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POSITIVE AIRWAY PRESSURE THERAPY FOR SLEEP APNEA IN ADULTS: FROM CPAP INITIATION TO FOLLOW-UP

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DOCTORAL DISSERTATION

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To Harri, Juho and Otto

ABSTRACT

Obstructive sleep apnea (OSA) is highly prevalent worldwide; the incidence of OSA is increasing along with the increasing prevalence of obesity. The main symptoms of OSA are snoring and daytime somnolence.

Continuous positive airway pressure (CPAP) therapy prevents sleep apneas and restores sleep. However, one third of patients abandon therapy within 1 year for several reasons, usually due to difficulties in falling asleep with the device, intolerance to pressure, and local disturbances related to the CPAP interface.

Similar to many patients with other chronic diseases, OSA patients on CPAP therapy require regular follow up. The purpose of follow up is to ensure good adherence to treatment and amelioration of symptoms with therapy. There are no international guidelines on the frequency of CPAP follow up. The number of OSA patients is increasing faster than the available economic and medical resources. Accordingly, medical staff must adjust the frequency of follow up.

We reviewed the reasons for patient contact between two routine visits for 1141 OSA patients. One third of these patients contacted our sleep unit between two routine appointments. The primary reason for an unscheduled contact was symptoms related to sleep apnea or CPAP treatment. The most common symptom was residual daytime somnolence while on CPAP therapy.

With increasing knowledge of OSA, increasing numbers of elderly patients are screened and treated for OSA. However, the benefit of CPAP therapy and the effect of age on CPAP adherence has not fully been studied. We evaluated CPAP adherence in patients >70 years compared with younger patients (<50 years). At the 1-year follow up after CPAP initiation, we found no statistically significant difference either in the number of patients abandoning CPAP therapy during the follow-up period or in the daily CPAP use in hours between older and younger CPAP patients.

One third of OSA patients abandon CPAP therapy within 1 year. As there is no good alternative treatment for OSA, patients are often referred for a new CPAP initiation trial. No data were available about the probability of success of CPAP therapy re-initiation after a previous failure. We therefore studied 224 subjects in the re-initiation group (reCPAP) and 228 subjects in a control group (CPAP virgin). At 1-year follow up, the success rate for the CPAP re-initiation group was 52%, which was significantly lower than that of the control group (67%). CPAP re-initiation therapy failed more often in women than in men (62% vs 40%).

We observed that routine CPAP follow up do not sufficiently prevent additional visits to the sleep clinic, advanced age is not an obstacle to CPAP initiation, and that the success rate for CPAP re-initiation was significantly lower than that of the control group.

TIIVISTELMÄ

Obstruktiivisen uniapnean (OSA) esiintyvyys on korkea maailmanlaajuisesti ja lisääntyy edelleen liikapainon lisääntyessä. Tavallisimmat oireet ovat kuorsaus ja päiväväsymys.

Jatkuva ylipainehoito (CPAP) estää hengityskatkokset ja tekee unesta virkistävää. Ensimmäisen vuoden aikana kolmasosa potilaista lopettaa hoidon erilaisista syistä. Erityisesti hankaluudet nukahtaa laitteen kanssa, ongelmat hoitopaineen kanssa, sekä paikallisoireet liittyen CPAP maskeihin ovat syynä tähän.

CPAP-hoidossa olevat uniapneapotilaat tarvitsevat säännöllistä seurantaa kuten yleensä muutkin kroonisia sairauksia sairastavat potilaat. Seurannan tarkoitus on varmistaa hoitoon sitoutuminen ja oireiden lievittyminen. Kansainvälisiä ohjeita seurannan taajuuden suhteen ei ole. Potilasmäärät lisääntyvät nopeammin kuin taloudelliset ja lääketieteelliset resurssit, mistä syystä seurantakäyntien järjestämistä joudutaan arvioimaan uudelleen

Selvitimme 1141 CPAP-hoidossa olevalla uniapneapotilaalla syitä, miksi he ottivat yhteyttä hoitavaan yksikköön etukäteen ohjelmoitujen seurantakäyntien (rutiinikontrollien) välissä. Kolmasosa potilaista otti yhteyttä uniyksikköön kahden rutiinikontrollin välissä. Suurin syy tähän oli erilaiset uniapneaan tai CPAP-hoitoon liittyvät oireet. Tavallisin oire oli CPAP-hoidosta huolimatta esiintyvä päiväsaikainen jäännösväsymys.

Yhä useammin myös ikääntyneitä henkilöitä tutkitaan ja hoidetaan uniapnean vuoksi. CPAP-hoitoon sitoutumista ei ole tutkittu iäkkäillä ihmisillä. Tämän vuoksi tutkimme CPAP-hoitoon sitoutumista > 70 vuotiailla potilailla, verrattuna nuorempiin potilaisiin (< 50 vuotiaisiin). Vuoden kuluttua CPAP-hoidon aloituksesta emme havainneet tilastollisesti merkitsevää eroa CPAP-hoidon keskeyttämisessä tai CPAP-laitteen käyttötunneissa vanhempien ja nuorempien potilaiden välillä.

Kolmasosa potilaista keskeyttää CPAP-hoidon vuoden sisällä hoidon aloituksesta. Hoidon keskeyttäneitä potilaita lähetetään usein myöhemmin CPAP-hoidon uudelleen aloitukseen. Tutkimustietoa CPAP-hoidon uudelleen aloituksen onnistumisesta aiemman keskeytyneen hoidon jälkeen ei ole käytettävissä. Selvitimme 224 CPAP-hoidon uudelleen aloittaneella potilaalla hoidon jatkumista vuoden seurannan jälkeen, kontrolliryhmässä oli 228 CPAP-hoitoa ensimmäistä kertaa aloittanutta potilasta. Vuoden kuluttua 52 % uudelleen aloittaneista ja 67% kontrolliryhmän potilaista jatkoi hoitoa. Ero oli tilastollisesti merkitsevä. CPAP-hoidon uudelleen aloitus epäonnistui useammin naisilla kun miehillä (62 % vs 40 %).

Totesimme tulosten perusteella että 1) huolimatta säännöllisistä etukäteen ohjelmoiduista CPAP-hoidon seurantakäynneistä, kolmasosa potilaista otti kuitenkin yhteyttä uniyksikköön seurantakäyntien välissä uniapneaan ja CPAP-hoitoon liittyvien ongelmien vuoksi 2) > 70 vuoden ikä ei vähennä CPAP-hoidon onnistumista, ja 3) että CPAP-hoidon aloittaminen uudelleen aiemmin keskeytyneen hoidon jälkeen onnistuu harvemmin kuin hoitoa ensimmäistä kerta aloitettaessa.

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CONTENTS

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following publications:

I Avellan-Hietanen H, Brander P, Bachour A. Symptoms During CPAP Therapy Are the Major Reason for Contacting the Sleep Unit Between Two Routine Contacts. J Clin Sleep Med. 2019 Jan 15;15(1):47-53. doi: 10.5664/jcsm.7568. PMID: 30621836; PMCID: PMC6329558.

II Avellan-Hietanen H, Aalto T, Maasilta P, Ask O, Bachour A. Adherence to CPAP therapy for sleep apnea in patients aged over 70 years old. Sleep Breath. 2022 Mar;26(1):325-331. doi: 10.1007/s11325-021-02398-w. Epub 2021 Jun 6. PMID: 34091854; PMCID: PMC8857145.

III Avellan-Hietanen H, Maasilta P, Bachour A. Restarting CPAP Therapy for Sleep Apnea After a Previous Failure. Respir Care. 2020 Oct;65(10):1541-1546. doi: 10.4187/respcare.07766. Epub 2020 Jul 21. PMID: 32694184.

The publications are referred to in the text by their roman numerals.

ABBREVIATIONS

AASM	American association of sleep medicine
APAP	auto adjusting positive airway pressure
ASV	adaptive servo ventilation
BIPAP	bi-level positive airway pressure
BMI	body mass index
CCI	Charlson comorbidity index
CPAP virgin	no previous CPAP treatment
CPAP	continuous positive airway pressure
DMII	type II diabetes
EEG	electroencephalogram
EF	ejection fraction
ENT	ear nose throat
ESS	Epworth sleepiness scale
HF	heart failure
MCC	morbus cordis coronarius
MMA	maxillomandibular advancement surgery
MMSE	mini mental state examination
NHPT	nine-hole peg test
NR	non-routine
OA	oral appliance
PG	cardiorespiratory polygraphy
PSG	polysomnography
PtcCO2	transcutaneous carbon dioxide
R	routine
reCPAP	CPAP re-initiation group
REI	respiratory event index
SpO2	oxygen saturation
TE	tonsillectomy
UPPP	uvulopalatopharygoplasty

1 INTRODUCTION

The prevalence of symptomatic obstructive sleep apnea (OSA) varies in adults in high-income countries (2% to 17%) and is related to the increasing prevalence of obesity worldwide (Heinzer et al., 2015). About 70% of OSA patients are obese (H. Tuomilehto et al., 2013). Other predisposing factors include male sex and age >50 years (Patil et al., 2019). Continuous positive airway pressure (CPAP) therapy is the internationally accepted, gold-standard treatment for OSA (Loube et al., 1999) (Sullivan et al., 1981). CPAP treatment eliminates obstructive respiratory-related events, apneas, hypopneas, oxygen desaturations, snoring, and respiratory-related arousals; i.e. CPAP treatment not only lowers the apnea-hypopnea index (AHI), but also reduces nocturnal hypoxemia (Kushida et al., 2006) and daytime somnolence and improves sleep regulation (Mysliwiec et al ., 2015) However, patient adherence to treatment is often suboptimal (optimal adherence is considered CPAP usage 4 hours/night) (Balakrishnan et al., 2016) (Bachour et al., 2016). Less than 70% of CPAP-naïve patients continue CPAP therapy after 1 year (Bachour & Maasilta, 2004). To improve patient long-term adherence to treatment and to manage problems related to the use of CPAP devices that may arise during treatment, patients are often routinely seen by trained health care personnel at regular intervals (Epstein et al., 2009).

Unfortunately, CPAP therapy fails in approximately 30% of cases. The reasons for poor therapy adherence and CPAP failure are multifactorial. The reasons include claustrophobia, poor mask fit, nasal obstruction, insomnia, and lack of motivation (Aloia, 2011). These factors may change over time, which suggests that a new CPAP trial after the first failure may be an option.

When CPAP therapy fails, alternative therapy choices should be discussed and planned. An oral appliance may be used as an alternative to CPAP, particularly in patients with less severe OSA and normal body mass index (BMI) (Palotie et al., 2017). Oral appliances have relatively acceptable adherence and efficacy.

The importance of surgery in sleep apnea therapy is declining due to mediocre results. New surgical procedures, such as hypoglossal nerve stimulation, are under evaluation (Kompelli et al., 2019), (Bachour et al., 2021). Surgery is a therapeutic option in certain conditions, such as tonsillar hypertrophy (Kotecha & Hall, 2014).

To obtain further information on how to adjust resources in the emerging OSA epidemic, we assessed the reasons for non-routine visits, CPAP adherence of elderly OSA patients, and the success of CPAP re-initiation.

Few studies have evaluated CPAP therapy in elderly patients. Elderly patients may present with reduced physical activity of the upper members that may interfere with CPAP mask adjustment. They may also suffer from memory loss and other diseases that may overlap with sleep apnea symptoms. Comparing CPAP success in patients >70 years with those <50 years may therefore provide further information on CPAP therapy in the elderly.

Because CPAP is regarded as safe and noninvasive, re-initiation after a previous failure should always be considered. In our study, we hypothesized that CPAP adherence is lower in individuals who have previously failed CPAP therapy when compared to CPAP-naïve patients. As the cost of CPAP initiation is not negligible (A. Bachour et al., 2007), it is important to evaluate the cost-benefit relationship of CPAP therapy re-initiation.

2 REVIEW OF THE LITERATURE

2.1 BACKGROUND

Sleep apnea is traditionally divided into the three following categories: obstructive sleep apnea (OSA; the most common form of sleep apnea), central sleep apnea, and mixed sleep apnea (combination of OSA and central sleep apnea). OSA was first described in 1966. Gastaut et al observed that obese subjects with daytime somnolence showed periodic airway obstruction during sleep with following arousals leading to sleep fragmentation (Gastaut et al., 1966). Central sleep apnea is characterized by recurrent cessation or attenuation of respiration during sleep due to a decline or absence of ventilatory effort. Heart failure is often associated with periodic central apneas, with a crescendo-decrescendo pattern of intervening breaths known as Cheyne-Stokes respiration (Donovan & Kapur, 2016). In OSA, the upper airways collapse either partly or completely due to relaxation of the upper airway musculature during sleep. These collapses are repeated during the sleep period. Total collapse of upper airways causes obstructive apneas, desaturations, and sleep fragmentation, while partial collapses cause obstructive hypopneas. The amount of hypopneas and apneas per hour is described by the apnea hypopnea index (AHI) or the respiratory event index (REI). The definition of apnea is a 10-second-long reduction of ≥90% of breathing amplitude combined with desaturation of ≥3% from the baseline level in arterial oxyhemoglobin saturation. Hypopnea is defined as a 10-second-long reduction in breathing amplitude of ≥30% associated with an ≥3% drop in oxygen saturation (SpO_2), an arousal, or both (Tietjens et al., 2019). The American Academy of Sleep Medicine (AASM) criteria for the definition of hypopnea changed in 2012. The previous AASM criteria from 1999 recommended defining hypopnea as a ≥30% reduction in breathing amplitude for ≥10 seconds associated with oxygen desaturation of ≥4%. Alternative criteria was a ≥50% reduction in breathing amplitude with ≥3% oxygen desaturation from the pre-event baseline, or the event is associated with arousal.

