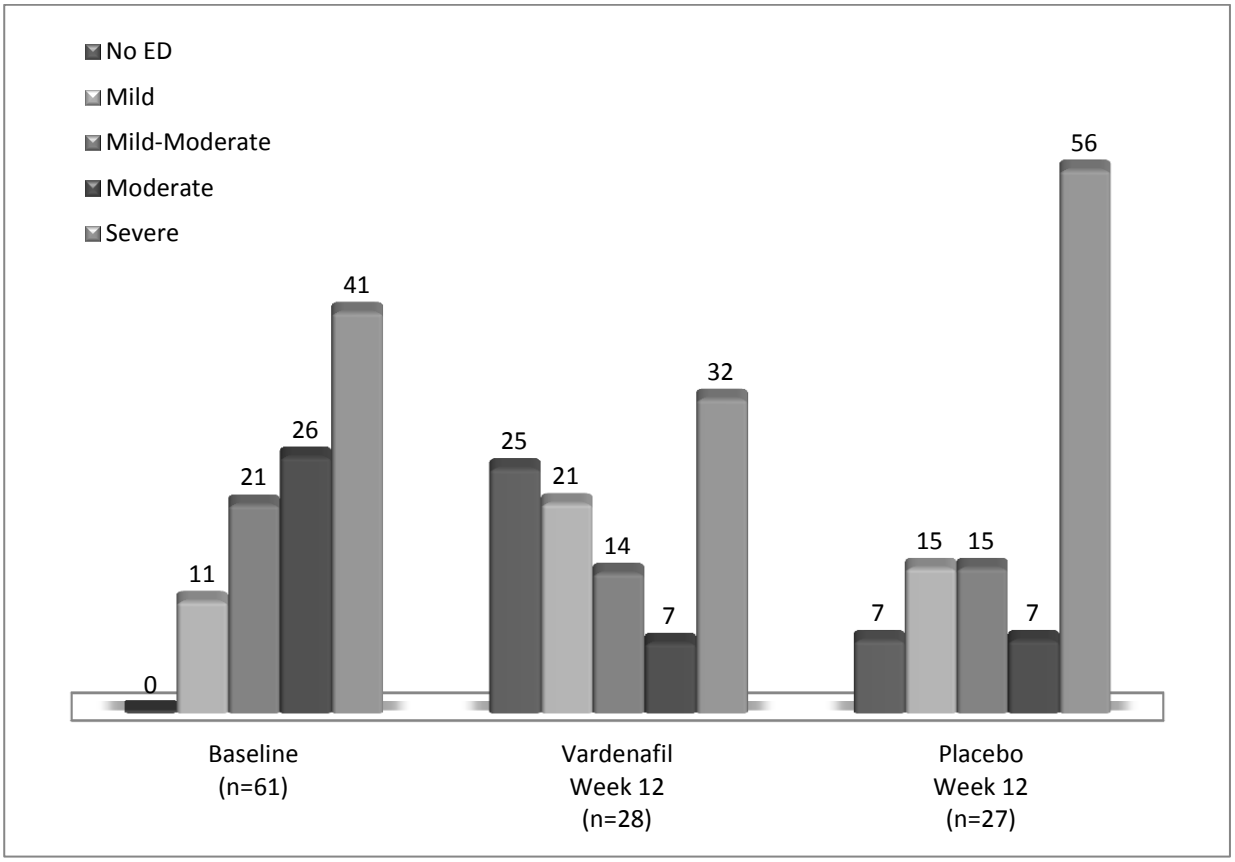

Figure 5.3 Distribution of Erectile Dysfunction Categories

Note: ED category defined by IIEF ED scores: No ED: >26; Mild ED: 22-26; Mild-Moderate ED: 17-21; Moderate ED:11-16; Severe ED: 6-10 [430]. Number displayed is percentage of participants at each visit.

Table 5.4 Effect of Vardenafil on Sexual function and Relationship: EMAS & SERS

Variable	Visit	Vardenafil (n=30)	Placebo (n=31)	Difference Mean (95% CI)	Effect size (d)	p-value
European Male Aging Study questionnaire (EMAS)						
Overall Score	Week 4	36.04 ± 8.96	31.83 ± 8.61	4.21 (-0.77 to 9.19)	0.55	0.052
	Week 8	36.84 ± 7.20	34.64 ± 8.17	2.20 (-2.18 to 6.58)	0.29	0.423
	Week 12	37.52 ± 7.16	33.15 ± 8.78	4.36 (-0.05 to 8.78)	0.57	0.060
Sexual	Week 4	7.36 ± 5.19	8.56 ± 4.93	-1.20 (-3.94 to 1.54)	-0.24	**0.004**
Function	Week 8	7.38 ± 6.54	9.93 ± 5.25	-2.54 (-5.81 to 0.72)	-0.51	**<0.001**
Distress	Week 12	6.89 ± 5.88	8.23 ± 5.32	-1.34 (-4.41 to 1.73)	-0.27	**0.007**
Change in	Week 4	0.48 ± 4.90	-3.68 ± 3.52	4.16 (1.89 to 6.43)	1.29	**0.001**
Sexual	Week 8	0.04 ± 4.55	-2.81 ± 4.60	2.85 (0.35 to 5.35)	0.89	**0.013**
Function	Week 12	0.68 ± 4.55	-2.93 ± 3.43	3.60 (1.42 to 5.79)	1.12	**0.005**
Overall	Week 4	17.21 ± 6.37	15.60 ± 5.83	1.61 (-1.75 to 4.96)	0.27	0.299
Sexual	Week 8	17.85 ± 6.14	16.68 ± 5.74	1.17 (-2.18 to 4.51)	0.20	0.249
Function	Week 12	18.85 ± 6.82	16.42 ± 6.33	2.43 (-1.20 to 6.06)	0.41	0.089
Masturbation	Week 4	2.32 ± 1.59	2.30 ± 1.61	0.03 (-0.84 to 0.89)	0.01	0.826
	Week 8	2.19 ± 1.64	2.50 ± 1.79	-0.31 (-1.26 to 0.63)	-0.18	0.622
	Week 12	2.11 ± 1.45	2.58 ± 1.98	-0.47 (-1.41 to 0.47)	-0.28	0.322
Self-Esteem and Relationship Satisfaction (SERS)						
Overall	Week 4	44.04 ± 14.53	39.38 ± 9.72	4.65 (-2.15 to 11.45)	0.41	**0.029**
Score	Week 8	44.08 ± 14.23	40.88 ± 11.45	3.20 (-4.18 to 10.58)	0.28	0.235
	Week 12	46.56 ± 14.91	40.81 ± 11.75	5.75 (-1.67 to 13.17)	0.50	**0.040**
Sexual	Week 4	23.50 ± 8.95	19.04 ± 5.95	4.46 (0.34 to 8.59)	0.60	**0.025**
Relationship	Week 8	22.88 ± 9.05	19.81 ± 7.60	3.08 (-1.58 to 7.73)	0.41	0.273
Satisfaction	Week 12	24.56 ± 9.77	19.89 ± 7.67	4.67 (-0.13 to 9.46)	0.63	0.055
Confidence	Week 4	20.54 ± 6.52	20.12 ± 5.14	0.42 (-2.80 to 3.64)	0.08	0.146
	Week 8	21.19 ± 6.22	20.72 ± 5.10	0.47 (-2.73 to 3.68)	0.09	0.301
	Week 12	22.00 ± 6.66	20.62 ± 5.31	1.38 (-1.95 to 4.71)	0.25	0.085
Self Esteem	Week 4	13.07 ± 4.80	12.88 ± 4.21	0.18 (-2.27 to 2.64)	0.04	0.166
	Week 8	13.56 ± 4.85	13.76 ± 4.06	-0.20 (-2.71 to 2.30)	-0.05	0.468
	Week 12	14.25 ± 4.90	13.23 ± 4.24	1.02 (-1.49 to 3.53)	0.23	0.059
Overall	Week 4	7.14 ± 2.53	7.19 ± 2.18	-0.04 (-1.32 to 1.24)	-0.03	0.667
Relationship	Week 8	7.31 ± 2.48	6.96 ± 2.19	0.35 (-0.97 to 1.67)	0.18	0.430
Satisfaction	Week 12	7.41 ± 2.41	7.38 ± 2.06	0.02 (-1.21 to 1.26)	0.02	0.768

