CPAP-MAD Combination Therapy For CPAP Intolerant Patients With Moderate to Severe OSA

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CPAP-MAD COMBINATION THERAPY FOR CPAP INTOLERANT PATIENTS WITH MODERATE TO SEVERE OSA

By

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A THESIS

Presented to the Faculty of
The Graduate College in the University of Nebraska
In Partial Fulfillment of Requirements
For the Degree of Master of Science

Medical Sciences Interdepartmental Area
Oral Biology

Under the Supervision of Associate Professor Thyagaseely Sheela Premaraj

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Omaha, Nebraska

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The treatment of obstructive sleep apnea (OSA) allows for a multidisciplinary approach between dentistry and medicine. Continuous positive airway pressure (CPAP) is the gold standard for OSA treatment, but the non-adherence rates are high. The mandibular advancement device (MAD) has a higher acceptance rate than the CPAP, however the efficacy is much lower in cases of moderate to severe OSA. This thesis attempted to evaluate if there was a change in compliance when a MAD was added as a combination therapy to moderate to severe OSA subjects that were currently non-compliant with their CPAP. In addition, the change in air pressure, Epworth Sleepiness Scale (ESS) scores, Apnea-Hypopnea Index (AHI) scores, and mask leaks were examined. Combination therapy showed a statistical significant increase in compliance (+23.1%) and decrease in ESS scores (-1.4) compared to CPAP therapy alone. There was also a decrease in air pressure (-0.1846 cmH₂O), AHI scores (-0.07), and mask leaks (-0.8538 leaks/min), but these decreases were not significant.
# TABLE OF CONTENTS

ACKNOWLEDGEMENTS........................................................................................................... i

ABSTRACT ................................................................................................................................. ii

TABLE OF CONTENTS.............................................................................................................. iii

LIST OF FIGURES .................................................................................................................... v

LIST OF TABLES ....................................................................................................................... vii

CHAPTER 1: INTRODUCTION .................................................................................................. 1

CHAPTER 2: LITERATURE REVIEW ......................................................................................... 3

  2.1 Sleep Disordered Breathing ......................................................................................... 3
  2.2 Obstructive Sleep Apnea .............................................................................................. 3
  2.3 Prevalence of OSA ....................................................................................................... 4
  2.4 Diagnosis of OSA ......................................................................................................... 4
  2.5 Health and OSA .......................................................................................................... 6
  2.6 Treatment Availibities of OSA .................................................................................... 7
    2.6.1 Continuous Positive Airway Pressure Treatment of OSA ...................................... 8
    2.6.2 Oral Appliances for Treatment of OSA ................................................................. 9
    2.6.3 Other Non-Surgical Treatments for OSA ............................................................. 10
    2.6.4 Surgical Treatment of OSA .................................................................................. 12

CHAPTER 3: STUDY AIMS .................................................................................................... 19

  3.1. Statement of the Problem ........................................................................................... 19
  3.2. Null Hypothesis ......................................................................................................... 19
  3.3. Specific aims of current study .................................................................................. 19

CHAPTER 4: MATERIALS & METHODS ............................................................................ 20

  4.1 Subject Acquisition ..................................................................................................... 20
4.2 CPAP Protocol ............................................................................................................. 20
4.3 MAD Protocol ............................................................................................................ 21
4.4 Subjective Assessment ............................................................................................... 21
4.5 Statistical Analysis ................................................................................................... 22

CHAPTER 5: RESULTS ............................................................................................................. 34

5.1 Patient Acquisition .................................................................................................. 34
5.2 Demographics .......................................................................................................... 34
5.3 Changes in Recorded Parameters ............................................................................. 34
5.4 Compliance Percentages ......................................................................................... 34
5.5 CPAP Air Pressure Levels ....................................................................................... 35
5.6. Epworth Sleepiness Scale ....................................................................................... 35
5.7. AHI Values ............................................................................................................. 35
5.8. Air Leaks with CPAP ............................................................................................. 36

CHAPTER 6: DISCUSSION ..................................................................................................... 48

6.1. Relevance of Study ................................................................................................. 48
6.2. Compliance Percentages ....................................................................................... 48
6.3. CPAP Air Pressure Levels ..................................................................................... 49
6.4. Epworth Sleepiness Scale ..................................................................................... 50
6.5. AHI Values ........................................................................................................... 51
6.6. Air Leaks with CPAP ............................................................................................ 52
6.7. Study Limitations and Future Studies .................................................................... 52

CHAPTER 7: CONCLUSION ................................................................................................. 55

BIBLIOGRAPHY .................................................................................................................. 56

Appendix A: Experimental Data ...................................................................................... 68
Appendix B: t-Test Data .................................................................................................... 72
LIST OF FIGURES