Symptoms related to OSA include daytime somnolence, memory deficit, difficulty concentrating, morning headaches, difficulties in falling asleep, insomnia, and depression. Untreated OSA causes activation of the sympathetic nervous system and increases the risk of elevated blood pressure, myocardial infarction, and cerebral infarction (Tietjens et al., 2019). The gold-standard treatment for OSA is CPAP. The AASM criteria for diagnosis of sleep apnea are either REI or AHI ≥15/h in polysomnography (PSG) or sleep polygraphy (PG) or REI or AHI ≥5/h and at least one of the following symptoms: sleepiness, fatigue, insomnia, suffocation during sleep, reported snoring or apneas during sleep, high blood pressure, depression, cognitive problems, coronary heart disease, cerebral infarct, heart failure, atrial fibrillation, and type II diabetes (American Academy of Sleep Medicine, 2014).

General awareness of OSA has been low in the past (Sia et al., 2017). Different campaigns have attempted to increase awareness. The Finnish National Sleep Apnea Programme was implemented from 2002 to 2010 to reduce the proportion of patients suffering from severe OSA, to maintain and enhance working and functional capacity in OSA patients, and to improve the cost-effectiveness of prevention and treatment of sleep apnea (Laitinen et al., 2003). Despite these goals, the prevalence of OSA in Finland and in other western countries has increased significantly in recent years (Bachour & Avellan-Hietanen, 2021). Some of the increase is due to changes in the AASM criteria for the definition of hypopnea, with the 3% desaturation index as described earlier.

2.2 EPIDEMIOLOGY

The prevalence of OSA in western countries is increasing. This is primarily due to the increased prevalence of overweight and obesity (Benjafield et al., 2019) and greater awareness due to national and international awareness campaigns (*Valtakunnallinen uniapneaohjelma 2002-2012.*, 2002). OSA still remains underdiagnosed, possibly because people are unaware of their own snoring and having apneas (Young et al., 1993). In older epidemiologic studies, OSA was reported to affect at least 4% of adult men and 2% of adult women (Young et al., 1993) (Punjabi, 2008). The prevalence of OSA is much higher in more recent studies. Some studies indicate that 17% of middle-aged men and 9% of middle-aged woman suffer from severe or moderate OSA (Peppard et al., 2013). It is estimated that there are 1.5 million people suffering from mild sleep apnea and 853 928 people suffering from moderate-to-severe OSA in Finland; persons 40-65 years are the primary age group (Benjafield et al., 2019), (Bachour and Avellan-Hietanen , 2021) (Partinen & Hublin, 2005). The number of referrals to sleep units has been growing consistently in Finland and throughout the developed world.

Until now, data on the heredity of sleep apnea have been inconclusive. Recent studies have shown that some genetic factors are involved in OSA development. A Finnish study showed that OSA and type II diabetes (DMII) have a partially common genetic background. This study also identified a genetic risk factor for OSA that was independent of obesity (Strausz et al., 2021).

Untreated severe OSA causes a large burden for healthcare through the many comorbidities associated with OSA. Untreated OSA increases the risk of sudden death mainly through cardiovascular events; this risk is highest for men <50 years (Lavie et al., 2005). This increased mortality risk is not present in OSA patients who are properly treated. Mild untreated OSA is not associated with increased mortality (Marti et al., 2002).

OSA patients are not a homogenous group (Chang et al., 2020). New means for classifying OSA have recently been developed. Saaresranta et al classified patients into the following four different clinical phenotypes according to their clinical manifestations: excessive daytime sleepiness, insomnia, no excessive daytime sleepiness or insomnia, and excessive daytime sleepiness and insomnia (Saaresranta et al., 2016). The insomnia phenotype represented more than half of the subjects; this group had more comorbidities than the rest of the OSA population. The excessive daytime sleepiness phenotype was linked to a higher CPAP usage than the other phenotypes. Eckert et al divided patients in the following three phenotypes: patients with a low genioglossus activity; patients with deviant chemoreflex response to CO_2 levels; and patients with a low respiratory arousal level (Eckert et al., 2013).

OSA is no longer considered to be a disease exclusive to males. The prevalence of mild-to-moderate OSA in women is estimated to be 6% to 20%. Menopause is associated with reduction of female sex hormones and with increased OSA risk. Pregnancy increases the risk of OSA. Weight loss is less effective in reducing OSA severity in women (Saaresranta et al., 2015). In sleep studies, women have lower AHI than men, but women with OSA are more symptomatic with low AHI (Anttalainen, Tenhunen, et al., 2016), (Anttalainen et al., 2010).

2.3 PATHOPHYSIOLOGY

The pathophysiology of OSA remains incompletely understood. It is thought to involve both anatomic and neuromuscular factors that influence breathing during sleep. Sleep apnea manifests only during sleep; the problem does not manifest when awake. The pharyngeal muscles relax during sleep and cause partial or total airway closure in anatomically narrowed upper airways. This narrowing causes repeated episodes of apneas and hypopneas, which usually result in arousals. These arousals lead to an increase in sympathetic activity, sleep disturbances, and daytime sleepiness. The sleep is not refreshing. Oxygen saturation decreases and CO_2 levels increase during apneas and hypopneas. Breathing efforts and intrathoracic pressure variations increase during sleep (Dempsey et al., 2010).

A review of publications from 1980 to 2002 revealed that the most common site of upper airway obstruction in sleep apnea was at the level of the oropharynx with extension to the laryngopharynx (Rama et al., 2002).

2.4 RISK FACTORS OF SLEEP APNEA

Obesity (BMI >30 kg/m^2) is by far the most prominent risk factor for OSA. At least 70% of OSA patients are obese (Young et al., 1993) (Patil et al., 2019) (H. Tuomilehto et al., 2013). Changes in lifestyle and environment in high-income countries during the last century have led to an increased prevalence of obesity observed in western countries (Williams et al., 2018). In Finland, 12% of men and 18% of women were obese in 1980; in 2017 the corresponding values were 26% and 28%, respectively. Thus, diseases associated with obesity become public health problems (Aromaa et al., 2017). The mechanism linking obesity and OSA is thought to be narrowing of the airways by pharyngeal fat deposition (Tuomilehto et al., 2013). The accumulation of fat narrows the pharyngeal tube mechanically and offsets the dilatory function in the neck muscles, resulting in an increased neck circumference. A neck circumference ≥40 cm is considered a risk factor for OSA (Marti-Soler, 2016). Fat deposition is increased retroglossally in OSA patients. Body mass index (BMI) is also associated with tongue weight (Kim et al., 2014). Furthermore, excess fat deposits around the thorax reduce ribcage mobility and decrease functional residual capacity (Abdeyrim et al., 2015). Visceral obesity is common in OSA patients (Romero-Corral et al., 2010) A 10% elevation in BMI is associated with a 30% elevation in AHI in patients aged 40 years but only a 21% elevation in patients aged 60 years (Liu et al., 2021).

Anatomical issues in the upper airways, such as micrognathia, enlarged tongue or tonsils, a long and large soft palate, and anatomical narrowing of the nose increase the risk of snoring and sleep apnea (Marti-Soler, 2016).

Nasal stuffiness leads to mouth breathing during the night; opening of the mouth increases the risk of upper airway narrowing during sleep (Bachour & Maasilta, 2004).

All medicines that affect the central nervous system and central regulation of breathing, such as sleeping pills and alcohol, predispose to snoring and OSA (*Sleep Apnea,Current care guidelines.Working group set up by the Finnish Medical Society Duodecim 2021 Available online at: www.kaypahoito.fi.*).

Several genetic factors may be involved in OSA, as suggested in recent studies. Strausz et al revealed genetic correlations between OSA and cardiometabolic diseases and risk factors. The strongest connections were between OSA and

BMI, hypertension, DMII, and coronary heart disease (MCC). This is consistent with previous epidemiological and clinical observations (Strausz et al., 2021)

Diseases such as acromegaly and floppy eyelid syndrome (McNab, 2007) and hypothyroidism predispose to OSA (Thavaraputta et al., 2019). The connection between hypothyroidism, respiratory diseases, and OSA is linked to ventilation regulation and diaphragm dysfunction (Sorensen et al., 2016). The lowered muscle activity in elderly persons predisposes to OSA. Therefore, reduction in BMI may not have the same effect in the elderly as in younger persons (Liu et al., 2021).

2.5 COMORBIDITIES IN SLEEP APNEA

Of the comorbidities related to OSA, the cardiovascular comorbidities are considered the most dangerous and include hypertension, MCC, arrythmias, stroke, and diabetes mellitus (Bonsignore et al., 2019). The recurring nocturnal hypoxemia associated with apneas and hypopneas in OSA has consequences involving hemodynamics, coagulation, endothelial function, and metabolic and inflammatory factors. Insulin resistance is linked to OSA (Kamble et al., 2020) (Mokhlesi et al., 2016) (Lindberg et al., 2012). Platelet activation and aggregation is affected by OSA and fibrinolytic activity is decreased, thereby increasing the risk of thrombosis (Dziewas et al., 2007). Endothelial dysfunction via endothelial apoptosis has been suggested as a thrombogenic pathway in OSA patients; endothelial dysfunction is considered a risk factor for atherosclerosis (El Solh et al., 2007) (Price & Loscalzo, 1999). Systemic inflammation and oxidative stress is associated with OSA and elevates C-reactive protein, interleukin-6, and tumor necrosis factor α levels (Ryan et al., 2009). These factors link OSA to cardiovascular diseases (Dempsey et al., 2010). Dempsey et al concluded that evidence is strongest to support daytime systemic hypertension as a consequence of severe OSA, with less conclusive effects of OSA on development of pulmonary hypertension, stroke, coronary artery disease, and cardiac arrhythmias; cognitive effects (daytime sleepiness and impaired memory and concentration) reflect hypoxia-induced neural injury (Dempsey et al., 2010).

Sleep fragmentation and hypoxia caused by OSA can influence glucose metabolism. OSA is considered an independent risk factor for diabetes (Reutrakul & Mokhlesi, 2017) In diabetic patients with OSA, the prevalence of neuropathy, nephropathy, retinopathy, and peripheral arterial disease increases (Bonsignore et al., 2019). Therefore, it may be essential to consider OSA when treating diabetic patients.

Respiratory diseases associated with OSA are asthma and COPD. The association between asthma and OSA has been considered causal and the link between asthma and OSA severity is controversial (Julien et al., 2009). However, asthma control can improve by treating an underlying OSA with CPAP (Kauppi et al., 2016). Women with obesity have a higher prevalence of asthma (Bonsignore et al., 2018). Patients who have severe asthma can experience symptoms similar to OSA, such as poor sleep quality and daytime sleepiness (Julien et al., 2009). The underlying inflammatory mechanism may be similar in asthma and OSA. Upper airways are smaller in size in both OSA and asthma patients (Dultra et al., 2017). COPD is known to coincide with OSA (Flenley, 1985) The prevalence of a OSA-COPD overlap syndrome ranges from 1% to 3.6% in the general population (Shawon et al., 2017). Due to reduced intercostal muscle activity and chest-wall mobility, OSA in COPD patients is mainly observed in the REM phase (Johnson & Remmers, 1984). OSA increases the rate of COPD exacerbations, hospitalizations, and even mortality when compared to COPD-only patients (Shawon et al., 2017). Overlap syndrome is also associated with pulmonary hypertension and respiratory failure (Singh et al., 2018).

2.6 DIAGNOSIS OF SLEEP APNEA

In the differential diagnostic pathway of OSA, voluntary sleep deprivation, other sleep-related disturbances, depression, fatigue due to work-related issues, hypothyroidism, and menopause should be considered. Blood glucose levels, thyroid function tests, hemoglobin, electrocardiogram, and blood lipid levels should be assessed before referral to specialized health care (*Sleep Apnea,Current care guidelines.Working group set up by the Finnish Medical Society Duodecim 2021 Available online at: www.kaypahoito.fi.*). Occasionally, even chest x-ray and lung function testing may be appropriate. Screening for sleep apnea is especially important in high-risk groups and may be helpful in the differential diagnostics. Various validated questionnaires are available for screening of sleep apnea symptoms. These clinical questionnaires are not to be used for diagnosing OSA; they do not replace PG or PSG in the diagnostic path but may be used as a tool to evaluate the probability of OSA in patients with high risk of OSA. Such persons include those with obesity, anatomical jaw issues, and those with sleepiness when differential diagnosis is sought (Kapur et al., 2017). There are no data on the value of the questionnaires in the diagnostic pathway.

The STOP-BANG questionnaire includes four subjective elements (STOP: Snoring, Tiredness, Observed apnea, and high blood Pressure) and four demographic items (BANG: BMI, Age, Neck circumference, Gender) (Nagappa et al., 2015). A STOP-BANG score of 3 to 4 or more (of a maximum of 8) is considered abnormal (Chung et al., 2012). BERLIN and The Basic Nordic Sleep Questionnaire are also used for screening of OSA (Chiu et al ., 2017). The Epworth Sleepiness Scale (ESS) is used to assess subjective daytime somnolence in OSA (Chiu et al., 2017) (Partinen & Gislason, 1995) (Johns, 1991). However, depression, elevated plasma glucose levels, hypothyroidism, post-menopause syndrome, and burnout may cause symptoms that mimic OSA symptoms; this should be considered when OSA symptoms are evaluated as differential diagnostic factors.

Evaluation of patient history should include, at a minimum, symptoms of sleep apnea and how the symptoms affect the patient's quality-of-life and ability to work, profession and working status, driving license, working hours, possible comorbidities, and medication, including medicines that may affect the central nervous system.