Note: Values are raw mean ± standard deviation at each visit. p-value obtained using mixed model analysis. Effect size (Cohen's d) calculated by dividing difference between CPAP and sham by the standard deviation at baseline.

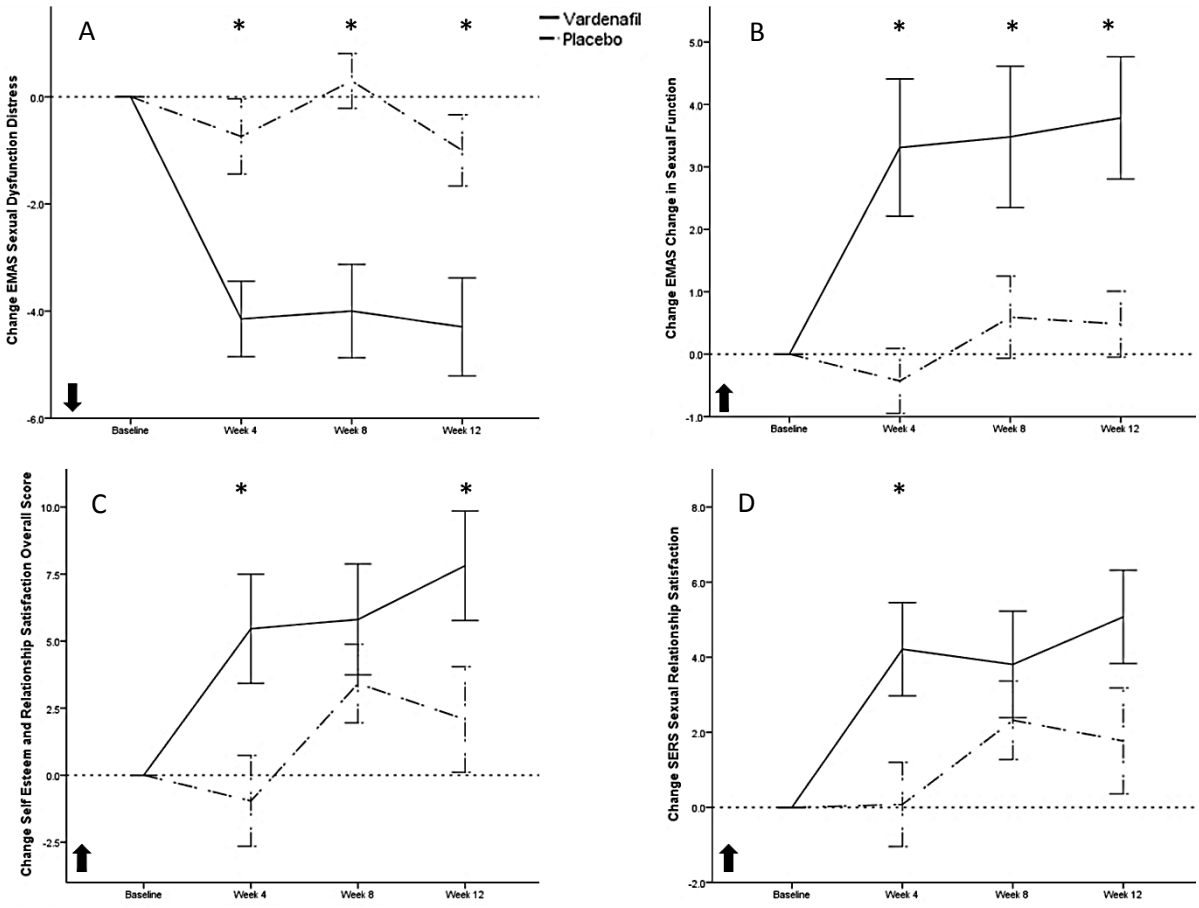

Figure 5.4 Changes from baseline, SERS and EMAS Sexual Functioning.