Figure 2.1 Polygraph reading from a patient with OSA. .......................................................... 15
Figure 2.2 Flow chart representing a pathway for patients to be recommended for portable
monitoring (PM) or polysomnography. .................................................................................. 16
Figure 2.3 Photographs of the different types of CPAP masks.............................................. 17
Figure 2.4 Lateral, anterior, and posterior views of the upper airway before (a) and during (b)
mandibular advancement device therapy........................................................................... 18
Figure 4.1. Inclusion and exclusion criteria for subject recruitment.. ................................. 23
Figure 4.2. Recruitment letter sent out to all prospective subjects. ..................................... 24
Figure 4.3. ResMed AirView summary..................................................................................... 25
Figure 4.4. George gauge........................................................................................................ 26
Figure 4.5. George gauge being used to record a subject’s anteroposterior mandibular range of
motion........................................................................................................................................ 27
Figure 4.6. George gauge bite forks....................................................................................... 28
Figure 4.7. Herbst style mandibular advancement device.. ..................................................... 29
Figure 4.8. Accu-Fit material in the Herbst style MAD......................................................... 30
Figure 4.9. Elastics worn on the Herbst style MAD................................................................ 31
Figure 4.10. MAD appliance advanced to 70% of full anteroposterior range. ..................... 32
Figure 4.11. Epworth Sleepiness Scale Survey....................................................................... 33
Figure 5.1. Pre- and post-treatment mean compliance percentage........................................ 38
Figure 5.2. A box-plot diagram comparing compliance percentage pre-and post-treatment........ 39
Figure 5.3. Pre- and post-treatment 95\textsuperscript{th} percentile air pressure.......................... 40
Figure 5.4. A box-plot diagram comparing 95\textsuperscript{th} percentile air pressure pre- and post-treatment . 41
Figure 5.5. Pre- and post-treatment mean ESS scores............................................................ 42
Figure 5.6. A box-plot diagram comparing ESS scores pre- and post-treatment...................... 43
Figure 5.7. Pre- and post-treatment mean AHI values.................................................................44

Figure 5.8. A box-plot diagram comparing AHI values pre- and post-treatment.......................45

Figure 5.9. Pre- and post-treatment mean leaks........................................................................46

Figure 5.10. A box-plot diagram comparing leaks pre- and post-treatment.....................................47
LIST OF TABLES

Table 5.1. Mean changes for all subjects. ................................................................. 37
CHAPTER 1: INTRODUCTION

The treatment of obstructive sleep apnea (OSA) allows for a true multidisciplinary approach between dentistry and medicine. OSA results from a collapse in the upper airway, which blocks oxygen intake despite continued respiratory effort (Leinum et al., 2009). Patients suffering from OSA experience increased morbidity such as heart failure, cerebrovascular insult, impaired neuro-cognition, and poorly controlled mood disorder (Stansbury & Strollo, 2015).

Treatment of OSA was not a common practice in the dental profession until recently. The use of the mandibular advancement device (MAD) for the treatment of OSA brought the treatment into the dental field. A MAD is often considered as a first line of treatment in patients with mild to moderate sleep apnea (Serra-Torres et al., 2016). However, a MAD is also used as an alternative in patients exhibiting suboptimal compliance with continuous positive airway pressure (CPAP) therapy due to CPAP intolerance (Kushida et al., 2006). The most common complaints associated with CPAP wear were the discomfort of the apparatus and the intolerance to air pressure (Gay et al., 2006). Improvements in CPAP and mask designs have changed tremendously to attempt to improve compliance. Although there were unwanted effects to the dentition associated with the MAD, patients subjectively prefer to use the MAD for treatment of sleep apnea instead of the CPAP (Hoffstein, 2007).

The MAD works by increasing the retropalatal and retrolingual spaces while decreasing the length of the soft palate and the angle of mouth opening (Lee et al., 2009). The drawback of the MAD is its decreased effectiveness in improving AHI scores when compared to the CPAP (Gagnadoux et al., 2009). One study showed that MADs reduced the average initial apnea-hypopnea index (AHI) by 42% while the more efficient CPAP reduced AHI scores by 75% (Gay et al., 2006). An additional study showed similar results of 42.8% AHI reduction with the MAD versus 73.2% with the CPAP (Ramar et al., 2015). Results showed that the best use of the MAD is in patients with a mild-to-moderate sleep apnea (Gay et al., 2006).
Clinicians are faced with the dilemma of choosing between the CPAP, which is highly effective but has suboptimal compliance, and the MAD, which is less effective but has greater compliance. The suboptimal compliance to CPAP undermines its effectiveness in treating OSA. The most critical time of the treatment is right after the patient is given their appliance, whether it’s a MAD or CPAP. Time is needed to adapt to the appliance due to the possible physical interferences in sleep and jaw function. The extent to which a patient will use an appliance is determined in the first month of treatment (Kribbs et al., 1993). While the CPAP and MAD have been around for years, it was only recently that a combination of the two treatments was studied. A pilot study, which looked at the efficacy of combination therapy, found that the combination treatment reduced the optimal CPAP pressure by 36% and decreased the apnea hypopnea index (AHI) score by 86% versus MAD alone. The subjects in this study also tolerated the combination therapy very well (El-Solh et al., 2011). Our study is the first to evaluate the efficacy of combination therapy with subjects diagnosed with moderate to severe sleep apnea. In addition, all subjects in our study used an automated CPAP, which recorded the parameters including air pressure, duration of use, AHI value, and mask leaks while in use.