Evaluation and recording of clinical status should include at least weight, height, nose breathing, status of mouth, teeth, and jaw movements, pharynx (using Mallampati score) (Nuckton et al., 2006), neck circumference, and assessment of ESS.

Typical clinical features, such as obesity (BMI >30 kg/m^2), daytime somnolence (ESS >10), male gender, and observed snoring and apneas should raise suspicion of OSA and trigger the next diagnostic step. Insomnia is also a typical symptom in OSA; although the patients are somnolent, they often have difficulty falling asleep (Lavie, 2007).

Demonstration of repetitive apneas and hypopneas during sleep and a history of symptoms related to OSA are required in making the diagnosis of OSA. Clinical examination with compatible history of OSA symptoms is followed by PSG or PG. PSG is usually performed in a sleep laboratory and is the gold standard for diagnosing OSA (Epstein et al., 2009). PSG includes electroencephalography, whereas PG does not. Therefore, PG cannot determine the sleep stages. PSG also includes detection of limb movement. PG includes at least electrocardiography (ECG), nasal inspiratory flow measurements, and analysis of thoracic and abdominal movements, and sleeping position. Arterial oxygen saturation is measured by finger pulse oxymetries (SpO_2) both during PSG and PG. In the hospital setting, transcutaneous carbon dioxide ($PtcCO_2$) measurement can be added. Both PG and PSG can be performed in hospital or in a sleep laboratory with continuous monitoring by a sleep technician or ambulatory at home, although PG is routinely performed at home (table 1). Video monitoring (time synchronized with all other PSG physiologic recordings) uses infrared-sensitive cameras and nonvisible infrared lighting during the study to capture abnormal movements or behaviors. Although PG is usually sufficient to make an OSA diagnosis (Kapur et al., 2017), PSG provides a more detailed picture of other sleep disorders, as it includes EEG, analyses the stages of sleep, and records leg movements. PSG is recommended if there is a discrepancy between symptoms and PG results, or if PG is considered insufficient in recognizing respiratory events and their effect on sleep (i.e in young patients with normal BMI) (*Sleep Apnea,Current care guidelines.Working group set up by the Finnish Medical Society Duodecim 2021 Available online at: www. kaypahoito.fi*) (Kapur et al., 2017). PG is insufficient to exclude OSA when the respiratory events are mainly associated with arousals. PSG is recommended when PG is "normal" and patients have symptoms of snoring and sleepiness or tiredness (Nerfeldt et al., 2014).

Table 1. PSG vs PG physiologic variables measured during sleep

	PSG	PG
Electroencephalography (EEG)	yes	no
Snoring microphone	yes	yes
Respiratory airflow channels	yes	yes
Respiratory effort channels	yes	yes
Pulse oximetry	yes	yes
CO_2 measurement	sometimes	seldom
Electrocardiogram (ECG)	yes	yes
Position	yes	yes
Limb movement	yes	sometimes
Video monitoring	yes, if inpatient	no

The AASM recommends (Kapur et al., 2017) that PSG or home sleep apnea testing with a technically adequate device is used for the diagnosis of OSA in uncomplicated adult patients with symptoms that indicate an increased risk of moderate-to-severe OSA. If a single home sleep apnea test is negative, inconclusive, or technically inadequate, PSG should also be performed for the diagnosis of OSA. The AASM also recommends that PSG, rather than home sleep apnea testing, is used for the diagnosis of OSA in patients with significant cardiorespiratory disease, neurological disease, awake hypoventilation or suspicion of sleep-related hypoventilation, chronic opioid medication use, history of stroke, or severe insomnia (Kapur et al., 2017).

The pathway for diagnosing and treating sleep apnea has been simplified in Finland in the past 20 years. PG is more commonly used in Finland compared to many western countries. At the beginning of the 21st century, diagnosis of sleep apnea and initiation of CPAP therapy were always performed in a hospital ward in secondary care. Today, the diagnosis of sleep apnea in Finland is mainly made in primary health care, according to current Finnish guidelines (*Sleep Apnea, Current care guidelines.Working group set up by the Finnish Medical Society Duodecim 2021 Available online at: www.kaypahoito.fi.*). PG at home is the most frequently used diagnostic tool. In many parts of Finland, primary healthcare doctors can order a PG from the clinical neurophysiology lab or a pulmonary unit after clinical suspicion of sleep apnea is raised. If OSA is diagnosed by PG, primary healthcare physicians refer the patient to specialist care (sleep unit or a pulmonary unit) for initiation of CPAP therapy or for consideration of an alternative therapy. A referral can also be made if there is a discrepancy between symptoms and PG result.

2.7 TREATMENT OF SLEEP APNEA

To standardize the diagnostics and treatment of sleep apnea, various national and international guidelines have been published in recent decades (Patil et al., 2019) (*Sleep Apnea,Current care guidelines.Working group set up by the Finnish Medical Society Duodecim 2021 Available online at: www.kaypahoito.fi.*). No major changes have been made in the guidelines in the last 20 years. CPAP therapy, originally introduced in 1983 with demonstrated evidence of efficacy, has been considered the treatment of choice for the past decades.

2.7.1 CONSERVATIVE THERAPY FOR OSA

The main objective in conservative treatment of sleep apnea is to reduce the risk factors of sleep apnea.

In obese OSA patients, weight loss is the most important form of conservative treatment. A weight-loss and maintenance program should be included in the treatment strategy in all patients. Strict and rigid programs that seek rapid weight loss seldom give permanent results, and treatment of obesity should therefore be considered as a life-long change in eating and exercise habits (Aro et al., 2021).

Patients (and even medical personnel) often hope that when treatment of OSA is optimized and sleeping becomes more consistent and regular, dietary habits and energy levels for exercise in patients will inevitably change. However, even when patients are treated properly with CPAP therapy, they do not lose weight. In fact, CPAP patients have been shown to gain more weight over long-term follow-up (Myllylä et al., 2016). On the other hand, studies have shown that in some OSA patients (up to 88% of patients with mild OSA) weight loss cured OSA or at least reduced its severity (Tuomilehto et al., 2009).

Exercise is known to reduce the severity of OSA even without weight loss (Carneiro-Barrera ym., 2019). Lack of exercise is associated with a higher severity of OSA (Peppard & Young, 2004). Smoking correlates with OSA severity (H. M. Zhu et al., 2019) and alcohol consumption increases the risk of OSA (Taveira et al., 2018). Combined lifestyle counseling for eating and exercise habits, smoking cessation, alcohol abstinence, and discontinuing or reducing medications that affect the central nervous system benefit all OSA patients.

Nasal obstruction is a risk factor for snoring and OSA. Treatment of nasal obstruction has been shown to decrease OSA severity and decrease daytime symptoms. Treatment of nasal obstruction and rhinitis with nasal corticosteroid sprays is associated with improved OSA severity and sleep symptoms (Cai et al., 2020).

Apneas are more prevalent in the supine position and some patients have apneas only in the supine position (positional OSA). Therefore, avoiding sleep in the supine position (positional therapy) can reduce the severity of sleep apnea and may be sufficient treatment for mild sleep apnea. In positional OSA, CPAP is more efficient in reducing AHI when compared with positional therapy alone, while positional therapy is better than no treatment in improving ESS and reducing AHI. However, positional therapy, (i.e. devices such as lumbar or abdominal binders, semi-rigid backpacks, full-length pillows, a tennis ball attached to the back of nightwear, and electrical sensors with alarms that indicate change in position) may be more readily acceptable than CPAP (Srijithesh et al., 2019).

2.7.2 POSITIVE PRESSURE VENTILATION

CPAP is the gold-standard treatment for OSA (Loube et al., 1999). CPAP treatment was first introduced in the 1980s by Sullivan et al who published the first reports of OSA patients treated with positive airway pressure (Sullivan et al., 1981). CPAP acts as a pneumatic splint as it elevates and maintains positive pressure in the upper airway during breathing (Sullivan et al., 1981). CPAP and its modification APAP (auto-adjusting positive airway pressure) are designed for long-term treatment for OSA (figure 1).

APAP automatically adjusts to meet each individual's breathing needs, which often change throughout the night as the individual moves in and out of different stages of sleep, while CPAP delivers one continuous pressure level of air.

Bi-level positive pressure (BIPAP) treatment provides inspiratory positive airway pressure and expiratory positive airway pressure that is lower than the inspiratory pressure. Randomized trials have not shown any major benefit of BIPAP when compared with CPAP (Jordan et al., 2014). BIPAP treatment should be considered if the patient feels expiratory pressure discomfort during CPAP. During BIPAP treatment, expiratory and inspiratory pressures can be adjusted separately, thus BIPAP can be used for ventilatory support for OSA patients with concomitant hypoventilation during sleep (i.e. COPD or restrictive pulmonary conditions and obesity hypoventilation).

ASV (adaptive servo ventilation) means that the timing, length, and volume of the breaths that the machine delivers vary. This form of therapy was originally targeted for patients with predominantly central apneas or Cheyne-Stokes breathing. Central apneas are associated with OSA, congestive heart failure, atrial fibrillation, cerebrovascular accidents, tetraplegia, and chronic opioid use. However, a recent randomized clinical trial in patients with predominantly central sleep apnea and heart failure (HF) with reduced ejection fraction (EF) revealed increased mortality in patients randomized to ASV (Cowie et al., 2015). Therefore, ASV is not indicated in central apnea patients with HF and a markedly EF (Aurora et al., 2016).

Figure 1. CPAP device, tube, and mask.

2.7.3 ORAL APPLIANCES

The objective of oral appliances (OA) for treatment of OSA is protrusion of the mandible, tongue, or both on the upper airway. These structural effects lead to enlargement of upper-airway dimensions with mandibular and tongue advancement.

Oral appliances are considered well tolerated; compliance is reported to be 40% to 80% (Ferguson et al., 1997). CPAP compliance has been reported to be lower than OA compliance by 1.1 hours per night. AHI and ESS are more effectively reduced with CPAP treatment (Schwartz et al., 2018)

The reasons for OA failure are individual; no single reason can be identified. Previous failed CPAP treatment is a predictor for OA treatment failure. Patients with previous CPAP treatment failure, who are overweight, or who have missing molars in both dental arches should be followed carefully to avoid treatment failure (Palotie et al., 2021).

In case of CPAP treatment failure, OAs are a non-invasive alternative and should always be considered.

In Finland, OA treatment is recommended for patients with BMI <30 kg/m^2 and with a suitable dental structure. According to AASM, the preferable OA model is a customized, titratable, and tooth-borne device that advances the mandible (Ramar et al., 2015)

2.7.4 SURGICAL THERAPY

In the 1990s, uvulopalatopharyngoplasty (UPPP) was a widely used operative form of treatment for sleep apnea. Since then, studies have shown that UPPP is effective for snoring over a period of time but not for apneas (Spicuzza et al., 2015). UPPP primarily addresses obstruction at the level of the soft palate. The results after UPPP are unpredictable. Anatomic factors (tonsil size and relatively normal palatal position) are better predictors of outcomes after UPPP than age, BMI, or AHI (Chang et al., 2020) (Choi et al., 2016).

In young persons, large tonsils may be the reason for snoring and may predispose to and increase the severity of OSA. Therefore, clinical examination of OSA patients should always include evaluation of tonsil size. In patients with enlarged tonsils, tonsillectomy (TE) may reduce the severity of OSA to the extent that additional therapy is not required.

Tracheostomy is the most extreme form of treatment for OSA. It was predominantly used in the 1960s to 1980s when other treatment options for severe sleep apnea were not available or failed (Guilleminault et al., 1981). Maxillomandibular advancement (MMA) surgery is currently considered the most effective surgical treatment option for OSA, with a success rate of 75% to

100% (Riley et al., 1993). MMA enlarges the upper airways and raises the hyoid bone such that the base of the tongue and the soft palate are drawn forward. A staged or phasic surgical protocol for OSA consists of a UPPP or genioglossus advancement with hyoid myotomi followed by a re-evaluation of OSA severity in 6 months, after which MMA is performed if the results are not satisfactory.

A novel surgical treatment method, electrical stimulation of the hypoglossal nerve, has been proposed as a physiologic method to maintain upper airway patency. A nerve stimulation cuff electrode is implanted surgically on the distal branch of the right hypoglossal nerve. A pressure-sensing lead is placed in the fourth or fifth right intercostal space, between the internal and external intercostal muscles. The device senses respiration and provides stimulation to the hypoglossal nerve (Woodson et al., 2014). This form of treatment is restricted to patients with low BMI and AHI <65/h (Wray & Thaler, 2016) (Bachour et al., 2021).

2.7.5 DRUG THERAPY FOR OSA

Several types of oral medication have been investigated in OSA to identify treatments when CPAP or OA therapy alternatives are not an option, fail due to compliance, or are declined by the patient. Although there are numerous potential drug targets in the field of sleep apnea, no approved pharmacotherapy is available to reduce OSA severity. A meta-analysis from 2019 (Gaisl et al., 2019) of 17 trials for seven drugs (acetazolamide, donepezil, mirtazapine, ondansetron, paroxetine, protriptyline, theophylline) revealed a small positive effect for acetazolamide. Nine drugs (tramazoline, liraglutide, spironolactone/furosemide, acetazolamide, dronabinol, zonisamide, phentermine, spironolactone, and ondansetron/fluoxetine) significantly lowered AHI compared to placebo. The meta-analysis concluded that these results were only valid for distinct OSA phenotypes or were not clinically significant, and that there is currently insufficient evidence to recommend any pharmacotherapy for OSA (Gaisl et al., 2019). Solriamfetol has undergone randomized controlled trials for treatment of subjective excessive daytime sleepiness, EDS, associated with both OSA and narcolepsy and exhibited robust efficacy. Solriamfetol is renally excreted, with no known drug interactions (Sogol, 2020).