Note: (A) EMAS Sexual function distress (B) EMAS Change in sexual functioning (C) Self-Esteem and Relationship Satisfaction overall score (D) SERS Sexual Relationship satisfaction. Values are mean change from baseline with one standard error. *$p<0.05$. Arrows indicate direction of improvement

5.4.3 Sleep Related Erections

Forty three participants (70%) were agreeable to undertake nocturnal penile tumescence (NPT) monitoring to assess sleep related erections. Of these, only 36 (59%) completed a successful recording (>4 hours) on the baseline PSG night. Five men chose not to use the device on this night after using the device at home the prior two nights of acclimitisation and two did not have sufficient data on PSG night due to dislocation of the loops during sleep. At Week 12, only 28 (46%) successful recordings occurred, due to withdrawal of participants (n=5), participant decision not to use the device at this visit (n=2) and technical difficulties (n=1). Of these, 15 were allocated to Vardenafil and 13 were on placebo. Participants who completed both Rigiscan recordings did not differ from those who declined in terms of age, severity of ED, sleepiness, testosterone or weight. However, those who did NPT monitoring had less severe OSA compared to those who did not (AHI: 41.5±22.7vs 56.9±29.9, p=0.033; Minimum SpO2: 78.5±9.0% vs 70.1±12.0, p=0.004; Oxygen Desaturation Index 37.9±25.1 vs 58.4±33.4, p=0.011).

Results for NPT monitoring are given in **table 5.5**. Data shown is from the night of polysomnography. At baseline, there were no differences in any NPT parameter between the Vardenafil or placebo groups (**table 5.1**). Vardenafil increased all parameters of NPT quality (base and tip tumescence and rigidity), but not number of erections compared to placebo (**table 5.5).** An example NPT recording for one participant, allocated to Vardenafil and sham, with concurrent sleep staging and pulse oximetry at baseline and week 12, is shown in **figure 5.5**.

Using predefined parameters (**section 3.2.6**) to categorise participants into those with ED of either organic and psychological origin, using the PSG night for those whom completed it, or the best at-home recording for those who did not, 16 (37%) of participants were categorised

as having ED of psychological origin. These participants did not differ from those categorised as having organic ED in terms of age, BMI, severity of OSA or blood parameters. However, there was a significant difference in terms of subjective ED severity, as measured by the IIEF questionnaire. Men who were classified as having psychological ED by the traditional criteria had less severe subjective ED (IIEF-ED 15.8±7.4 vs 10.5±7.9, p=0.036). Of all mood and quality of life parameters measured, only those related to mental health differed between men classified as having psychological versus organic ED. Those men with organic ED were more depressed (12.44±10.9 vs 5.6±4.4, p=0.022), and scored lower in the domain of mental health (65.3±22.7 vs 80.7±12.15, p=0.016) and the mental health dimension (69.04±25.2 vs 84.3±14.1, p=0.033) in the SF-36 questionnaire. A trend toward being more stressed (14.8±8.6 vs 10.1±4.9, p=0.054) was also noted.

Table 5.5 Effect of Vardenafil on Sleep Related Erections

	Vardenafil		Placebo			
	Baseline (n=17)	Week 12 (n=15)	Baseline (n=20)	Week 12 (n=13)	Effect size (d)	p-value
Number of Erections	3.00 ± 2.09	3.40 ± 2.10	2.24 ± 2.10	3.23 ± 2.13	0.08	0.495
Tip RAU	25.18 ± 22.60	58.87 ± 58.05	22.95 ± 26.19	31.77 ± 31.85	1.12	**0.010**
Tip TAU	20.18 ± 17.84	48.47 ± 48.57	19.10 ± 21.10	19.23 ± 18.48	1.51	**0.010**
Base RAU	49.00 ± 63.74	82.73 ± 66.79	31.85 ± 29.08	40.23 ± 35.34	0.88	**0.003**
Base TAU	30.53 ± 31.33	63.87 ± 65.29	31.30 ± 41.86	23.54 ± 23.94	1.09	**0.010**

Note: Values given are mean ± standard deviation. *p-value obtained using mixed model analysis, RAU = Rigidity Activity Units, TAU = Tumescence Activity Units. Effect size (Cohen's d) calculated by dividing difference between CPAP and sham by the standard deviation of all participants at baseline.