With the continued problem of suboptimal CPAP compliance in OSA treatment, combination CPAP-MAD therapy offers a promising alternative. This study aims to improve the body of scientific knowledge regarding the efficacy and compliance of the CPAP-MAD combination therapy. If the combination therapy is shown to be highly effective and well tolerated in treating OSA, this novel multidisciplinary approach can vastly improve the quality of life for numerous patients.
2.1 Sleep Disordered Breathing

Sleep disordered breathing (SDB) is a term that is used to describe several sleep-related abnormalities, including obstructive sleep apnea (OSA), central sleep apnea, and hypoventilation. SDB is defined by sporadic periods of apnea, hypopnea, or respiratory effort-related arousals (RERAs) (Panossian & Daley, 2013). OSA syndromes include those where there is a blockage of the airway causing increased breathing effort and inadequate ventilation. Central sleep apnea (CSA) has an unknown cause but is defined by repeated episodes of cessation of breathing during sleep without associated ventilatory effort (Cowie, 2017). CSA is often associated with heart failure, but it has also been seen in patients with stroke, renal failure or opiate use (Cowie, 2017). Hypoventilation syndromes include several disorders, but all are related to an elevation of arterial carbon dioxide tension or reduced oxygen saturation during sleep (Thorpy, 2012). There is a subtype of SDB called upper airway resistance syndrome (UARS) where the patient primarily suffers from RERAs, without exhibiting significant oxygen desaturations or apneas and hypopneas. The respiratory issues that happen in SDB are often temporary and self-limited (Panossian & Daley, 2013). OSA is the most common disease within SDB (Cowie, 2017).

2.2 Obstructive Sleep Apnea

Obstructive sleep apnea results from the upper airway collapsing during sleep, which blocks oxygen intake despite continued respiratory effort (Leinum et al., 2009). A systematic review suggested that the most important anatomical characteristic of the upper airway related to the pathogenesis of OSA is a small cross-sectional area (Chen et al., 2016). The airway blockage is often associated with cortical microarousals and oxygen desaturation, which in turn leads to sleep disruption and increased sympathetic neural activity (Caples et al., 2005). The cost burden of OSA and its comorbidities is extremely high. In 2015, it was estimated that the cost burden for the diagnosis and treatment of OSA in the United States was 12.4 billion dollars. Even more staggering is the cost burden of undiagnosed OSA in the United States; in 2015 it was 149.6
billion dollars. This number factored in comorbidities and mental health, motor vehicle accidents, workplace accidents and lost productivity (Frost and Sullivan, 2016).

2.3 Prevalence of OSA

The prevalence of obstructive sleep apnea has seen a substantial increase in the last 20 years. One study found the prevalence of moderate to severe OSA is 10% for men 30-49 years old, 17% for men 50-70 years old, 3% for women 30-49 years old, and 9% for women 50-70 years old (Peppard et al., 2013). Over the 20 years prior to this study, these prevalence numbers have increased anywhere from 14% to 55% depending on the age group (Peppard et al., 2013). Across the world the prevalence of OSA ranges from 6% to 49% (Senaratna et al., 2017). Increased prevalence of OSA may be due to higher rates of obesity and the increased testing for OSA (Kunisaki et al., 2016). The ratio of men to women with clinically significant sleep apnea (AHI ≥10 with daytime symptoms) was 3.3:1 (Bixler et al., 2001). Risk factors for OSA include old age, male gender, African-American or Asian ethnicity, short neck, retrognathia, obesity, and heart failure (Cowie, 2017). While OSA is often considered to be a disease affecting adults, the prevalence of childhood OSA is on the rise as well. OSA affects 1% to 6% of all children and up to 59% of obese children (Schwengel et al., 2014). OSA is the most common respiratory disorder to be acknowledged as a serious public health problem (Ahrens et al., 2011).

2.4 Diagnosis of OSA

The gold standard for diagnosing OSA is the overnight polysomnogram (PSG) (Lee et al., 2008). The PSG includes several physiologic recordings including electroencephalogram, electrooculogram, electrocardiogram, chin and leg electromyograms, body position, finger pulse oximetry, measurements of airflow, and measurements of thoracic and abdominal respiratory effort (Lee et al., 2008). In the traditional model, primary care providers refer patients with suspected sleep apnea to a sleep specialist physician. The patient’s first visit with the specialist includes a consultation, followed by an appointment scheduled for an in-lab PSG that may or may not include a Continuous Positive Airway Pressure (CPAP) titration. The problems with this
traditional model are expense and ineffectiveness for evaluation and treatment of patients at high risk of OSA (Phillips et al., 2015). Some newer models use at home sleep testing (HST) for the diagnosis, followed by administration of an auto-titrating CPAP device, which automatically adjusts the pressures to keep the airway patent during sleep (Collop et al., 2007, Morgenthaler et al., 2008). The HST usually monitors oxygen saturation, nasal airflow and chest and abdominal movement (figure 2.1) (Cowie, 2017). One study found that evidence showed the HST with auto-titratable CPAP provided similar results to fixed pressure CPAPs titrated from an in lab PSG (Kunisaki et al., 2016). The Portable Monitoring Task Force, appointed by the American Academy of Sleep Medicine (AASM), says that the HST should only be used in conjunction with a comprehensive sleep evaluation from a board certified sleep specialist (BCSS) (Collop et al., 2007). Figure 2.2 depicts a flow chart to represent a pathway for patients to be considered for portable device monitoring (PM). The taskforce says HST should not be used for diagnosis in patients with significant comorbid medical conditions, patients with other sleep disorders, or as general screening of the asymptomatic population (Collop et al., 2007). Both PSG and HST use the same type of scoring for the OSA diagnosis. The presence and severity of the sleep apnea is determined through a score on the apnea-hypopnea index (AHI). The AHI defines the average number of apneas and/or hypopneas a patient has per hour (Lee et al., 2008). An apnea is defined as a reduction in airflow greater than or equal to 90% of baseline for at least 10 seconds, while hypopnea is defined as a reduction in airflow greater than or equal to 30% of baseline for at least 10 seconds that is associated with a 4% reduction in oxygen saturation (Stansbury & Strollo, 2015). In adults, if the patient has an AHI less than 5, it is considered normal. If a patient has an AHI above 5 but below 15, it is considered as having mild sleep apnea. Moderate sleep apnea is defined as an AHI above 15 but below 30, while severe sleep apnea is any AHI score over 30 (Lee et al., 2008). Several subjective tests can also be administered to measure daytime sleepiness. Many of these subjective tests include questionnaires to establish whether the patient suffers from daytime sleepiness (Lee et al., 2008). One study looked at three OSA screening
questionnaires (SACS, Berlin and STOP-Bang) and the results showed that none of the three had adequate sensitivity and specificity to be sufficiently reliable in a clinical setting to rule in or to rule out OSA (Pereira et al., 2013). The accuracy and reliability of the questionnaires varies depending on the diagnostic AHI used. When an AHI threshold of 5 events/hour was used, the questionnaires showed a higher sensitivity and specificity (Chung et al., 2008, Sharma et al., 2006). Out of four screening questionnaires (Berlin, STOP-BANG, STOP, and Epworth Sleepiness Scale (ESS)) the STOP-BANG was shown to be the most accurate tool for detecting mild, moderate, and severe OSA (Chiu et al., 2016).