2.8 CPAP TREATMENT

2.8.1 CPAP INDICATION

CPAP is safe and highly effective. When used during sleep, CPAP inhibits snoring and apneas, reduces arousals, increases oxygen saturation, and improves sleep structure, which subsequently reduces daytime somnolence. Regular use of CPAP may lower mortality (Kreivi et al., 2020).

There is no international consensus of when CPAP therapy is considered successful; use of CPAP at least 4 h/night is the most commonly used cutoff. CPAP compliance (continued usage 4 h/night) in Finland is estimated to be 57% to 67% (Kreivi et al., 2016). CPAP compliance is different between women (60.5%) and men (56.9%) (Anttalainen et al., 2007).

The indication for CPAP therapy for OSA patients in Finland is if the patient suffers from moderate-to-severe symptoms and if AHI is >15/h.

2.8.2 CPAP CONTRAINDICATIONS

There are only a few contraindications for CPAP treatment, such as recent pneumothorax, cerebrospinal fluid leak through nose or mouth, or floppy epiglottis. Floppy epiglottis is a rare condition where the epiglottis blocks the upper airway when positive air pressure is applied. Diagnosis can be performed clinically. The patient may complain of noisy breathing, a high-pitched sound, and may pull in the neck and chest with each breath. An ENT doctor can confirm the diagnosis using nasal fiberoscopy (Shimohata et al., 2011).

2.8.3 CPAP ADVERSE EFFECTS

The major side effect of CPAP is caused by the mask itself, as it may induce claustrophobia.

The mask itself may cause skin irritation. However, skin allergy to masks is rare. In patients with skin-related problems, special precautions should be taken to reduce skin irritation caused by the mask. Before applying the mask, the skin must be clean (Bachour et al., 2019).

A poorly fitting mask is a source of unintentional air leak. This may disturb the patient or the bedpartner (Bachour et al., 2019). The CPAP device generates continuous noise at a level of 35 to 45 dB. This sound increases with increasing air leak.

Traveling with CPAP may be cumbersome. Although CPAP device manufacturers offer travel CPAP devices that are lighter and smaller, such devices are noisier and slightly less effective than the standard devices.

The most common reason for CPAP therapy failure is persistent or emerging upper airway symptoms (Kreivi et al., 2016). Nasal symptoms, such as dryness or congestion, are common. Physiologically, breathing primarily occurs through the nose. Nasal obstruction requires the patient to breathe through the mouth, which causes mouth dryness, reduction in buccal health conditions, and may increase snoring and apnea prevalence. One of the major causes of nasal obstruction during CPAP therapy is unidirectional air leak. This occurs when the patient has a nasal mask and opens their mouth, after which the air goes first in through the nose and out through the mouth. This unidirectional air flow overrides the nasal mucosal capacity to heat and humidify the inspired air. As consequence, the nasal mucosa starts to show signs of inflammation and the patient has nasal stuffiness and rhinorrhea. Although nasal steroids may help, treating the cause is the main objective. A nasal and buccal mask may help, and chinstraps may also be beneficial.

Prophylactic local intranasal steroids are not recommended except when indicated for allergies or chronic rhinitis. Nasal humidification in the form of saline spray or oil may help. The use of CPAP humidification helps reduce upper airway symptoms, but has less effect on overall CPAP adherence (Boyer et al., 2019),(Kreivi et al., 2016), (Kreivi et al., 2010).

CPAP pressure through a nasal mask pushes the soft palate and tongue forward, which keeps the upper airways open. The oronasal mask violates these principles. Previous studies have shown that CPAP with oronasal mask is effective in treating OSA (A. Bachour et al., 2016), (Prosise & Berry, 1994). (Borel et al., 2013). However, oronasal masks are associated with higher CPAP levels, higher residual AHI scores, and poorer adherence than nasal masks (Rafaela GS Andrade,Fernada M Viana, 2018)

Chinstraps placed around the chin and attached to the headgear of the mask prevent the patient's mouth from opening. By using chinstraps, most patients have fewer mouth leaks and the arousal index may be moderately reduced. However, a chinstrap may also increase snoring by pushing the jaw backward, thus reducing the upper airway space. In rare cases, use of a chinstrap can worsen the respiratory disturbance index (Bachour, Hurmerinta 2003). The upper part of the straps should be adjusted as forward as possible to reduce the jaw's backward displacement (Bachour et al., 2019).

2.8.4 CPAP INITIATION AND SHORT-TERM FOLLOW UP

According to international and domestic guidelines, the indication for initiating CPAP therapy in OSA is a REI ≥15 events/h in PG or REI ≥5 events/h if the patient has daytime hypersomnolence or significant comorbidities (*Sleep Apnea,Current care guidelines.Working group set up by the Finnish Medical Society Duodecim 2021 Available online at: www.kaypahoito.fi*). Originally, CPAP treatment was always initiated in a sleep laboratory or in a hospital ward by manually titrating the pressure such that the apneas and hypopneas were treated. However, after autotitrating CPAP devices were developed, manual titration has been very seldom used in clinical practice in Finland.

There is no international consensus on a CPAP initiation protocol. Outpatient initiations with APAP devices and initiations in sleep laboratories with titration during PSG (Tsuyumu et al., 2020) are used depending on the country and hospital.

In the Helsinki Sleep Unit, patients starting CPAP therapy at home (Bachour et al., 2007) have a 1-hour familiarization session with the CPAP device and masks at the sleep clinic, supervised by a specialized sleep nurse. During these sessions, the patients can ask questions, practice putting on the masks, and learn how to use and take care of the devices (Kreivi et al., 2014). The sessions can be for an individual patient or for a group, with several patients participating at the same time. Nowadays, there are digital materials available for the patients to read in advance to prepare the patients for CPAP treatment and make the familiarization sessions more effective.

The first treatment follow up is 1 to 2 weeks after initiation with a specialized sleep nurse, and includes therapy response assessment either from the CPAP device memory card or a cloud server. Follow up is conducted either face to face or as a telephone contact. The second follow up is 2 to 3 months later and includes assessment for good therapy response, usage, and mask leak. If treatment is working well and compliance is good, follow up thereafter is mainly on demand (via telephone contact or electronic patient portal) if problems emerge or is conducted yearly via distance contact when a sleep nurse analyzes and documents therapy and compliance reports from a cloud server.

Due to availability of advanced technologies, such as telemonitoring of CPAP treatment, follow-up visits can be either telemedicine or face-to-face appointments. There are no differences in compliance or treatment efficacy when compared with traditional face-to-face visits (Anttalainen et al., 2016).

2.8.5 LONG-TERM CPAP FOLLOW UP

Similar to treatment of other chronic diseases, such as diabetes or hypertension, sleep apnea is a chronic long-term disease that requires lifelong treatment and treatment follow up to ensure adherence and efficacy, even after years of treatment. The first 3 months are considered essential for treatment success, which is why a more rigorous follow up is justified at treatment initiation. There is no international consensus on how long-term CPAP follow up should be arranged; even national follow-up conventions differ locally. Preliminary studies on a large number of patients in Europe and worldwide in need for efficient follow-up strategies have shown that follow up in primary health care is non-inferior to specialized health care (Sánchez-de-la-Torre et al., 2015). A structured and individually adapted follow up is considered important and attention in CPAP therapy follow up should be given to troubleshooting, feedback, education, and motivation (Ritter et al., 2018). After the first 3 months, if therapy continues without problems, annual follow up may be recommended, either as a telemedicine video appointment or as a face-to-face appointment. If resources must be optimized, an alternative method for follow up may be on-demand contact (i.e. the patient initiates contact when problems arise).

In most parts of Finland, specialized healthcare is responsible for CPAP initiation and follow up. To treat patients as a whole entity, it would be a logical process to follow up CPAP patients in primary healthcare, where comorbidities linked to sleep apnea (such as diabetes or hypertension) are also treated and followed up. Recommendations for lifestyle changes, from increasing physical activity to behavioral treatment, also occur in primary healthcare. In some parts of Finland, primary healthcare has assumed responsibility of follow up after therapy initiation and initial acceptance. The follow-up protocol varies in different parts of the country (Bachour & Avellan-Hietanen, 2021). However, CPAP patients with long-lasting adherence, mask, or sleeping problems and patients experiencing difficulties with treatment, occupational drivers on CPAP, and other special groups should still be followed in secondary care (Bachour & Avellan-Hietanen, 2021).

2.8.6 TECHNOLOGICAL DEVELOPMENTS FOR FOLLOW-UP

Digitalization has played a central role in the change of treatment pathways in recent years.

The development of CPAP devices, from basic devices that collect minimal data, to devices with a memory card that store a large amount of data on various treatment parameters (such as overall CPAP usage, usage time [h/night], air leak, on-off time, and flow signals) has changed treatment follow up. The parameters that should be examined in routine follow up are results of therapy (specifically CPAP-AHI), mask leak, hours used per night, and percentage of days used. In addition, patient symptoms, potential side effects, and problems related to CPAP therapy should be discussed.

Cloud storage of CPAP data has made follow-up visits easier and more practical. Cloud services make it possible for personnel to read device data remotely and allow the patient to see how the therapy is working. For example, several CPAP device manufacturers provide secure, cloud-based patient management systems for patient monitoring, which allows sleep nurses and doctors to evaluate CPAP therapy success remotely. This enables the medical team to quickly access patient data, share clinical insights with other health professionals, and reduce costs related to patient follow up. The devices can transmit therapy data through the cloud to a central station. Data are transmitted once daily. The medical team can also perform remote adjustments. The programs offer information about the patient's CPAP use and allows assessment of detailed data, such as air leak, pressure level, and distribution of respiratory events. Device manufacturers also offer online services that allow patients to follow their own therapy. These programs provide a daily score on the success of CPAP therapy and also provides mask-fitting events per hour and mask on-off periods. These applications and services show promise as feasible and acceptable tools for personal OSA management for both compliance and adherence (Suarez-Giron et al., 2020).

The Rescan™ system from Resmed is used to download data from the device memory card. This differs from AirView™, a cloud-based service, as Airview data on airflow are not shown (Figure 2). Philips has similar programs, namely EncoreAnywhere™ for sleep professionals and the DreamMapper™ website for patients using CPAP.

Data are scarce on the benefits of these new forms of telemedicine. Telemonitoring of CPAP treatment for OSA may be relevant in closing the gap between increasing demands and available healthcare resources. Telemonitoring has been suggested to save nursing time without compromising short- or long-term efficacy, effectiveness, or adherence to CPAP treatment (Anttalainen et al., 2016). Randomized trials are needed to determine if routine follow up is needed at all in the future or if on-demand visits when problems emerge are sufficient.

The primary objective in telemedicine with cloud devices is to increase treatment efficacy and to make treatment cost-effective and accessible for more patients. Previous studies have shown that telemedicine for CPAP treatment is cost effective (Isetta et al., 2015) (Turino et al., 2017). People who have difficulty attending follow-up visits, such as older patients who require assistance, may benefit from telemedicine. Data on this are still scarce and not conclusive on

Figure 2. AirView detailed data. The upper panel displays unintentional leak values. The middle panel displays CPAP pressure values.

adherence and patient satisfaction (Anttalainen et al., 2016) (Fox et al., 2012). Patient applications for following CPAP success (i.e. MyAir, DreamMapper) and educational videos may improve compliance and reduce time spent in face-to-face patient education (Hwang, 2016) (Munafo et al., 2016).

2.8.7 CPAP INTERFACE

A critical factor in maintaining compliance and ensuring CPAP therapy success is proper mask fit (Bachour et al., 2016). A poorly fit mask may leak, irritate skin, increase aerophagia, and increase CPAP pressure demands (in case of oronasal mask use). Unintentional air leak may stem from a poorly fit mask, defective CPAP tube, or improperly adjusted humidifier. If air leak emerges later during the night after suitable mask fit at the beginning of the night, this is usually related to patient movement during sleep. Air leak should be assessed during follow up of CPAP therapy (Bachour et al., 2019). When the original mask must be switched, the risk for later therapy failure increases sevenfold (Bachour et al., 2016).

It is important to address the cause of nasal problems before and during CPAP therapy. The major reason for nasal stuffiness that emerges during CPAP therapy is air leak through the mouth.

2.9 TRAFFIC AND SLEEP APNEA

OSA is a documented risk factor for motor vehicle accidents. The risk for motor vehicle accidents may be affected by multiple factors other than OSA, including time of day, number of hours driven, insufficient sleep, medications, or alcohol or substance abuse.

Internationally, specific regulations regarding identification and management of OSA in professional drivers vary widely or do not exist (Gurubhagavatula et al., 2020). Previous studies have shown that 7% of motor vehicle accidents in males is related to OSA (Garbarino et al., 2015).

In Finland, the regulations for evaluating driving health are set by Traficom (Department of the ministry of traffic). Group 1 drivers are not permitted to drive if the driver suffers from severe daytime somnolence. Group 2 drivers, including also professional drivers, are not permitted to drive if they have a mild disturbance in alertness, which should be verified with an objective measurement of alertness or with a voluntary driving assessment. If a subject does not fulfill the requirements set for the driver's license class in question, police authorities should be notified by the medical team (https://www.traficom.fi/sites/default/files/media/fil).

Traficom regulations stipulate that Group 1 drivers with OSA should be followed with an interval of 3 years in terms of efficacy of and adherence to sleep apnea therapy and daytime symptoms; Group 2 drivers should be followed annually. In a recent Finish study, adequate CPAP therapy for drivers with OSA did not decrease the incidence of motor vehicle accidents (Myllylä et al., 2020).