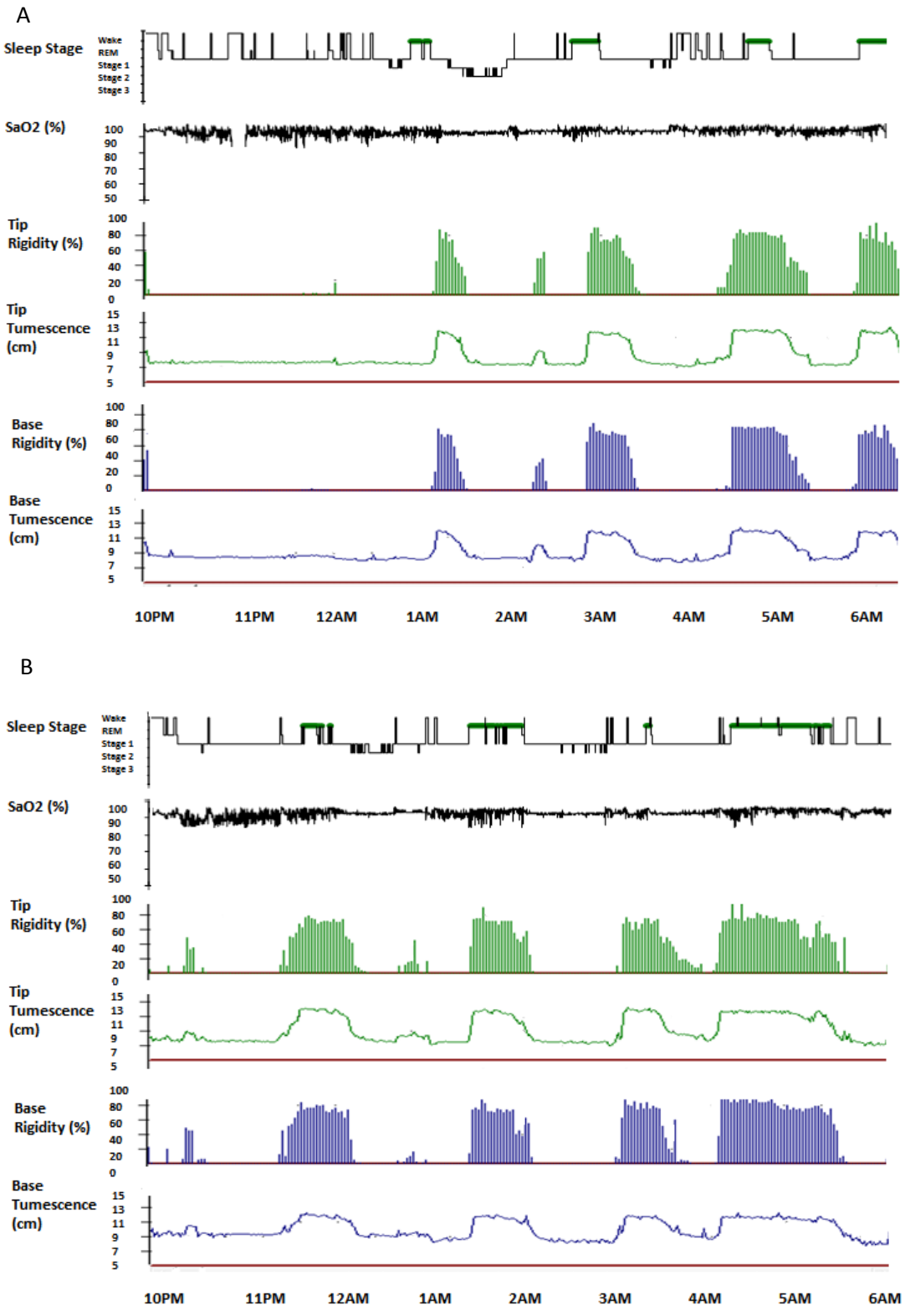

Figure 5.5 Sleep staging, pulse oximetry and NPT for a patient allocated to Vardenafil.

NOTE: (A) Baseline recording with no treatment. Several erectile episodes are seen mostly during REM sleep. (B) Recording at Week 12 using Vardenafil. The number of episodes has not changed, however the total duration and quality has increased. SaO2 = Oxygen saturation

5.4.4 Hormonal Analysis

At study commencement, testosterone levels were borderline low (10.2±3.7 nmol/L). Those allocated to Vardenafil had a minor increase in testosterone levels from baseline to Week 12 (12.3±3.0, p=0.023) although this was no different than the change with placebo (11.1±4.5, p=0.384). There was no change in luteinizing hormone, follicular stimulating hormone, or thyroid stimulating hormone.

5.4.5 Quality of Life

Very little change was found with Vardenafil on quality of life compared to placebo. There was no change in levels of sleepiness in the ESS, anxiety or stress in the DASS questionnaire or any parameter in the FOSQ questionnaire (**Table 5.6**). Only at week 8 were two domains improved with Vardenafil compared to placebo, firstly the SF-36 domain of vitality (p=0.01) and secondly, the depression domain in the DASS questionnaire, due to a worsening of depression with placebo (p=0.01).

Table 5.6 Effect of Vardenafil on quality of life

Variable	Visit	Vardenafil (n=30)	Placebo (n=31)	Difference Mean (95% CI)	Effect size (d)	p-value
Epworth	Week 4	9.1 ± 5.4	8.9 ± 5.3	0.3 (-2.6 to 3.1)	0.04	0.663
Sleepiness	Week 8	9.3 ± 5.3	8.5 ± 5.0	0.8 (-2.1 to 3.6)	0.17	0.516
Score	Week 12	8.0 ± 4.6	8.5 ± 5.1	-0.5 (-3.1 to 2.2)	-0.10	0.625
Functional Outcomes of Sleep (FOSQ)						
Overall	Week 4	97.4 ± 14.2	97.0 ± 14.6	0.4 (-7.5 to 8.2)	0.02	0.813
Score	Week 8	98.4 ± 16.2	97.3 ± 15.0	1.1 (-7.5 to 9.7)	0.06	0.628
	Week 12	98.5 ± 17.5	97.9 ± 17.2	0.6 (-9.2 to 10.4)	0.03	0.706
Activity	Week 4	3.4 ± 0.4	3.3 ± 0.6	0.0 (-0.3 to 0.3)	0.14	0.675
	Week 8	3.4 ± 0.5	3.4 ± 0.6	0.0 (-0.3 to 0.3)	0.00	0.911
	Week 12	3.4 ± 0.6	3.4 ± 0.7	-0.1 (-0.4 to 0.3)	0.00	0.611
Vigilance	Week 4	3.3 ± 0.7	3.3 ± 0.6	0.0 (-0.4 to 0.4)	0.00	0.408
	Week 8	3.4 ± 0.6	3.4 ± 0.6	0.0 (-0.3 to 0.3)	0.00	1.000
	Week 12	3.3 ± 0.8	3.3 ± 0.8	0.0 (-0.4 to 0.4)	0.00	0.941
Intimacy	Week 4	3.0 ± 0.1	3.0 ± 0.6	0.0 (-0.4 to 0.5)	0.00	0.657
	Week 8	3.1 ± 0.8	3.2 ± 0.9	-0.1 (-0.6 to 0.3)	-0.11	0.653
	Week 12	3.2 ± 0.8	3.0 ± 1.1	0.2 (-0.6 to 0.7)	0.22	0.525
Productivity	Week 4	3.6 ± 0.4	3.6 ± 0.5	0.0 (-0.3 to 0.2)	0.00	0.889
	Week 8	3.6 ± 0.4	3.7 ± 0.4	-0.1 (-0.3 to 0.2)	-0.18	0.828
	Week 12	3.5 ± 0.6	3.6 ± 0.5	-0.1 (-0.4 to 0.3)	-0.18	0.888
Social	Week 4	3.7 ± 0.6	3.8 ± 0.5	0.1 (-0.4 to 0.2)	-0.13	0.756
Outcomes	Week 8	3.8 ± 0.4	3.9 ± 0.4	0.1 (-0.3 to 0.2)	-0.13	0.778
	Week 12	3.6 ± 0.6	3.7 ± 0.7	0.0 (-0.4 to 0.3)	-0.13	0.794
Depression Anxiety Stress Scale (DASS)						
Depression	Week 4	6.6 ± 9.3	8.5 ± 10.4	-1.9 (-7.1 to 3.4)	-0.22	0.105
	Week 8	6.4 ± 10.0	9.0 ± 11.0	-2.7 (-8.4 to 3.1)	-0.29	**0.006**
	Week 12	6.8 ± 9.0	7.7 ± 10.1	-0.9 (-6.1 to 4.3)	-0.10	0.066
Anxiety	Week 4	3.8 ± 3.9	6.4 ± 5.9	-2.6 (-5.3 to 0.0)	-0.45	0.272
	Week 8	3.3 ± 3.8	8.0 ± 7.7	-4.7 (-8.1 to -1.4)	-0.82	0.167
	Week 12	2.7 ± 3.6	6.0 ± 6.9	-3.3 (-6.3 to -0.3)	-0.57	0.745
Stress	Week 4	9.4 ± 7.7	10.4 ± 9.1	-1.0 (-5.4 to 3.5)	-0.14	0.255
	Week 8	9.1 ± 8.7	11.3 ± 10.4	-2.2 (-7.4 to 3.1)	-0.30	0.197
	Week 12	9.9 ± 8.0	11.0 ± 11.2	-1.1 (-6.4 to 4.2)	-0.15	0.388

Note: Values are raw means ± standard deviation. p-value determined using mixed model analysis. Effect size (Cohen's d) calculated by dividing difference between CPAP and sham by the standard deviation at baseline.