2.5 Health and OSA

Deleterious effects of OSA are due to airway obstruction, associated activation of the sympathetic nervous system, hemodynamic issues, and sleep disruption (Leinum et al., 2009). People suffering from untreated OSA have exhibited increased inflammation with elevated levels of inflammatory mediators such as tumor necrosis factor-alpha, interleukin 1β, interleukin 6, ICAM, coagulation factors (factor VIII), and C-reactive protein (Kokturk et al., 2005, Minoguchi et al., 2004, Ohga et al., 2003, Ryan et al., 2005, Yokoe et al., 2003). Untreated OSA has been associated with cardiovascular disease, cancer, chronic obstructive pulmonary disease (COPD), stroke, and type II diabetes (Leinum et al., 2009). OSA as a risk factor for arterial hypertension has been well documented. There is a strong bi-directional relationship between OSA and arterial hypertension, with about 30-40% of patients with arterial hypertension exhibiting clinically relevant OSA and about 50% of patients with OSA having arterial hypertension (Somers et al., 2008). Prevalence of arterial hypertension increases with the severity of OSA (Hla et al., 1994). OSA is associated with an increased risk for congestive heart failure in middle-aged and older men (Gottlieb et al., 2010).

Over half of patients with paroxysmal or persistent atrial fibrillation (AF) have exemplified SDB (Bitter et al., 2010). Severe OSA has been shown to increase the risk of AF,
ventricular premature beats, non-sustained ventricular tachycardia, and nocturnal sudden cardiac
death (Mehra et al., 2006).

Prevalence of coronary artery disease (CAD) is much higher in patients with OSA than
the general population (Andreas et al., 1996). Men have a 68% higher chance of developing CAD
when they suffer from severe sleep apnea (Gottlieb et al., 2010). Patients who have suffered a
stroke often have OSA, and the prevalence of this occurrence is 71% based on case-controlled
studies (Arzt et al., 2005). Not only is there a correlation between OSA and the risk of stroke, but
OSA is also an independent risk factor for a subsequent stroke (Dziewas et al., 2005).

With obesity being one of the main risk factors for OSA, it’s not surprising that there is a
high prevalence of OSA patients with type 2 diabetes mellitus. The Sleep Heart Health Study
showed that OSA was associated with impaired fasting glucose, glucose intolerance, and type 2
diabetes mellitus (Punjabi et al., 2004).

While OSA doesn’t cause COPD, it can make the problems of COPD much worse. OSA
may exacerbate COPD through vagally-mediated bronchoconstriction and an increase in resistive
load in the lower airways due to high negative intrathoracic pressure (Ioachimescu & Teodorescu,
2013). Patients with COPD and OSA suffer from high rates of morbidity and mortality as well as
a decreased quality of life (Shaya et al., 2009).

The association between OSA and cancer is hypothesized to be a direct result of
repetitive hypoxia (Leinum et al., 2009). When cancer cells are subjected to repetitive hypoxia in
vitro, instantaneous angiogenesis occurs which in turn causes a proliferation of blood vessels and
cancer cells (Harris, 2002). In animal experiments, intermittent hypoxia has been linked with
increased tumor cell proliferation and metastases (Almendros et al., 2014).

2.6 Treatment Availability of OSA

Treatment of OSA requires a multidisciplinary approach that includes the medical and
dental fields. The American Academy of Sleep Medicine (AASM) and the American Academy of
Dental Sleep Medicine (AADSM) have collaborated to develop treatment guidelines. Their meta-
analysis showed that there was no significant difference between oral appliances and Continuous Positive Airway Pressure (CPAP) in the percentage of mild OSA patients achieving their target AHI (Ramar et al., 2015). When it came to patients with moderate to severe OSA, the chances of reaching the target AHI were significantly greater with the CPAP than the oral appliance (Ramar et al., 2015). The academies recommend that sleep physicians consider prescribing an oral appliance for adult OSA patients that aren’t tolerant of CPAP therapy or prefer an alternative approach (Ramar et al., 2015).