2.10 SLEEP APNEA IN SENIOR PATIENTS

The prevalence of OSA in persons >65 years is high (Sforza et al., 2012) (McMillan et al., 2014) and is estimated to be 90% in men and 78% in women. However, it is unclear if OSA in the elderly needs CPAP treatment. Some studies recommend CPAP (McMillan et al., 2014) and some conclude that it is uncertain (Senaratna et al., 2017). CPAP daily use in senior patients has been reported (McMillan et al., 2014) to be very low at 1 year (median usage 2 h and 22 min per night). McMillan et al recommend CPAP therapy in senior patients with OSA and showed that CPAP reduces sleepiness and is more cost effective than best supportive care alone. CPAP treatment is shown to increase quality-of-life and cognition in elderly people.

Memory and physical dexterity may become impaired with aging and memory loss may lead to reduced therapy adherence (Dolansky et al., 2016). Mild forms of Alzheimer's disease do not appear to reduce adherence (Ayalon et al., 2006).

The role of AHI in diagnosing OSA in elderly patients has been questioned. The appropriate AHI value for making the diagnosis is unknown in this group of patients. There are no validated diagnostic and therapeutic tools for the elderly and this is an obstacle for diagnosing and treating OSA in the elderly (Posadas et al., 2020). In some studies, up to 80% of men >70 years have AHI >5/h (Fietze et al., 2019). A meta-analysis evaluated the normal range of AHI in a healthy population and revealed that mean AHI was 15.5/h in persons 65 to 79 years and was 30/h in those >80 years (Boulos et al., 2019).

The symptoms of OSA in elderly patients are mostly the same as in the general population. However, the symptoms may overlap with other conditions (i.e. sedative effects of medications or neurologic issues) (Young et al., 2008). Decrease in cognitive function may be associated with nocturnal hypoxemia (Blackwell et al., 2015) (Yaffe et al., 2011).

The association of untreated OSA with cardiovascular events has not been documented in the elderly as in younger patients (Punjabi et al., 2009) (Gottlieb et al., 2010). The association of OSA with ischemic stroke in older patients has been documented (Redline et al., 2010).

Treatment of OSA in elderly people follows the same rules as in the general population. CPAP is the first choice and OA can be used when the dental situation allows it. Adherence to CPAP therapy has been shown to be good in those >70 years (Woehrle et al., 2011). The existing evidence on the effect of CPAP treatment in very elderly (>80 years) and frail populations is scarce. However, it is believed that age should not be considered a barrier to assessment and treatment of OSA in older patients (McMillan & Morrell, 2016).

3 AIMS OF THE STUDY

The aim of this work was to further study OSA and to understand the mechanisms behind therapy success.

The specific aims of each study are as follows:

I The demand for CPAP therapy exceeds available resources in most health care settings and there is no international consensus on how CPAP follow up should be organized. We aimed to identify the reasons for patients' contacts in between two routine visits and their timing related to the previous routine contact and to identify predictors for these non-routine contacts in OSA patients on CPAP therapy.

II Adherence to CPAP for OSA has not been established in patients >70 years. We aimed to address this evidence gap and evaluate CPAP adherence in the elderly compared to younger OSA patients.

III CPAP therapy fails in about one third of patients within 1 year of initiation. Although re-initiating CPAP therapy after previous failure is an alternative, data on the success of CPAP re-initiation are scarce. We aimed to determine the success rate of re-initiation of CPAP therapy after a previous failure.

4 MATERIALS AND METHODS

4.1. CPAP TREATMENT AND FOLLOW-UP IN HELSINKI SLEEP UNIT

This research was conducted in the Sleep Unit, Heart and Lung Centre, Helsinki University Hospital, Finland. The sleep unit includes a sleep laboratory that provides services for a catchment area of approximately 1.5 million inhabitants and a sleep apnea unit that covers the population of the Helsinki region (approximately 630 000 inhabitants).

The diagnosis of OSA is mainly made in primary care with PG and the patients are referred to our sleep unit for CPAP therapy evaluation. The indication for CPAP therapy initiation in OSA in our clinic is a REI ≥ 15 events/h, or REI ≥ 5 events/h and daytime hypersomnolence or significant comorbidities, as stated in the AASM guidelines and Current care guidelines (*Sleep Apnea,Current care guidelines.Working group set up by the Finnish Medical Society Duodecim 2021 Available online at: www.kaypahoito.fi.*) (Patil et al., 2019)

CPAP therapy initiation (same procedure during all three studies) includes a 1-hour familiarization session at the sleep clinic with the CPAP device and masks. Two to three months after CPAP initiation, patients were also assessed for adherence and good therapy response. Subsequently, follow-up contacts were routinely planned every 12 to 15 months to ensure good therapy response and adherence. This is conducted either face-to-face or via telemedicine, either by a specialized nurse or a doctor (Figure 3). We use APAP devices and interfaces purchased by the hospital following competitive tendering as stipulated in public procurement legislation. The public hospitals own the CPAP devices and devices are offered to the patients free of charge. If the patients discontinue treatment, they return the device to the clinic. We used auto CPAP devices for the entire duration of this study.

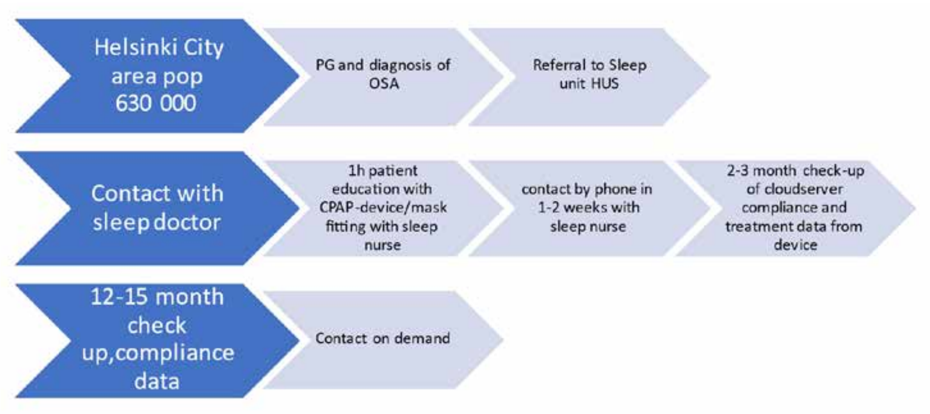

Figure 3. CPAP therapy in public health care in the Helsinki region.

4.2. PARTICIPANTS

All patients included in the three studies were collected from the OSA patients treated in the sleep unit with CPAP. The protocols of all three studies included in this thesis were approved by the local ethics committee.

OSA diagnosis was performed with a sleep study with a type-3 cardiorespiratory device NOX T3 (Noxturnal, Iceland) according to AASM classifications. The sleep studies were performed in primary health care and analyzed by clinical neurophysiologists. Primary care physicians evaluated the patients clinically and thereafter referred the patients to PG. The AASM criteria for apnea and hypopnea were applied. The indication for CPAP therapy initiation in OSA was a REI ≥15 events/h or REI ≥5 events/h and daytime hypersomnolence or significant comorbidities as described previously. Patients with diagnosed obesity hypoventilation syndrome (OHS), central sleep apnea, and patients using bi-level CPAP therapy were excluded from the studies.

The CPAP Initiation protocol included a 1-hour familiarization session at the sleep clinic with the CPAP device and masks. Therapy response was evaluated at 2 to 3 months and yearly follow ups after that point were scheduled. Rescan™, a PC-based clinical analysis and patient management software, was used for downloading CPAP data.

4.2.1 STUDY I

For study I, we selected all our patients with CPAP therapy duration >1 year. The study started in 2015 and related only patients still on CPAP therapy. The longest follow-up was since 1989 and the shortest since 2014. Of these

2466 patients using CPAP, 1225 patients (50%) were randomly selected for further analysis. As data work analyses exceeded clinical research capacity, we adjusted the number of selected subjects to 50% and therefore we randomized selection. Randomization was performed with IBM SPSS Statistics software version 22.0.0.1 (IBM Corp, Armonk, NY, US). The selected study population did not differ from the remaining population regarding age or BMI. After excluding patients with OHS and treatment with BIPAP (total 84 patients), the final study population consisted of 1141 patients.

4.2.2 STUDY II

Patients with a REI ≥5 events/h were recruited from 2017 to 2018 at our sleep unit. We included only patients > 70 years in the senior group. For the control group, we included patients aged between 18 and 50 years (junior group), figure 4. Patients with previous CPAP therapy experience, non-cooperative patients, and patients with a concomitant severe disease with life expectation <1 year or with a severe and unstable psychiatric disorder were excluded.

We estimated sample size by using Clincalc.com (https://clincalc.com/stats/samplesize.aspx). We used the non-inferiority study principle and hypothesized that CPAP daily use in senior patients during the first year of follow up is not inferior to CPAP daily use in junior patients; namely, senior patients use the CPAP device daily at least as often as junior patients do. The mean daily CPAP use was estimated to be 4 ± 2 h. We set the margin of non-inferiority at 1 h of CPAP use, α-value at 0.05, and β-value at 0.1 for one-sided test. The number of subjects needed was 69 for each group.

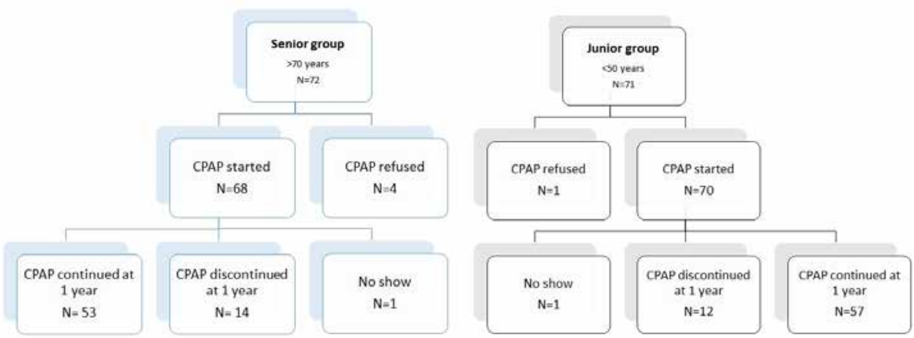

Figure 4. Patient groups in Study II.

4.2.3 STUDY III

The data pool was selected during the years 2005 to 2016. Recruiting patients was performed sporadically due to logistic restrictions during a 5-year period. A total of 6231 subjects were referred to our sleep unit; of these, 3913 patients (62.8%) initiated CPAP (Koivumäki et al., 2018). A total of 224 patients attempted CPAP re-initiation after a period ≥6 months following the first CPAP failure (figure 5).

The number of subjects needed for the study was unknown during the initiation of this study, as no previous data were available about the prevalence of re-CPAP. We aimed to collect all our re-CPAP patients first to estimate the prevalence and second to evaluate the success of re-CPAP. The basis of this study could be considered as a pilot.

For the control group, we selected 228 subjects from the subjects referred to our clinic and who underwent CPAP initiation for the first time in 2015. The control group consisted of CPAP-naïve subjects.

We defined CPAP therapy as failed when the patient discontinued treatment and returned the device to the hospital regardless of the time between initiation and discontinuation.

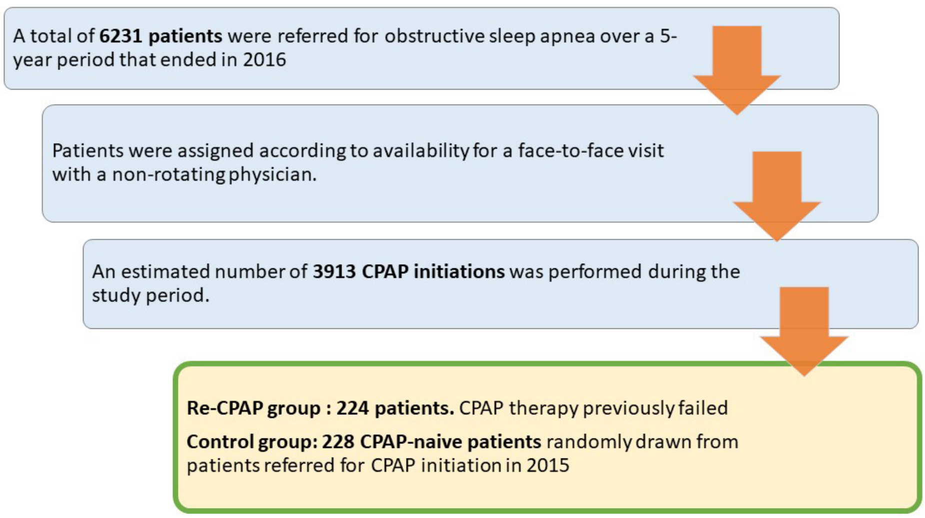

Figure 5. Patient groups in Study III.

4.3. METHODS

4.3.1. STUDY I

4.3.1.1. ORGANIZATION OF CPAP FOLLOW UP

Study I was a retrospective cross-sectional study. Every patient file was examined once for inclusion and data collection during the period 2015 to 2017. The annual follow-up was performed in four ways; therefore, the patients were categorized into four groups according to the follow-up modality used (physician 1, physician 2, nurse 1, nurse 2; Figure 5)

1. Physician 1: included patients who were professional drivers or had high comorbidities and who always were seen at 1-year follow up by a physician
2. Physician 2: Included patients who presented with CPAP-related problems that exceeded the sleep nurse's competence, such as patients seeking alternative therapy; patients seeking any kind of medical certification, and patients that required evaluation of working capacity or other medical problems and were therefore further referred to the physician by the sleep nurse.
3. Nurse 1: This group consisted of patients who required (i.e. patients with limited physical mobility or communication difficulties, or patients needing help when handling the CPAP device) or wanted face-to-face contact with a professional but did not meet the physician 1 or 2 group criteria.
4. Nurse 2: Included all patients who did not fulfill the criteria of the other groups and whose therapy responses were analyzed by a nurse trained in sleep medicine without face-to-face contact (i.e. by phone).