(Continued over)

Table 5.6 Effects of Vardenafil on quality of life (continued)

Variable	Visit	Vardenafil (n=30)	Placebo (n=31)	Difference Mean (95% CI)	Effect size (d)	p-value
Short-form 36 (SF-36)						
Physical	Week 4	79.5 ± 19.8	73.2 ± 27.3	6.3 (-6.5 to 19.2)	0.26	0.694
Function	Week 8	82.1 ± 21.1	79.4 ± 24.2	2.7 (-9.9 to 15.2)	0.11	0.823
	Week 12	82.3 ± 15.2	82.4 ± 22.3	-0.1 (-10.4 to 10.2)	0.00	0.365
Role	Week 4	74.2 ± 30.4	66.9 ± 37.9	7.2 (-10.4 to 24.9)	0.21	0.497
Physical	Week 8	75.9 ± 29.5	66.9 ± 37.9	8.9 (-8.7 to 26.6)	0.26	0.359
	Week 12	75.9 ± 29.5	66.9 ± 37.9	8.9 (-8.6 to 26.4)	0.26	0.632
Body Pain	Week 4	74.2 ± 21.9	70.8 ± 29.2	3.4 (-10.3 to 17.0)	0.16	0.773
	Week 8	74.0 ± 22.7	69.0 ± 27.1	5.0 (-8.6 to 18.7)	0.23	0.421
	Week 12	75.5 ± 20.1	75.8 ± 26.6	-0.3 (-13.0 to 12.4)	-0.01	0.794
General	Week 4	68.1 ± 19.9	58.6 ± 26.0	9.5 (-2.9 to 21.9)	0.50	0.447
Health	Week 8	71.0 ± 19.4	66.1 ± 24.9	4.9 (-7.3 to 17.1)	0.26	0.588
	Week 12	67.7 ± 20.7	67.2 ± 24.3	0.5 (-11.7 to 12.7)	0.03	0.128
Vitality	Week 4	59.3 ± 21.9	56.4 ± 21.7	2.9 (-8.7 to 14.5)	0.13	0.187
	Week 8	63.3 ± 16.8	56.5 ± 24.7	6.9 (-4.7 to 18.4)	**0.31**	**0.013**
	Week 12	61.6 ± 20.4	59.6 ± 23.6	2.0 (-10.0 to 13.9)	0.09	0.157
Social	Week 4	81.2 ± 23.7	73.4 ± 26.1	7.8 (-5.4 to 21.0)	0.31	0.367
Function	Week 8	84.8 ± 20.8	79.8 ± 26.8	5.0 (-8.1 to 18.1)	0.20	0.518
	Week 12	84.5 ± 20.8	79.2 ± 25.9	5.3 (-7.4 to 18.0)	0.21	0.521
Role	Week 4	79.8 ± 35.6	69.2 ± 40.3	10.6 (-9.9 to 31.1)	0.30	0.275
Emotional	Week 8	81.5 ± 32.5	70.4 ± 39.6	11.1 (-8.7 to 30.9)	0.31	0.335
	Week 12	71.4 ± 34.9	72.9 ± 37.0	-1.5 (-21.0 to 18.0)	-0.04	0.658
Mental	Week 4	76.3 ± 19.7	69.3 ± 20.3	7.0 (-3.8 to 17.8)	0.38	0.197
Health	Week 8	78.1 ± 18.7	71.0 ± 22.2	7.1 (-4.1 to 18.3)	0.39	0.271
Scale	Week 12	78.3 ± 19.8	74.1 ± 21.3	4.2 (-6.9 to 15.3)	0.23	0.745
Physical	Week 4	71.9 ± 17.1	67.2 ± 22.3	4.7 (-6.2 to 15.5)	0.26	0.275
Health	Week 8	73.2 ± 17.1	67.6 ± 25.1	5.7 (-6.3 to 17.7)	0.32	0.215
	Week 12	73.8 ± 14.9	71.8 ± 23.7	2.0 (-8.6 to 12.7)	0.10	0.696
Mental	Week 4	80.3 ± 22.0	71.8 ± 25.5	8.6 (-4.4 to 21.6)	0.38	0.204
Health	Week 8	81.4 ± 19.0	73.7 ± 24.3	7.7 (-4.2 to 19.7)	0.35	0.330
Dimension	Week 12	78.0 ± 23.8	75.4 ± 25.5	2.6 (-10.8 to 15.9)	0.12	0.959

Note: Values are raw means ± standard deviation. p-value determined using mixed model analysis. Effect size (Cohen's d) calculated by dividing difference between CPAP and sham by the standard deviation at baseline.

5.4.6 Adherence to medication

Medication adherence, defined as the proportion of tablets taken over a given period was assessed. Despite requests, not all participants returned unused tablets at each visit. Although 30 participants were allocated to Vardenafil, data is only available for 21 as 8 participants did not return medication bottles, and 1 withdrew before treatment commenced. For placebo, data is only available for 24 participants as 5 did not return medication bottles, data was missing for 2 participants and 2 withdrew before treatment commenced.

On the basis of those for whom data was available, medication adherence was not different between Vardenafil (84.0%) and placebo (84.5%) (p=0.915). Adherence to medication, defined as taking 80% or more prescribed tablets was achieved by 71% of those taking Vardenafil, and 75% of those taking placebo (p=0.999).