2.6.1 Continuous Positive Airway Pressure Treatment of OSA

The use of Continuous Positive Airway Pressure (CPAP) is considered the gold standard for OSA treatment (Spicuzza et al., 2015); however, CPAP compliance is one of the biggest challenges. CPAP users have shown average non-adherence rates of 36% (Rotenberg et al., 2016). Patient education, health and quality-of-life benefits, proper mask selection, and supportive management of adverse effects are all ways to increase adherence (Cowie, 2017). Common side effects of CPAP usage are mask leakage, mask pressure, dry mouth, nasal stuffiness, claustrophobia, and difficulties exhaling (Brostrom et al., 2010). Nasal obstruction, dry mouth and an increased number of awakenings were side effects that were found to lower objective adherence (Ulander et al., 2014). Patients that experienced side effects or anxiety in the first 2 weeks of CPAP treatment were more likely to stop using the CPAP in the first year (Ulander et al., 2014). Also, patients that reported CPAP problems on the first night were less likely to maintain compliance (Lewis et al., 2004).

Initially, CPAP therapy was delivered at a fixed pressure that was determined during an overnight titration study (Vennelle et al., 2010). More recently, the CPAP therapy is often prescribed using a device that can vary the pressure delivered. The advantages of these variable pressure CPAPs are the ability to adjust the pressure based on factors such as posture, alcohol, nasal congestion, weight change, and older age (Vennelle et al., 2010). In one randomized controlled study comparing fixed versus variable pressure, results showed slightly improved ESS
scores and CPAP use with variable pressure CPAP. (Vennelle et al., 2010). The ESS score difference was 0.6 and the difference in average CPAP use was 0.2 h/night (Vennelle et al., 2010). There were no significant differences in objective sleepiness, vigilance, quality of life or nocturnal symptoms (Vennelle et al., 2010). Patients also had no preference between the two methods (Vennelle et al., 2010).

Another point of variance between CPAPs is the mask selection. The four types of masks used are the nasal mask, the oro-nasal mask, the nasal pillows and the oral masks (figure 2.3). The nasal pillows have a higher initial acceptance, and they have been proven to be effective even at higher pressures (>12 cmH₂O) (Zhu et al., 2013). Oro-nasal masks often require higher CPAP air pressure levels and are associated with a higher residual AHI and lower compliance rate (Bettinzoli et al., 2014). Oral masks have been shown to be effective because they hold the tongue in place with a tongue guide, however, their acceptance is very low (Andrade et al., 2014). Nasal masks and nasal pillows are recommended as the first choice, but if oro-nasal masks are prescribed they need to be monitored closely due to the risk of failure (Andrade et al., 2014).

2.6.2 Oral Appliances for Treatment of OSA

Oral appliances for treating OSA include mandibular advancement devices, tongue retaining devices, and soft palate lifters (Schmidt-Nowara et al., 1995). MADs (mandibular advancement devices) are the most commonly used oral appliance in OSA therapy (Schmidt-Nowara et al., 1995). The American Academy of Sleep Medicine suggested the use of oral appliances in patients suffering from snoring, mild-to-moderate OSA, or severe OSA if CPAP has failed (Kushida et al., 2006). MADs are used on average 1.1 hours a night more than CPAPs (Schwartz et al., 2017).

A CBCT study showed that a mandibular advancement device increased the anteroposterior dimension at the smallest cross-section of the airway by an average of 3.02 mm and in the transverse dimension by an average of 4.27 mm (figure 2.4) (Shete & Bhad, 2017). Another study showed that airway collapse occurs in the anteroposterior direction when a patient
is in centric occlusion, but when the mandible is advanced the airway collapse is observed in the transverse dimension (Isono et al., 1997).

Several types of mandibular advancement appliances have been created for OSA treatment. Some appliances have a fixed advancement, where the distance of advancement can’t be adjusted, whereas others are adjustable. The Herbst appliance, an adjustable MAD, has been shown to provide better results for daytime sleepiness (Itzhaki et al., 2007). One study showed that adjustable appliances resulted in a greater reduction in AHI and improvements in ESS compared to fixed appliances (Lettieri et al., 2011). Prefabricated appliances have been shown to be less effective than custom-made appliances (Vanderveken et al., 2008).

MADs have a variety of side effects with many of them being only temporary. Side effects were reported in a little over 50% of patients and include jaw discomfort, tooth tenderness, excessive salivation and occlusion changes (Mehta et al., 2001). The compliance rates for MAD are higher than those for CPAPs, and MADs are often preferred by patients when given the choice (Gagnadoux et al., 2009, Tan et al., 2002). A pilot study investigating the use of combination therapy of CPAP with a MAD showed that the pressure needed to reduce obstructive events was reduced. Daytime sleepiness was also reduced with the combination therapy (El-Solh et al., 2011).

Another form of oral appliance is a tongue retaining device (TRD). TRDs work by suctioning the tongue into an anterior bulb, which moves the tongue forward and widens the upper airway dimensions (Randerath et al., 2011). A randomized study showed similar AHI reduction in mild to moderate OSA patients using TRDs and MADs; however, patients preferred to use the MAD (Deane et al., 2009).