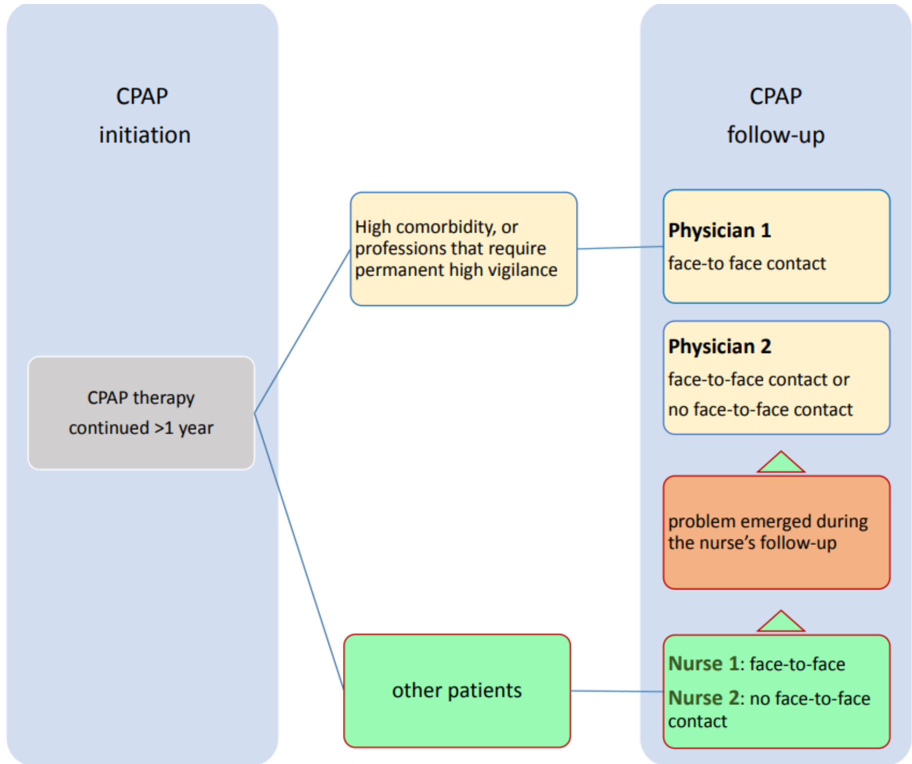

Figure 6. Different forms of CPAP follow up.

4.3.1.2. ROUTINE AND NON-ROUTINE CONTACTS

Study subjects were divided into two groups (routine [R] and non-routine [NR]) based on their contacts with the sleep unit. A R contact was defined as a pre-planned contact with a time interval of at least 1 year. A NR contact included all other contacts with the sleep unit. Subjects who had at least one NR contact with the sleep unit were included in the NR group. The remaining subjects were assigned to the R group. Subjects with multiple NR contacts were analyzed separately.

4.3.1.3. DATA COLLECTION

The baseline data (i.e. before CPAP treatment) on patient characteristics, comorbidities, diagnostic sleep study, and data related to CPAP treatment (device, interfaces, treatment results [i.e. daily usage of CPAP]), treatment duration, time since the last contact, and cessation of CPAP treatment were collected for all study subjects. We defined duration of CPAP treatment (months) as the time between CPAP initiation and the last contact with the sleep unit. Charlson comorbidity index (CCI) was used to evaluate comorbidity (Hall et al., 2004).

All contacts and types of contacts (R or NR) with the sleep unit were recorded. Reasons for the NR contacts were recorded as the following: patient symptoms; side effects related to CPAP; and need for administrative procedures (i.e. need to obtain medical certificates for insurance or driving authorities) (Figure 9). The patients were classified as symptomatic (if any symptom emerged) or as non-symptomatic (no symptom was present).

Both baseline and treatment data were compared for the physician 1, physician 2, nurse 1, nurse 2, R, and NR groups.

4.3.2. STUDY II

4.3.2.1 COGNITIVE AND PHYSICAL TESTS

Study II was a prospective, non-randomized, case-controlled study into which patients >70 and <50 years were recruited in a consecutive manner. Each patient underwent cognitive and physical tests before starting CPAP.

The Nine-Hole Peg Test (NHPT) assesses finger dexterity, also known as fine manual dexterity (Oxford Grice et al., 2003). The patient is asked to take the pegs from a container and place them into the holes on the board one by one. The patient then removes the pegs from the holes and places the pegs back into the container as quickly as possible one by one. The test is performed twice, once by the dominant hand then by the non-dominant hand (Oxford Grice et al., 2003).

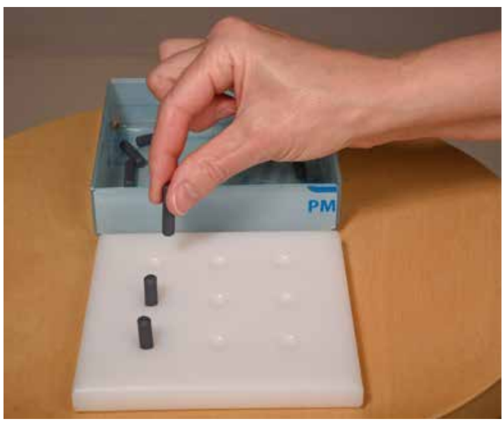

Figure 7. Nine-hole peg test.

Pinch-strength testing was performed with a pinch grip, whereby an object is pinched in three ways (lateral, three-point, and tip pinch; described below) (Mathiowetz ym., 1984) (Figure 8). Three trials of each of the three pinch positions were performed. We documented the highest score of all positions.

Lateral pinch: The pinch meter is positioned between the thumb pulp and the lateral aspect of the middle phalanx of the index finger.

Three-point pinch: The pinch meter is positioned between the subject's thumb pulp and the pulps of the index and middle fingers.

Tip pinch: The pinch meter is positioned between the tip of the thumb and tip of the index.

All measurements were performed with the dominant and non-dominant hand.

Figure 8. Pinch test.

Measurements of shoulder movement range were performed on study subjects.

For forward flexion measurement, the straight arm is raised in front of the body, with the palm down, as high as possible.

For abduction measurement, the straight arm is raised at the side, with the palm down, as high as possible.

For external rotation measurement, the elbows are held by the sides of the body and bent at 90° and palms are facing each other. The elbows are in contact with the body, the hands are then spread outwards as far as possible.

For internal rotation measurement, the arm is put behind the back and the elbow is bent. The subject tries to reach as far up the back as possible. This distance is measured from a certain point on the spine.

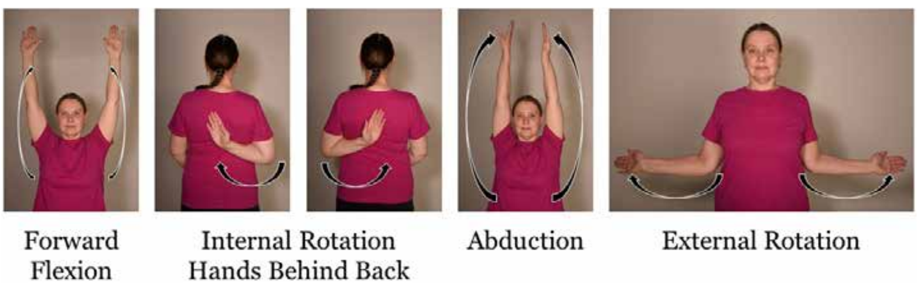

Figure 9. Shoulder movements.

The Mini mental state examination (MMSE) was preformed on all participants at the same time as the other physical and cognitive tests.

4.3.2.2. DATA COLLECTION

Data at baseline (before CPAP initiation) was collected regarding gender, BMI, sleep study parameters, ESS and comorbidities. Each patient also performed cognitive and physical tests at baseline. All patients were also evaluated at 1 year from CPAP initiation; data on CPAP and ESS were collected at this time.

4.3.3 STUDY III

4.4.3.1 DEFINITION OF CPAP FAILURE

Study III was a retrospective medical chart review study. We defined CPAP therapy as failed when the patient discontinued the therapy and returned the device to the hospital regardless of the time between initiation and discontinuation.

4.3.3.2 DATA COLLECTION

To assess CPAP adherence in the CPAP re-initiation (re-CPAP) group, data on age, apnea index, sleep study, comorbidities, and CPAP adherence were recorded.

4.4. STATISTICAL METHODS

We used analysis of variance, chi-square test, and the *t*-test as appropriate. A P-value value <0.05 was considered statistically significant. IBM SPSS Statistics software (Version 25; IBM, Armonk, New York) was used to compute differences in demographic, clinical, and measured variables.

In Study I, both stepwise and forced models of logistic regression analysis were used to define factors that could predict the patient having a NR contact by using the variable NR as the dependent factor. Patient age, sex, CCI, REI baseline, CPAP-AHI, education level, psychiatric disorder, or belonging to a specific follow-up group were independent factors.

In Study II, normal distribution was examined using Kolmogorov-Smirnov and Shapiro-Wilk tests. We calculated skewness and kurtosis values. Mann-Whitney *U* test was used to compare two samples and data were reported as median and lower to upper quartile for non-parametric continuous variables without normal distribution.

In Study III, a Bonferroni correction for multiple comparisons was used as necessary.

5 RESULTS

5.1 STUDY I

5.1.1. PATIENT CHARACTERISTICS

A total of 1141 patients were included in the study group; 771 patients were assigned to the R group and 370 to the NR group.

Table 2. Patient characteristics

	All patients		Routine contact (R)		Non-routine (NR)		
	Mean or count	SD or %	Mean or count	SD or %	Mean or count	SD or %	p
Patients, n	1141		771		370		
Women, n, %	300	26%	194	25%	106	29	**0.119**
Age, years, SD	60	11	60	11	59	12	**0.135**
BMI, kg/m2	32.6	7.2	32.4	7.1	33	7.4	**0.238**
ESS	9.2	4.7	9.4	4.7	8.9	4.6	**0.176**
REI baseline	38.2	23.7	38.0	23.3	38.7	24.7	**0.647**
Education in years	13.8	2.7	13.8	2.7	13.8	2.7	**0.632**
Patients with psychiatric disorders, n, %	133	12	82	11%	51	14%	**0.067**
CCI	1.01	1.87	1.01	1.99	0.95	1.59	**0.224**
CPAP duration (months) (Range 12-361 months)	78.4	59.4	80.9	59.6	73.3	58.9	**0.043**
CPAP daily usage (hours: minutes)	6:34	2:06	6:34	2:02	6:34	2:18	**0.992**
Abandoned CPAP therapy, n, %	51	3.7	12	1.3	39	8.7	**<0.001**
Interval between two contacts, (months)	12.2	6.4	15.0	4.6	6.4	5.7	**<0.001**
Symptoms, n, %	218	19	76	10	142	38	**<0.001**
Physician 1, n, %	54	5	34	4	20	5	**NS**
Physician 2, n, %	100	9	48	6	52	14	**<0.001**
Nurse 1, total n, %	183	16	129	17	54	15	**NS**
Nurse 2, total n, %	804	70	560	73	244	66	**NS**

Abbreviations: BMI = body mass index; CCI = age-adjusted Charlson comorbidity index; CPAP = continuous positive airway pressure; ESS = Epworth Sleepiness Scale; NS = not significant; REI=respiratory event index.

5.1.2. ROUTINE VERSUS NON-ROUTINE CONTACTS

Thirty-nine patients in the NR group and 12 patients in the R group abandoned CPAP therapy ($P<0.001$). The yearly abandoning rate was 3.7% for all patients and was 1.3% and 8.7% for the R and NR group, respectively.

5.1.3. PREDICTORS FOR NON-ROUTINE CONTACTS

The only independent factor for a NR contact was the follow-up group (physician 1, physician 2, nurse 1, or nurse 2). The probability of a patient in the physician 2 group initiating a NR contact with the sleep unit between the two routine controls was higher than patients in the other groups (odds ratio [OR] 1.44). Fifty-two percent of the patients belonging to the physician 2 group initiated a NR contact, whereas this percentage was significantly lower in the other groups (34%, $P<0.001$). Symptoms of suffocation (OR 10.4) and somnolence (OR 34.8) were significant predictors of NR visits.

5.1.4. REASONS FOR NON-ROUTINE CONTACTS

Disturbing symptoms were the first reason for a NR contact (41%). The main symptoms that led the patient to initiate a NR contact were somnolence (29%), nasal stuffiness (9%), feeling of suffocation during CPAP therapy (9%), persistence of snoring (7%), appearance or persistence of mouth dryness (4%), and other causes (42%).

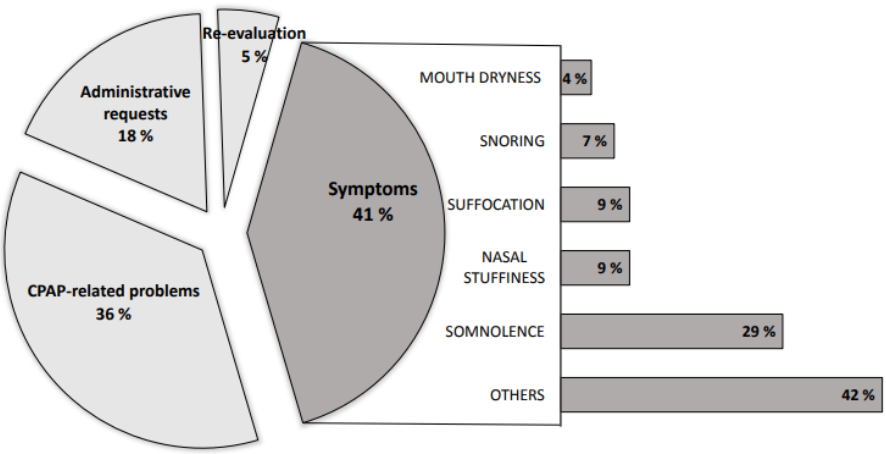

Figure 10. Symptoms were the primary reason for NR contacts.