5.4.7 Treatment Satisfaction

At Weeks 4, 8 and 12, participants were asked about their satisfaction with treatment as it referred to erectile function using the Erectile Dysfunction Inventory of Treatment Score (EDITS). All items on the EDITS were scored from zero (no satisfaction or dissatisfaction) to four (high satisfaction). The mean satisfaction score for each patient was calculated. Each mean score was multiplied by 25 giving a range between 0 (extremely low treatment satisfaction) to 100 (extremely high treatment satisfaction). At all timepoints, those who received Vardenafil were more satisfied overall than those who received placebo (**table 5.7**).

A score of over 50 in the Erectile Dysfunction Inventory of Treatment Score (EDITS) is considered to represent satisfaction with treatment [525]**. Figure 5.6** shows the percentage of participants satisfied with treatment for Vardenafil versus placebo. Only at Week 4 was there a

significant difference (p=0.0001) in the number of participants considered to be satisfied with treatment with Vardenafil over placebo.

Table 5.7: Treatment Satisfaction Score for Vardenafil

	Vardenafil (n=28)	Placebo (n=27)	p-value
Week 4	72.4 ± 15.3	46.3 ± 21.7	**<0.001**
Week 8	67.2 ± 21.5	51.0 ± 22.4	**0.007**
Week 12	70.5 ± 19.9	50.4 ± 23.8	**0.004**

Note: Values are mean ± standard deviation. p-value determined using mixed model analysis

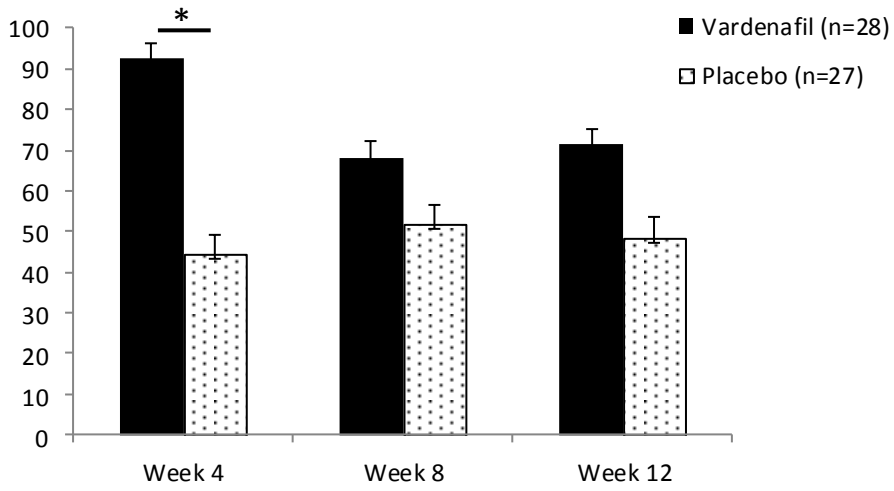

Figure 5.6: Percentage of participants satisfied with treatment for erectile function

Note: Treatment satisfaction defined as a score of more than 50 in the EDITS questionnaire.
*p<0.05 determined using Fishers exact test.

5.5 DISCUSSION

This is the first randomised controlled trial to study the effects of daily low dose Vardenafil in men with OSA and ED on subjective sexual function, sleep related erections, and quality of life. We have studied 61 men with severe OSA and moderate ED. At Week 12, Vardenafil did not improve subjective erectile function more so than placebo, however, it did improve nocturnal erections, as well as self-confidence, reduced distress due to erectile dysfunction, and there was a higher degree of satisfaction, although there was no difference in the number of men satisfied with Vardenafil compared to placebo. There were very minimal improvements in mood and quality of life with Vardenafil.

5.5.1 Effect of Vardenafil on OSA

The current study provided an opportunity to investigate the effect of a lower daily dose (10mg) of Vardenafil on breathing during sleep in untreated OSA by assessing the effect in those allocated to sham CPAP, that is, those who were untreated for their sleep apnoea. Unlike that of a previous study using an on-demand 50mg dose of Sildenafil [464], daily dose 10mg Vardenafil did not show any worsening of OSA in terms of AHI, ODI, minimum oxygen saturation, nor time with oxygen levels below 90%, compared to placebo. This difference may also be due to a different PDE-5 inhibitor, or a lower dose, both of which may reduce unwanted side effects in regards to unintentional upper airway muscle relaxation or other sleep apnoea-worsening effects.

5.5.2 Subjective Erectile Function

The present study is the first to investigate the efficacy of low dose daily Vardenafil on subjective erectile function, specifically in patients with OSA. A low daily dose was used rather than a higher dose on-demand in an effort to obtain efficacy without the risk of worsening OSA. In a previous study of men with OSA status not reported, a 12 week daily dose 10mg versus on-

demand 10mg use of Vardenafil showed no difference between the two in regards to treatment efficacy [119]. However, another study showed a reduced efficacy with daily dosage over on-demand administration of Vardenafil in men with after a prostatectomy [120]. This difference may be due to differing patient groups. The first study recruited patients with ED of unspecified cause; the other studied all patients undergoing prostatectomy who previously had normal erectile function. The former more closely matches the present study population. In this OSA population, 12 weeks of a daily dose of 10mg Vardenafil did not improve subjective erectile function compared to placebo. These results support those found in a previous study of Sildenafil on-demand in men with OSA in which the efficacy was found to be reduced in men with OSA compared to other populations studied [485]. Potentially, the presence of OSA may limit the efficacy of Vardenafil. One potential mechanism to explain this may be due to repetitive hypoxic episodes which may limit the amount of circulating nitric oxide, which is imperative to dilate vessels for erections to occur. Another may be due to the presence of psychological factors, such as depression, due to untreated OSA, influencing erectile function, which Vardenafil does not overcome.

The majority of studies of PDE-5 inhibitor efficacy have mostly been conducted in non-OSA populations. A meta-analysis of 9 non-OSA studies, comprising 6809 participants, found overall, an increase of 6.2 points in the IIEF-ED domain with at least 12 weeks of Vardenafil. In the present study, at the end of the first and second months of treatment, Vardenafil improved erectile function compared to placebo by 5.4 and 5.3 points in the IIEF-ED domain respectively. However, the increase at study endpoint was 4.0 points, which was not statistically different from placebo. However, an increase of 4 points is considered clinically meaningful [412]. No

other study has reported a decline in responsiveness to Vardenafil or any other PDE-5 inhibitor over time; however, such regular assessments in the first 3 months have not been reported.