2.6.3 Other Non-Surgical Treatments for OSA

The least invasive treatment modality for OSA is lifestyle change. Weight loss is one of the most effective methods of reducing AHI scores. A 10% weight loss has been predicted to
have a 26% decrease in AHI score (Peppard et al., 2000). A meta-analysis showed that weight loss programs resulted in a mean reduction in AHI of 6 events/hour (Araghi et al., 2013).

Positional therapy can also be effective for patients that sleep on their backs. The use of a wedge or sewing items on the back of shirts to make it uncomfortable to sleep on your back are two ways to help break the supine sleeping habit (Cowie, 2017). Alcohol, sedatives, narcotics and muscle relaxants should be avoided due to the increased chance of upper airway muscle tone reduction (Cowie, 2017).

Myofunctional therapy has been prescribed as a treatment for OSA in some patients. The therapy involves exercising the soft palate, tongue, and facial muscles and addressing stomatognathic functions. Soft palate exercises were pronouncing a vowel intermittently (isotonic exercise) and continuously (isometric exercise) daily for three minutes. The tongue exercises included brushing the super and lateral surfaces of the tongue while the tongue is positioned on the floor of the mouth (five times of each movement, three times a day), placing the tip of the tongue against the front of the palate and sliding it backwards (three minutes a day), forced tongue sucking upward against the palate (three minutes a day), and forcing the back of the tongue against the floor of the mouth while keeping the tip of the tongue in contact with the lower incisors (three minutes a day). The facial muscle exercises included orbicularis oris muscle pressure, suction movements contracting only the buccinators, recruitment of the buccinator muscles against a finger in the oral cavity pressing the muscle outward, alternated elevation of the mouth angle muscle, and lateral jaw movements. The stomatognathic function exercises included forced nasal inspiration and oral expiration in conjunction with saying open vowels, balloon inflation with prolonged nasal inspiration and forced mouth expiration, and bilateral chewing of bread using the tongue in the palate with closed teeth and no perioral contraction (Guimaraes et al., 2009). A meta-analysis showed that myofunctional therapy reduced the AHI score in adult patients by 50% and in children by 62% (Camacho et al., 2015).
In some OSA cases, drug therapies have been used. These drugs aim to treat the OSA by increasing respiratory drive, changing sleep structure, increasing upper airway muscle tone, changing respiratory and cardiovascular reflexes, and/or reducing surface forces that encourage closure of the upper airway (Randerath et al., 2011). Acetazolamide was administered to inhibit carbonic anhydrase, which produced metabolic acidosis that increased respiratory drive (Whyte et al., 1988). Drugs that facilitate an increase in serotonin have been evaluated for their possible improvement of REM sleep, but they have all been shown to be ineffective for the treatment of OSA (Brownell et al., 1982, Kraiczi et al., 1999, Marshall et al., 2008). One study showed a significant reduction in AHI using cholinergic agonists, but it is still not recommended due to the lack of long-term follow-up (Hedner et al., 2003). Drug therapies that focus on decreasing nasal obstruction using nasal steroids have been scarcely studied in adults, but have shown success in treating children with upper airway obstruction due to adenotonsillar hypertrophy. One study in adults showed a modest decrease in AHI score, however, no improvements in oxygenation indices, sleep quality or snoring noise were observed (Kiely et al., 2004).

2.6.4 Surgical Treatment of OSA

Nasal obstruction has been demonstrated to cause an increased number of arousals, more frequent sleep stage changes, and/or an increase in the number of apneas and hypopneas (Lavie et al., 1983). A review of evidence showed that nasal surgery as a single intervention is not recommended for treating OSA, but it is recommended for reducing high therapeutic CPAP pressures that are caused by nasal obstruction (Randerath et al., 2011).

Tonsillectomy and tonsillotomy are additional surgical approaches being recommended for the treatment of OSA. The reasoning behind this is the upper airway anatomical structures correlating with OSA include an enlarged tongue, thick soft palate, long and thick uvula, and/or hypertrophic tonsils (Randerath et al., 2011). Evidence shows that the only time tonsillectomy is recommended as a single intervention is in the presence of tonsillar hypertrophy. Adenotonsillectomy is recommended as treatment for children with OSA if there is adenotonsillar
hypertrophy (Randerath et al., 2011). In order to decrease the morbidity associated with surgical tonsillectomy, radiofrequency tonsil reduction has been introduced (Friedman et al., 2003).

In the past, one of the most common surgical treatments for OSA was uvulopalatopharyngoplasty (UPPP). UPPP works by increasing the retropalatal airway through trimming and reorienting the posterior and anterior lateral pharyngeal pillars, as well as excising the uvula and posterior soft palate (Won et al., 2008). The issue is that in OSA the upper airway can collapse at multiple levels and UPPP is only successful when the problem is limited to the retropalatal area. This is rarely the case in severe sleep apneic patients (Sher, 2002). Although UPPP may appear beneficial in the short-term, the efficacy diminishes over time, and overall the procedure is less effective than the use of an oral appliance (Walker-Engstrom et al., 2002). A newer approach to the UPPP is a uvulopalatal flap. Tonsillectomies are performed with each procedure. The mucosa, submucosa with glands, and fat on the lingual surface of the uvula is first removed. The uvular tip is then amputated and the uvula is reflected back toward the soft palate and fixed with sutures (Powell et al., 1996). The uvulopalatal flap achieves the same results as the UPPP, but there is less postoperative discomfort, less risk of developing velopalatal insufficiency, and fewer complaints of a thickened foreign body sensation (Neruntarat, 2011). The uvulopalatal flap shows significant decreases between short-term and long-term results, but has an approximately 50% long-term success rate (Neruntarat, 2011). Uvulopalatal flaps can be recommended for treating OSA patients that have a palatal obstruction (Randerath et al., 2011).