CPAP-related problems included interface problems, device problems, and administrative requests (i.e. mainly certificates for sick-leave or pension-related issues).

5.2 STUDY II

5.2.1 PATIENT CHARACTERISTICS

Seventy-two patients starting CPAP treatment were included in the senior group (age >70 years) and 71 were included in the junior group (age 18-50). The proportion of women was significantly higher in the senior group (49%) than in the junior group (24%). Mean SpO_2, SpO_2 awake, and cumulative time below 90% (CT 90%) were significantly lower in the senior group than in the junior group. The incidence of MCC and hypertension was significantly higher in senior patients than in junior patients. BMI did not differ between the two groups. Comorbidities were more frequent in the senior group.

Table 3. Patients characteristics in Study II

	Seniors	Juniors	P
Number	72	71	
woman, number (%)	35 (49)	17 (24)	0.003
age, year, mean (SD)	75 (4)	40 (8)	<0.001
BMI baseline, mean (SD)	31 (8)	31 (5)	0.996
REI, baseline, mean (SD)	34 (17)	37 (23)	0.390
REI supine baseline, mean (SD)	47 (19)	52 (28)	0.205
ODI3 baseline, mean (SD)	32 (18)	38 (23)	0.126
Pulse oximetry, SpO2 mean (SD)	92 (2)	93 (2)	<0.001
SpO2 wake, mean (SD)	96 (1)	97 (1)	<0.001
CT 90% baseline, mean (SD)	23 (25)	13 (16)	0.009
ESS, mean (SD)	7.7 (4,8)	9.9(3,2)	0.227
Hypertension, number (%)	49(68)	14 (20)	<0.001
DMII number (%)	23 (32)	8 (11)	0.002
Asthma, number (%)	5 (7)	6 (9)	0.500
Coronary heart disease, number (%)	16 (22)	1(1)	<0.001
Alzheimer's disease, number (%)	2 (3)	0(0)	0.252
Rheumatoid arthritis, number (%)	5 (7)	2 (3)	0.226
Chronic obstructive pulmonary disease, number (%)	4 (6)	1 (1)	0.187
Chronic rhinitis, number (%)	1 (1)	8 (11)	0.016
Still on CPAP at 1 year,(%)	53	57	0.428

Abbreviations: BMI = body mass index; REI=respiratory event index; ODI3=oxygen desaturation index; CT=cumulative time; ESS = Epworth Sleepiness Scale; DMII=diabetes mellitus type II; CPAP = continuous positive airway pressure.

5.2.2 CPAP ACCEPTANCE AND DAILY USE

Senior patients continued CPAP therapy as often as junior patients after 1 year of CPAP use.

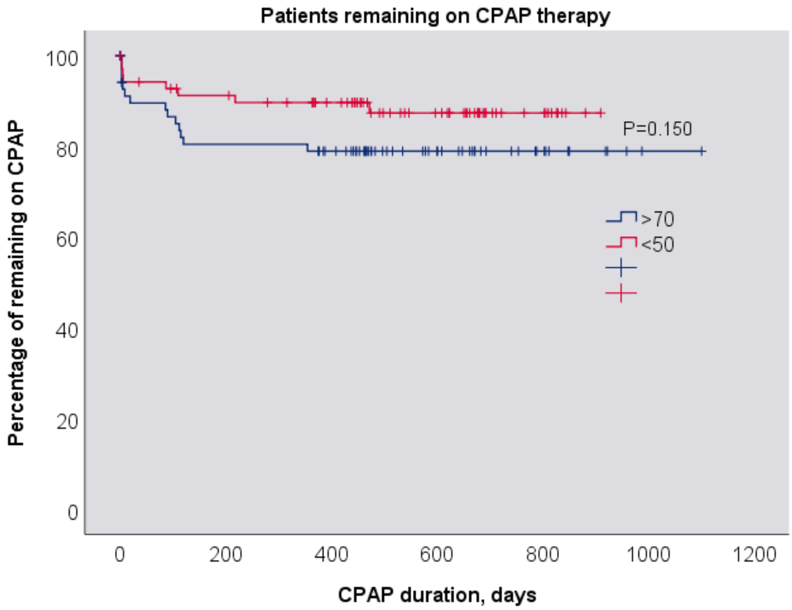

Figure 11. Senior and junior patients remaining on CPAP

There was no significant difference in daily CPAP use between senior and junior patients (4:53 ± 2:44 hh:min vs. 4:23 ± 3:00 hh:min)

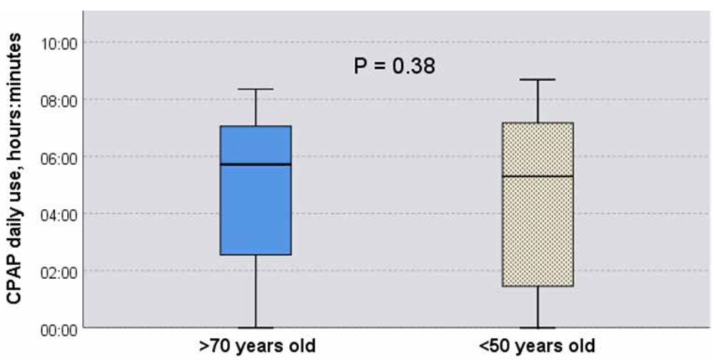

Figure 12. CPAP daily use between senior and junior patients.

5.2.3. COGNITIVE AND PHYSICAL TESTS

The nine-hole peg test, pinch test, and shoulder movement values were significantly higher in the junior group.

Table 4. Physical tests.

		Seniors	Juniors		Seniors	Juniors		Seniors	Juniors		Seniors	Juniors	
Shoulder movements,		**Forward flexion**		**P**	**abduction**		**P**	**external rotation**		**P**	**internal rotation**		**P**
Mean, angle in degree °		177	179		177	179		64	73		26	22	
Median		180	180	0.002	180	180	0.700	70	80	0.028	26	22	0.023
Percentiles	25	180	180		180	180		45	55		22	18	
	75	180	180		180	180		80	90		30	27	
Pinch test		**Tip**			**Lateral**			**Three-point**					
Mean	lbs	12	15		19	24		16	20				
Median		12	15	<0.001	18	25	<0.001	15	20	<0.001			
Percentiles	25	10	13		16	21		13	18				
	75	15	18		22	28		19	24				

There were no significant differences in MMSE scores between senior (median 27.00, range 15–30) and junior patients (median 28.00, range 21–30).

5.3 STUDY III

5.3.1 PATIENT CHARACTERISTICS

BMI was higher in the re-CPAP group and patients were older than those in the control group. Mean BMI was 34.8 kg/m² and mean REI was 39.4 in the re-CPAP group and 31.6 kg/m² and 32.6 in the control group, respectively. Mean age was 57.8 years at the first CPAP initiation in the re-CPAP group and 55.0 years in the control group (Table 5).

There were no significant differences regarding ESS, oxygen desaturation index at 4% threshold, or SpO_2 values between the groups. ESS, median leak, and leak 95^{th} with CPAP therapy did not differ significantly between the re-CPAP and control groups. CPAP daily use (in hh:min) was significantly lower in the re-CPAP group than in the control group (2:37 vs 3:58, respectively; $P<0.001$).

Table 5. Characteristics of the study subjects in Study III.

	Re-CPAP group N = 224		Control group N = 228		P-value 2-tailed
	Mean	SD	Mean	SD	
Age, years	57.8	11.0	55.0	13.5	0.017
BMI, kg/m2	34.8	10.2	31.6	7.0	0.001
ESS baseline	9.5	5.4	9.1	5.1	0.351
ESS CPAP	7.8	5.1	6.4	4.0	0.012
REI baseline	39.4	24.4	32.6	22.2	0.011
ODI4	36.8	25.8	32.3	21.9	0.174
mean nocturnal SpO2 baseline, %	92.2	3.1	92.2	2.7	0.546
CPAP duration, days	483	763	357	246	0.011
CPAP daily use, hh:min	2:37	2:19	3:58	2:46	0.000
AHI-CPAP	5.0	7.0	2.8	4.5	0.000
Leak median, L/minute	4.8	7.9	5.2	10.0	0.759
Leak 95th, L/minute	18.3	12.7	18.5	13.8	0.208
Humidification, %	81.7		99.1		0.000
previous UPP, %	6.3		1.3		0.005

The prevalence of comorbidities was higher in the re-CPAP group than in the control group (table 6). However no significant differences were observed in abandoning CPAP therapy regarding the following comorbidities: asthma, psychiatric disease, COPD, DMII, heart arrhythmia, or hypertension. Patients with coronary heart disease were more likely to abandon CPAP therapy in both re-CPAP and control group [χ^2 (1, N = 206) = 8.418, (P = .006)]

Table 6. Prevalence of comorbidities in Study III.

	Re-CPAP		Control		P-value
	number	%	number	%	
Asthma	30	28	32	14	0.004
COPD	12	12	10	5	0.018
Heart arrhythmia	21	21	27	12	0.043
Hypertension	72	66	107	48	0.002
Psychiatric disorders	56	51	56	25	<0.001
Diabetes mellitus II	51	45	40	18	<0.001
Coronary heart disease	18	18	18	8	0.013

CPAP therapy for OSA was re-initiated after a mean lapse time of 5.2 years from the first initiation. During the time lapse, BMI increased significantly from 32.6 to 38.8 kg/m^2, reflecting a weight gain of 1.5 kg/m^2/year for a person of 175 cm. The lapse time was not related to the outcome of CPAP re-initiation (Figure 13).

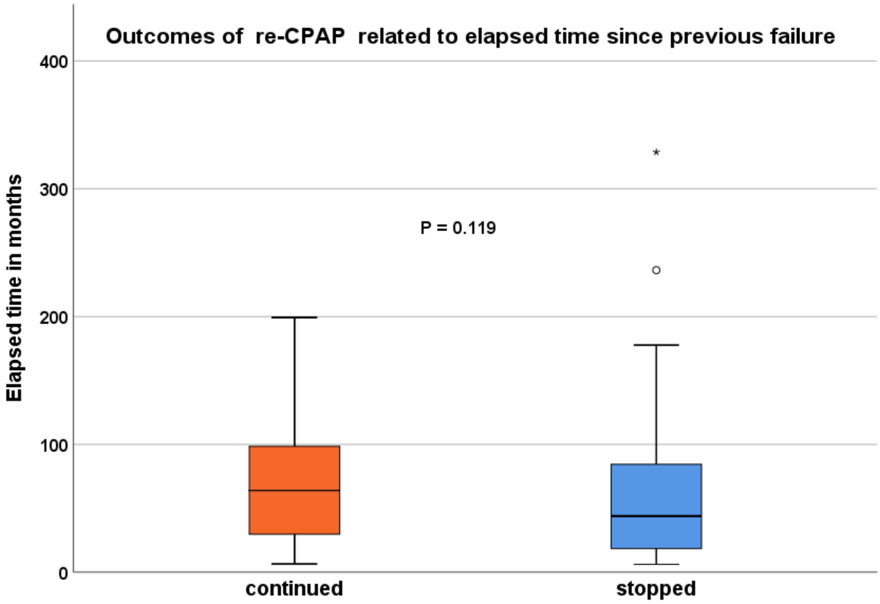

Figure 13. Outcomes of re-CPAP related to elapsed time.

The follow-up period in the re-CPAP group was mean 483 days (range 1 day to 11 years); the mean follow-up period of the control group was 357 days (P=0.011).

5.3.2 ADHERENCE TO CPAP THERAPY

In the re-CPAP group, 52% were still on CPAP therapy after a mean period of 483 days, and in the control group, 67% were still on CPAP after a mean period of 357 days. The follow-up period was not identical in the two groups. Therefore we re-calculated the CPAP success rate. We have previously shown that t 2.8% abandoned CPAP therapy yearly. We adjusted the follow-up period of the re-CPAP group to that of the control group and 66% of the patients in the control group stayed on CPAP (Figure 14)

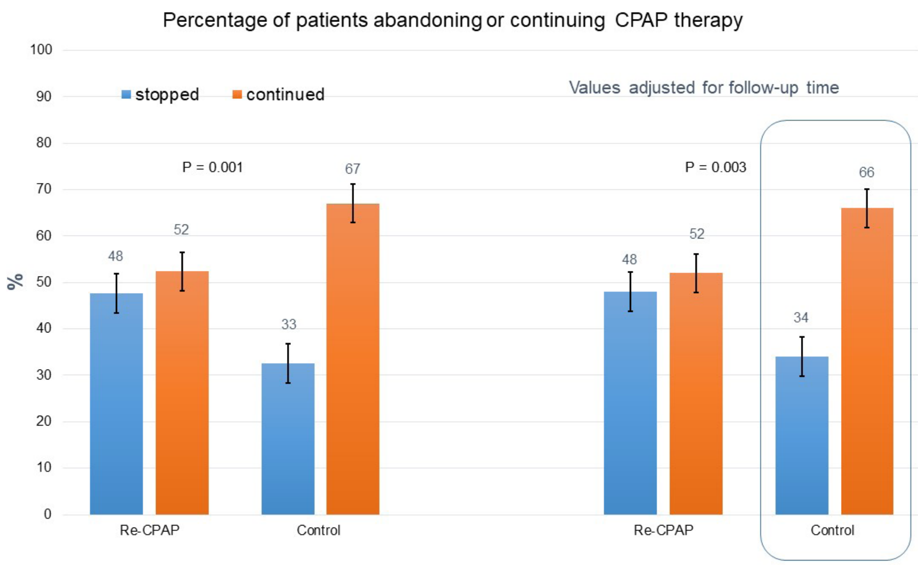

Figure 14. Percentage of subjects abandoning CPAP therapy in the re-CPAP and control group.