The majority of previous studies have been performed using Vardenafil in an on-demand administration regime, rather than daily dose [571-573]. In previous studies, in men with OSA status undefined, the first multicentre randomised controlled trial in 580 patients using differing doses of Vardenafil on-demand showed an improvement of 8.8 points in the ED domain when 10mg was used [571]. None of these patients had diabetes and overall had less severe ED, were younger and thinner than the present study. In a follow up study, a large multisite randomised controlled study of 760 patients, again using differing dosages of Vardenafil on-demand, the patient population was similar to that of the current study in terms of ED severity, age, proportion of patients with diabetes, hypertension, but were slightly less overweight (BMI 28.8 vs 32.9kg/m^2) than the current study [572], but the status of OSA was unknown and not listed as an exclusion criteria. In this latter study, the IIEF-ED domain increased by 7.2 points with 10mg Vardenafil used on demand. The current study, using the same dosage, but more often, was only able to increase IIEF-ED domain by 4.4 points, suggesting there may be some inhibitory factor reducing efficacy in OSA patients.

In the current study, only 44% of men of men allocated to Vardenafil (and sham CPAP, that is, being untreated for OSA) reported an improvement in ED, as measured by an increase by more than 4 points in the IIEF-ED domain. This supports the results of the only other study investigating the effects of PDE-5 inhibitors in men with OSA, in which only 44% of men had an improvement in erectile function with 20mg Vardenafil [431]. Similarly, a meta-analysis of 15 studies showed that Vardenafil on-demand was found to improve erections in 77% of men (with OSA status undefined) compared to 27% of those on placebo [121]. A return to normal

erectile function, that is, an IIEF-ED score of greater than 26, was achieved by only 25% of those randomised to Vardenafil in the current study, compared to 7% of those allocated to placebo. Stratification by baseline ED severity did not show any differences with response to Vardenafil, perhaps due to insufficient power to detect such a change. In a study of a non-OSA population, 6 months of Vardenafil 10mg on-demand was sufficient for 43% of men to return to a normal level of erectile function (compared to 12.6% with placebo), with severity of baseline ED significantly influencing this rate (89% for those with mild ED down to 25% of those with severe ED).

The effect of Vardenafil on sexual function in the presence of other medical conditions has previously been explored in a small number of studies. A prospective study investigating the effects of Vardenafil **a**fter nerve sparing prostatectomy, recruited 440 men with ED of similar age to that of the current study to take part in a dose comparison study [574]. In those allocated to take 10mg on-demand, an improvement in ED by 6 points in the IIEF-ED domain was seen. In a study of men with diabetes and ED, those allocated to 10mg Vardenafil on-demand also found an improvement in IIEF-ED of 6 points [573]. The population in this study all had diabetes and more severe ED than the current study, though they were of a similar age and BMI. The presence or absence of OSA was not reported, or excluded. The current study found less efficacy, with an improvement by 4-5 points in the IIEF-ED domain. The reasons for this discrepancy may be due to a difference in ED severity, or that OSA may inhibit the efficacy of this medication through exposure to repetitive intermittent hypoxia, or an on-demand regime may be more effective in this population.

5.5.3 Sleep Related Erections

Although subjective erectile function did not improve, significant improvements in objectively measured sleep related erections (SRE's) were seen with Vardenafil compared to placebo in this OSA population. In two previous studies of young healthy men with normal erectile function, a dose of 100mg of Sildenafil increased SRE parameters as measured by Rigiscan [130, 131]. Additionally, in a study of men with ED, 100mg of Sildenafil at bedtime also improved SRE's in terms of Rigiscan tumescence activity units (TAU) and rigidity activity units (RAU) at both the base and the tip of the penis, without an increase in the number of episodes during sleep [569]. The current study mirrors these results. A study conducted in 1996, soon after the measurement units RAU and TAU were included in the assessment software, concluded that tip TAU was the best overall measurement correlating with the diagnosis of erectile dysfunction, closely followed by both base TAU and RAU [575]. In those allocated to Vardenafil, the current study found improvements in all four parameters, suggesting that Vardenafil is effective in improving nocturnal erections in the presence of obstructive sleep apnoea**.** Normative values are not available for sleep related erections, which may have provided some insight into the extent of improvements with Vardenafil, given the finding that Vardenafil increases the tumescence and rigidity of sleep related erections in young healthy men without ED, as well as in older men with OSA with ED. Despite this increase in SRE's, this did not translate to an improvement in subjective functioning, suggesting there may be another factor involved. The small numbers of participants monitored limit the interpretation of this result, which warrants further investigation.

5.5.4 Quality of Life

Several studies have shown that ED can have a negative impact on quality of life [530, 531, 558] however, many of the major studies in the efficacy of Vardenafil on erectile function do not

report on this aspect [119, 132, 571, 572]. In the current study of men with OSA, the only improvement in quality of life parameters seen was that of the domain of Vitality at the week 8 time point, but this was no longer different at week 12. The change seen was an improvement between 9.5-13.5 points with Vardenafil at the different time points (compared to placebo 2.5-5.5) which, using a definition of 7.5 as being clinically meaningful [576], suggests that the use of Vardenafil treatment in those with ED in OSA can improve quality of life in terms of Vitality. This supports the findings of a study in 121 Spanish men with ED, in which 12 weeks of flexible dose Vardenafil (administration method not described) improved the SF-36 domain of Vitality compared to placebo, but no other domain [577]. The domain of Vitality has been shown in several clinical trials to be sensitive to treatment effects in areas such as hypertension, AIDS and prostate disease, with a 5 point reduction associated with a significant risk of social consequences such as being unable to work and hospitalisation [576]. Unlike the present study, an uncontrolled study in 40 Japanese men with ED, but otherwise healthy, at least one month of on-demand Sildenafil showed improvements from baseline in physical function, general health and role emotional domains however there was no control group, making interpretation difficult [578].

The majority of studies assessing the effect of PDE-5 inhibitors on quality of life have been in disease specific populations, with effects dependent upon the disease studied. In a randomised controlled study of male and female subjects (n=42) with tinnitus, 12 weeks of twice daily Vardenafil did not improve tinnitus levels, nor any domain of the SF-36 compared to placebo [579]. The use of Sildenafil in patients with pulmonary arterial hypertension has been shown to improve the domains of physical functioning, general health and vitality in the SF-36 compared to placebo, which was attributed to a greater exercise capacity due to Vardenafil by

the correlation with improvements in the 6-minute walk test [580, 581]. A study of patients with benign prostatic hyperplasia had an improved quality of life due to Vardenafil, compared to placebo, which may be due to its effect on lower urinary tract symptoms [582]. In an uncontrolled study of hemodialysis patients with ED, improvements in the two domains of physical and mental components of the SF-36 have been noted with 4 weeks of open label 10mg on-demand Vardenafil [583]. Unlike these studies, Vardenafil does not appear to improve other non-erectile dysfunction facets of OSA, and as such, does not improve quality of life.