One surgical approach that is as effective as CPAP therapy in patients with OSA is the maxillomandibular advancement (MMA) (Randerath et al., 2011). This surgery requires an advancement of the maxilla and mandible 10-15mm when there is no maxillomandibular abnormality. The surgery enlarges the retrolingual and retropalatal airway (Hochban et al., 1994). The main disadvantage of the MMA is the plethora of side effects that can accompany the surgery. These complications include cardiac arrest without sequellae and dysrhythmia, local infection, perforation of the palate, maxillary pseudoarthrosis, malocclusion, and dysgnathia (Li
et al., 2000, Riley et al., 1989, Waite et al., 1989). In addition, patients develop transient anesthesia of the cheek and chin. Residual neurosensitive deficit was the most common complication, but this didn’t affect the patient’s view on their quality of life (Randerath et al., 2011).

Another surgical approach to treat OSA is hypoglossal nerve stimulation. An implantable device is placed to stimulate the hypoglossal nerve in response to apnea or hypopnea. The mechanism of action is a unilateral stimulation of the hypoglossal nerve to activate the genioglossus muscle. The activated genioglossus muscle causes an anterior displacement of the tongue and dilation of the pharynx, which leads to a relief of the airway obstruction (Schwartz et al., 2001). One study showed a mean AHI reduction of 68% over 12 months using this therapy (Strollo et al., 2014). Another study observed that hypoglossal nerve stimulation demonstrated the adverse effect of patient arousal due to muscle contraction (Oliven et al., 2007).
Fig 2.1 Polygraph reading from a patient with OSA. The top panel is noise related to snoring, second panel is nasal air flow, third panel is thoracic and abdominal wall movement, fourth panel is arterial oxygen saturation, and the fifth panel is pulse rate. (Cowie, 2017)
Fig 2.2 Flow chart representing a pathway for patients to be recommended for portable monitoring (PM) or polysomnography (PSG). Good candidates for PM should have moderate to high risk for OSA, no comorbid medical conditions and no comorbid sleep disorders. (BCSS = Board Certified Sleep Specialist) (Collop, et al., 2007)
Fig 2.3 Photographs of the different types of CPAP masks. A: nasal mask, B: oronasal mask, C: nasal pillows, D: oral mask (Andrade et al., 2014)
Fig 2.4 Lateral, anterior, and posterior views of the upper airway before (a) and during (b) mandibular advancement device therapy (Shete & Bhad, 2017).
CHAPTER 3: STUDY AIMS

3.1. Statement of the Problem

Treatment of obstructive sleep apnea with CPAP can be highly ineffective due to low compliance rates with CPAP wear. MADs have become an alternative treatment for sleep apnea, however, with much lower success rate in reducing AHI in moderate to severe obstructive sleep apnea. While the MAD was less effective in reducing the AHI in moderate to severe sleep apnea, the compliance rates for wearing the MAD were much higher than the CPAP. CPAP and MAD therapy are frequently used in treatment of OSA, however the scientific knowledge regarding the efficacy and compliance of CPAP-MAD combination therapy is lacking.

3.2. Null Hypothesis

There is no difference in compliance of wear, air pressure, ESS, AHI, or mask air leaks when comparing CPAP therapy alone to combination CPAP-MAD therapy in subjects with moderate to severe obstructive sleep apnea.

3.3 Specific aims of the current study

- Compare CPAP compliance rate before and during combination CPAP-MAD therapy
- Compare air pressure values from CPAP alone to combination CPAP-MAD therapy
- Compare Epworth Sleepiness Scores from CPAP alone to combination CPAP-MAD therapy
- Compare AHI scores from CPAP alone to combination CPAP-MAD therapy
- Compare CPAP mask air leaks from CPAP alone to combination CPAP-MAD therapy
CHAPTER 4: MATERIALS & METHODS

4.1 Subject acquisition

All subjects were patients of the University of Nebraska Medical Center (UNMC) Sleep Medicine Clinic. Each subject had previously been diagnosed with moderate or severe sleep apnea via a polysomnography (PSG) and had been prescribed continuous positive airway pressure (CPAP) for at least 6 months. Suboptimal compliance with the CPAP had been documented within 3 months prior to recruitment and was defined as using the device less than or equal to 4 hours a night for greater than or equal to 30% of the nights. Each subject had a complete or functional dentition to support a mandibular advancement device (MAD). The inclusion and exclusion criteria are listed in figure 4.1. The study was started as a randomized clinical control study, where the subjects would be randomly chosen to receive either a MAD or a sham occlusal splint. In recruitment, we only had one subject willing to volunteer, and therefore the study was changed to a crossover study. A letter was sent out to prospective subjects as a tool to increase recruitment (figure 4.2)