Values in the encircled figure were adjusted for the same follow-up period of the re-CPAP group.

The number of subjects still on CPAP after 1 year did not differ significantly between men in the re-CPAP group and men in the control group. This difference was statistically significant for women in the re-CPAP group (P=0.002)

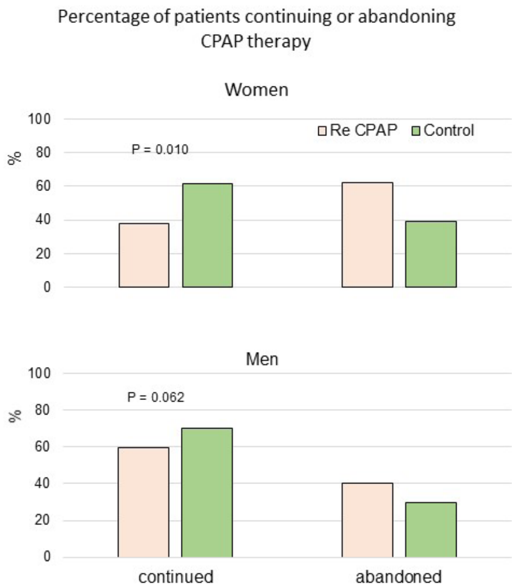

Figure 15. Percentage of women and men continuing or abandoning CPAP therapy after 1 year.

5.3.3 PREDICTIVE FACTORS FOR SUCCESS OF CPAP RE-INITIATION

CPAP re-initiation failed significantly more often in women than in men (62% vs. 40%, respectively; P=0.002). Women were 6.8 times less likely to continue CPAP therapy after a previous failure (likelihood ratio 6.7600) than men. As the women were older than the men, we explored whether gender difference was associated with age in women. CPAP therapy abandonment did not correlate with age (r=0.086; P=0.068). Subjects who stayed on CPAP therapy after re-initiation had significantly higher baseline ESS and ESS CPAP values (both in men and women) than in subjects who abandoned CPAP therapy. No differences in BMI or age were observed.

The mean CPAP daily use was significantly higher in the control group (3:58) than in the re-CPAP group (2:37) (P<0.0001).

6 DISCUSSION

In this thesis, we explored the reasons why patients initiated NR contact with our sleep unit (Study I), evaluated whether older patients succeeded with CPAP therapy as well as younger patients (Study II), and analyzed the probability of CPAP success after a previous failure (Study III).

Our primary finding was that patients contacted the sleep unit because they had disturbing symptoms during CPAP therapy. Moreover, we observed that patients aged >70 years had the same success rate of CPAP initiation as patients <50 years. Finally, we observed that previous failure in CPAP therapy constituted a risk factor for subsequent CPAP therapy failure and that CPAP acceptance after re-initiation was higher among men than women.

6.1 STUDY I

In our sleep unit, we follow up our patients who are prescribed CPAP routinely at 12- to 15-month cycles after their first year of therapy. One-third of our patients initiated NR contact for disturbing symptoms as the main reason, followed by issues associated with CPAP devices (despite routine follow up system). Somnolence has been shown to increase motor vehicle accidents and near misses (Ward et al., 2013). Our patients were instructed to contact the sleep unit if they become somnolent, or if their capacity for driving was decreased. We found that patients with emerging somnolence during CPAP therapy were 35 times more likely to contact our sleep unit than those without this symptom. The second major symptom was a sensation of suffocation at night. This may indicate insufficient device pressures, emergence of an extra air leak from the mask, or other causes. Management usually requires evaluation by a CPAP therapy specialist. The feeling of suffocation is an important symptom that patients want to get eliminate; immediate action is required if this symptom persists or emerges. Therefore, the patient cannot wait for the subsequent follow-up visit or contact.

The second major reason for NR contacts were problems related to CPAP devices or interfaces. Replacing the CPAP device resolves most of the device-related issues. As CPAP devices become relatively outdated after 5 years, replacing outdated devices increases the need for sleep unit contact and should be pre-planned. Problems related to CPAP interfaces are challenging to resolve; mask switching resolves mask-related issues in only 61% of cases (Bachour et al., 2016).

Adherence to CPAP therapy improves with the severity of sleep apnea (Kreivi et al., 2014) (Yetkin et al., 2008). During our follow-up period, the severity of OSA in the diagnostic sleep study before treatment initiation had no effect on the frequency of contacts during CPAP.

Daily adherence to CPAP therapy in our patients was good, with daily use of over 6 hours. A linear correlation between hours of CPAP use and reduction in health care utilization has been shown (Walter et al., 2017). We found no differences in CPAP use (hours) between the R and NR groups. The yearly abandoning rate was 3.7%. This is consistent with a previous report (van Zeller et al., 2013). The risk for treatment failure was considerable in patients in the NR group (yearly abandoning rate of 8.7%) but was only 1.3% in the R group. This was also reported by Bachour et al (Bachour et al., 2016), who showed a high rate of abandoning CPAP therapy (12.7%) in patients who switched their CPAP interface within 1 year. Kreivi et al. (Kreivi et al., 2016), who reported that nasal stuffiness during CPAP may lead to abandoning CPAP therapy, also arrived at the same conclusions. It seems logical that patients with more problems with CPAP would have a lower threshold for abandoning CPAP therapy than patients with few problems.

It has been suggested that the proliferation of information on the internet and consumerism leads patients to demand more expensive tests and treatments. However, our patients had justified reasons for their contacts, as these were associated with symptoms or the CPAP device. Seventy percent of our CPAP follow ups could be organized without face-to-face contact. This consistent with a previous study in which an annual follow up was more likely to lead to administrative intervention than face-to-face clinical intervention (Nannapaneni et al., 2014).

When medical resources are scarce, CPAP follow up should be intensified during the first year of CPAP therapy (van Zeller et al., 2013). The optimal follow-up interval remains unknown. A shorter interval between R contacts would reduce NR contacts but may increase health care costs. We showed that a 12- to 15-month follow-up interval was associated with 30% extra contacts, which seems considerable. Shortening the interval to 6 months would not reduce these extra contacts, as they occurred within the first months after the previous visit. On-demand follow up for patients with symptoms may be an alternative policy. Our results indicate that after the first year, CPAP treatment follow up could be targeted to patients with symptoms. Further studies are required to investigate this approach. These include a randomized study to assess two modes of CPAP follow up; a comparison of regular yearly follow up to follow up on demand; and a multi-center study from different countries that considers different insurance coverage and CPAP follow-up practice.

6.2 STUDY II

The main finding in Study II was that there was no difference in CPAP adherence at 1 year between senior OSA patients aged >70 years and junior patients aged <50 years. This has a clinical implication when evaluating therapy options for senior OSA patients. The number of patients who abandoned CPAP therapy in the senior group was not statistically different from that of the junior group.

Our conclusions are consistent with previous studies that recommended CPAP for senior patients with sleep apnea. Patients in this study used CPAP therapy 4 hours a day, whereas those reported by MacMillan et al used CPAP for 2 hours a day. Even with such low daily CPAP use, they reported reductions in ESS scores (McMillan ym., 2014, (Roche et al., 2014). Our mean ESS scores at baseline were not high and did not change with CPAP therapy. ESS scores do not correlate well with daytime hypersomnolence (Chervin & Aldrich, 1999) and may not predict CPAP success (McMillan et al., 2014). We have no explanation for these CPAP therapy outcomes. CPAP adherence is influenced by multiple factors, such as diagnostic methods, symptoms, psychological profile, CPAP initiation information, modalities, and follow up. Further studies are needed on senior patients.

Memory deficit may interfere with therapy adherence (Dolansky et al., 2016). Our patients had no significant memory loss as measured by MMSE. Mobility and physical tests did not influence CPAP adherence. This situation could have been different a decade ago, when CPAP devices and interfaces were bulky and cumbersome.

As AHI may increase with age (Boulos et al., 2019), the indication for CPAP therapy in elderly patients needs further studies to evaluate its effect on sleep apnea cardiovascular risks. Currently, the main goal of sleep apnea therapy in the elderly is to alleviate sleep apnea symptoms.

6.3 STUDY III

The main finding in Study III was that a previous failure in CPAP therapy constituted a risk factor for subsequent CPAP therapy failure. The failure rate of CPAP re-initiation was 48% in subjects with a prior failure. In contrast, in the control group with no previous CPAP experience, only 33% of subjects abandoned their therapy within 1 year.

No difference in CPAP adherence between women and men was observed after the original CPAP initiation, as reported previously (Aro et al., 2020). However, women failed CPAP re-initiation more often than men. This gender difference in adherence at re-initiation may be related to the way men and women approach CPAP therapy. Previous studies on relapses in smoking-cessation trials revealed that women were more likely to convert from former smokers to current smokers than men (Smith et al., 2016). Further studies are needed to evaluate the higher rate of CPAP re-initiation failure in women.

Snoring is considered a masculine trait in many cultures. Women with OSA use health care services more frequently than men. In women with OSA, the prevalence of depression and anxiety is higher than in men (Ye et al., 2009) (Cairns et al., 2016). We hypothesize that when women accept a CPAP trial, they are more motivated in their therapy at their first trial than men are. As women are more invested in the therapy than men, when accepting a CPAP trial for the first time, women have less effort to offer in a re-initiation.

The women were slightly older than the men in our study population, but this did not explain our results. Continuing CPAP therapy did not correlate with age, consistent with a previous study that also reported the success of CPAP therapy to be higher in subjects with a higher REI (Turnbull et al., 2016). Despite having a higher REI (i.e. more severe sleep apnea), staying on therapy was significantly lower in the re-CPAP group than in the control group.

While humidification is known to reduce the adverse effects of CPAP therapy (Kreivi et al., 2016), the impact of humidification on CPAP adherence is still controversial (D. Zhu et al., 2018). The first, more primitive humidification devices were costly and bulky and their use was restricted. Early progress in mask comfort or CPAP device characteristics did not considerably affect therapy adherence (Kreivi et al., 2016). We believe that interfaces are currently more suitable and comfortable, and this may affect CPAP outcomes.

A previous UPP has been reported as a risk factor for CPAP failure (Mortimore ym., 1996). The prevalence of UPPP was only 6.3% in this study and may have played a minor role in compromising the success of CPAP re-initiation.

A higher prevalence of comorbidities was observed in the re-CPAP group than in the control group, possibly because these subjects did not use any effective sleep apnea therapy for a period of time. The success of CPAP therapy after re-initiation was not influenced by the prevalence of comorbidities.

6.4 STRENGTHS

All three studies included a long follow-up period and a relatively large number of subjects. The diagnosis of OSA was made according to AASM criteria and the decision to initiate CPAP was made according to AASM criteria. CPAP initiation was performed according to AASM recommendations. As all three studies were conducted in the same hospital, the protocols of diagnosis, CPAP initiation, and follow up did not differ.

6.5 LIMITATIONS

All three studies had some common limitations. All studies were single-center studies and we cannot generalize our results to other centers. CPAP devices are provided free of charge for everyone regardless of working status by public health care in Finland (treatment is fully compensated by tax funding). As this is not the case everywhere, our results cannot be directly compared with countries with different health care and health insurance systems.

6.5.1 STUDY I

We did not collect data on the intervention from NR visits or the consequences of our interventions. Only subjects who had been treated for at least 1 year were included to exclude early dropouts from the study. The percentage of and reasons for NR contacts during the first year of treatment might be different.

6.5.2 STUDY II

Quality-of-life questionnaires were not used to evaluate the effect of CPAP therapy. We also did not measure the effect of CPAP therapy on reducing cardiovascular risks. The proportion of women was significantly higher in the senior group than in the junior group. This reflects the population of Finland, where the proportion of women increases with age.

6.5.3 STUDY III

We defined a minimum period of 6 months between discontinuing CPAP therapy and re-initiation for the inclusion of subjects with CPAP failure. This subject has not been previously studied and therefore this period was not supported by the literature. If the subject abandoned CPAP therapy and returned the CPAP device to the hospital, it was considered as CPAP failure.

In some cases, patients keep the device at home but rarely use it. CPAP therapy in Finland is fully compensated by public health insurance and this may suggest that patients are willing to re-initiate CPAP therapy with a lower degree of motivation than if the therapy was not fully insured. We did not report data on CPAP pressure levels or address all the potential causes of CPAP failure, such as complex sleep apnea. We did not evaluate other therapeutic ventilation modes. We also did not assess or report the subject's psychological profile, which may affect CPAP adherence.

7 CONCLUSIONS

According to the aims of the study, the main results were as follows:

- Our yearly routine follow up for CPAP patients did not prevent extra visits to our sleep unit between routine appointments, as one-third of our patients contacted our sleep unit mainly because of persistent or emerging symptoms. The routine CPAP follow up with a regular interval may still be necessary to ensure good CPAP adherence, and on-demand service remains necessary to resolve emerging problems in between routine visits.
- Senior CPAP patients aged >70 years managed to use their CPAP device as well as younger patients aged <50 years despite other problems related to advanced age, such as reduced physical dexterity.
- We showed that it is useful to re-initiate CPAP therapy after previous failure as every second patient succeeded. However, as the success of CPAP re-initiation was lower in women than in men, women may require closer follow up and further interventions to adhere to CPAP therapy.

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