5.5.5 Treatment Satisfaction

Although the overall score regards treatment satisfaction was higher with Vardenafil compared to placebo, there was no difference between Vardenafil and placebo in the number of individuals who found the treatment satisfactory. This suggests there was individual variability regards to treatment response. Only 70% were satisfied with Vardenafil, compared to 48% of placebo. This result, however, should be interpreted within the context of CPAP treatment also being concurrently used. There was no distinction made when the questionnaire was asked, as to which treatment (CPAP or Vardenafil) the questionnaire referred. Treatment satisfaction was similar (75% vs 48%) when CPAP and sham CPAP was compared.

A recent large (n=7496) multicentre study of 12 months duration reported that 95% of participants were satisfied with the efficacy of Vardenafil [584]. This study used a variety of doses of Vardenafil, titrated for each patient, with the most common dose (66%) being 20mg. There is no detail regarding if administration regime was on demand or daily. Potentially, this study may differ from the current study, since the dosage was customised to each patient, whereas this study was a standard dose. Given the higher BMI in this study, 10mg may not be

sufficient. A larger (n=73,946), older non-placebo controlled study, also found more than 90% of participants satisfied with Vardenafil [585]. The current study did not show such high satisfaction rates, which may be due to dilution by the influence of CPAP/sham CPAP or dosage. Given the lack of subjective improvement with Vardenafil, however, this level of treatment satisfaction may well be representative despite these differences.

5.5.6 Strengths and Limitations

This is the first placebo controlled study assessing the efficacy of daily dose Vardenafil in men with OSA and ED. Placebo control is imperative in this area of research, given the subjective nature of the reporting of sexual function. Additionally, the addition of the objective measure of erectile function, nocturnal penile tumescence, provides an insight into the physiological aspects of erectile function, which is often not measured in clinical trials. A limitation of the study, however, is low patient numbers. More participants may have revealed more information, and provided sufficient power to investigate more sub-analyses to further understand the influence of psychological factors and initial ED severity.

5.6 CONCLUSION

This study showed that 10mg daily Vardenafil did not worsen sleep disordered breathing. An improvement in sleep related erections occurred, however, this did not translate to an improvement in subjective erectile function in this group of men with OSA and ED. The physiological basis of sleep related erections is not completely understood, however, they may act to prevent fibrosis in the corpora cavernosa. Vardenafil improved these erections, which may act to maintain erectile capacity. The efficacy of Vardenafil in men with OSA appears to be less effective than in that of the general population, the cause of which is unknown but may be due to repetitive hypoxia limiting nitric oxide, or psychological factors. Clinically meaningful improvements may occur with Vardenafil use; however, this is not statistically different than placebo. Although distress caused by erectile dysfunction was alleviated by 10mg Vardenafil in this population, quality of life, overall, was not improved. A low daily dose of Vardenafil may be of clinical benefit to some patients with OSA and ED, and can be used without risk of worsening sleep disordered breathing.

6. Overall Conclusions

OSA and erectile dysfunction are frequently associated with each other. Currently, there is no high level evidence to inform decisions on how best to treat men with OSA and erectile dysfunction. This thesis investigated the relationship between the triad of OSA, sexual function, and testosterone using two randomised controlled trials.

The first randomised controlled trial of compared exogenous testosterone administration with placebo in men with untreated OSA and obesity. The second study, designed as a factorial study, assessed the impact of CPAP versus sham CPAP, as well as the PDE-5 inhibitor, Vardenafil versus placebo on sexual function and quality of life parameters.

On an intention to treat basis, neither CPAP use, exogenous testosterone treatment nor a PDE-5 inhibitor improved erectile function. In contrast, post-hoc analysis revealed that adherent CPAP use did improve erectile function over the same period. Similarly, sexual desire was increased by the adherent use of CPAP, as well as by testosterone treatment, but not by a PDE-5 inhibitor. Importantly, for a practical clinical point of view, only one third of participants were adherent with CPAP, leaving two-thirds of men with OSA inadequately treated, or not at all.

This thesis also showed that efficacious use of CPAP treatment improves not only sexual health, but many other facets of quality of life. The psychological factors related to ED have not been mentioned in previous literature related to OSA and ED. Given the high rates of depression, sleepiness, and relationship breakdown with OSA, there may be a tri-directional relationship between OSA, psychological factors and erectile dysfunction. Breaking this cycle by successfully treating OSA with CPAP has been shown in this study to improve rates of

sleepiness, depression, stress, as well as erectile function and sexual function. Providing PDE-5 inhibitors does not improve any psychological factors measured in this study and was not effective in increasing either erectile function or sexual desire. Further research is required to investigate this potential causal pathway, in order to fully understand the mechanisms behind the association of OSA and ED.

Detailed review of the literature reveals that the widely held belief that OSA is associated with reduced libido may not be the case. Many papers do not cite a reference, and those that do often cite Guilleminault, et al 1977, as robust evidence that OSA is associated with low libido, with no current evidence to corroborate this assertion. When this paper was written in 1977, there was no distinction made between libido and erectile dysfunction in the medical literature, which is apparent in the wording "*Twelve patients reported impotence. Abatement of sexual drive had progressed slowly*…". At present, there is no evidence clearly demonstrating a robust independent link between OSA and reduced libido. The research reported in this thesis, however, has been the first to clearly show, via a randomised controlled study that regular use of CPAP increases sexual desire. This conclusion however, due to study inclusion criteria, applies only to men with erectile dysfunction. Further studies are needed to widen this understanding to include men who do not present with erectile dysfunction.

The importance that many men place on good sexual health should be used as an incentive to encourage regular CPAP use. This thesis provides high quality evidence that the use of CPAP for more than four hours a night is able to improve erectile function and sexual desire. Given the poor adherence rates achieved not only in this study, but many others, the knowledge of the positive impact on sexual health by CPAP should be widely disseminated, in an effort to improve adherence with treatment, and reduce cardiovascular risk.

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