4.2 CPAP protocol

All subjects were using a ResMed AirSense 10 AutoSet CPAP machine with the ability to automatically upload a compliance report to ResMed AirView (cloud-based system) or an SD card that can be uploaded for review. The compliance report consists of information regarding the usage, pressure, apneas (number and central vs obstructive), and RERAs. The CPAP machine, based on how much air pressure is needed to treat the airway obstruction, adjusts the pressure automatically. The data used from the CPAP machine were the subject’s usage, 95th percentile air pressure, AHI score and mask air leaks (figure 4.3). Subjects were instructed to wear their CPAP throughout the experiment.
4.3 MAD protocol

All subjects reported to the UNMC Adult Dental Clinic to see Dr. Jacob Stadiem. Impressions of the upper and lower teeth were taken using Identic® 100 - hour stability alginate and models were poured up immediately in buff stone. A George Gauge (figure 4.4-4.5) was used to determine where the bite registration was recorded. A 5mm anterior bite fork was used for vertical opening (figure 4.6). The initial bite registration was taken with the patient at 50% of their anteroposterior range of motion. The bite registration was taken using Exabite® II NDS vinyl polysiloxane. The stone models and bite registration were sent off to DynaFlex® labs for the fabrication of an adjustable Herbst-design MAD (figure 4.7). The MAD was made with a thermal acrylic material called Accu-Fit on the inside to allow for realignment at any time (figure 4.8). At the second visit, the MAD was delivered and subjects were taught how to properly insert and remove the MAD. Upon delivery of the MAD, subjects were asked to wear the appliance for 2 weeks with their CPAP and return to the UNMC Adult Dental Clinic for evaluation regarding the wear. Each subject was instructed to wear a 3/16 inch 3.5 oz. elastic from upper to lower anterior hook bilaterally every night (figure 4.9). After two weeks, subjects were assessed for comfort with the appliance. If there was any temporomandibular joint discomfort, the appliance was modified to decrease the vertical dimension. Subjects were then asked to wear the appliance for another 2 weeks and return for an assessment. Four subjects needed vertical modification, but all of them were symptom free at the following visit. When subjects were free of discomfort, they were advanced to 70% of their anteroposterior range of motion (figure 4.10). Subjects were then instructed to wear the MAD with their CPAP for four weeks. All data was recorded from the ResMed CPAP machine.

4.4 Subjective assessment

Each subject was given an Epworth Sleepiness Scale survey at their first appointment at the UNMC Adult Dental Clinic to assess their subjective daytime sleepiness (figure 4.11). After the final 4-week session of combination therapy, each subject was again given an Epworth
Sleepiness Scale survey. An increase in ESS score indicated an increase in daytime sleepiness
while a decrease in ESS score indicated a decrease in daytime sleepiness.

4.5 Statistical analysis

Means for 95th percentile pressure, compliance percentage, AHI value, and leaks were
determined for pre-treatment (CPAP only) and during treatment (combination therapy). Means
for ESS score pre-treatment and post-treatment were also determined. A paired two-sample T-test
was performed using SAS® to determine the significance of change in compliance, air pressure,
AHI, mask air leaks, and ESS score. An unpaired two-sample T-test of equal variance was
performed to determine the significance of the change in air pressure, compliance, and ESS score
between males and females. An unpaired two-sample T-test of unequal variance was performed
to determine the significance of the change in AHI and mask air leaks between males and
females. An F-test was run for each data comparison between males and females to determine
variance.
Inclusion Criteria:
1. Confirmed diagnosis by polysomnogram of moderate to severe OSA as defined by an AHI score of $\geq 15$ within the preceding 2 years
2. Inability to tolerate CPAP or reported history of CPAP noncompliance as defined by $\leq 4$ hrs/night for $\geq 30\%$ of the nights over the preceding 3 months
3. Complete or functional dentition
4. Ages of 21 and older
5. Auto-CPAP therapy using ResMed device that is linked to ResMed AirView or has an SD card

Exclusion Criteria:
1. Patients on oxygen therapy
2. History of alcohol, narcotic, or daily sedating psychoactive medications
3. Serious nasal passage obstructions or allergies that would prevent the CPAP use
4. Previous history of surgical treatments including uvulopalatopharyngoplasty or BSSO mandibular advancement
5. Age $< 21$
6. History of Temporomandibular joint dysfunction (TMD)
7. Significant weight loss or gain (10%) since diagnosis
8. History of claustrophobia or nasal airway obstruction (such as uncontrolled allergic rhinitis)
9. Other untreated sleep disorders (e.g. PLMD, RLS, Narcolepsy, CSA or insomnia)
10. History of CHF, COPD, or psychiatric disorder other than controlled anxiety and/or depression

Fig 4.1 Inclusion and exclusion criteria for subject recruitment. All of the criteria were confirmed before the subjects were seen for the first study visit other than the functional dentition.
As a patient of the Nebraska Medical Center’s Sleep Medicine Clinic you have been identified as someone who may benefit from participation in a research study titled Improving compliance in CPAP-intolerant patients by using a combination therapy with CPAP and MAD in moderate to severe OSA patients. IRB#017-16-EP. The mainstay of treatment for obstructive sleep apnea has been CPAP. However, this device is often difficult for people to tolerate. Our study is looking at a way to improve comfort with CPAP use. One reason a CPAP device can be difficult to wear is the need to breathe out against a higher pressure. You can think of it this way, if you put your head out of a car window going 80 mph it feels difficult to breathe out. We want to identify ways we can reduce the CPAP pressures that people require. Oral appliances, specifically mandibular advancement devices, are sometimes used for the treatment of mild obstructive sleep apnea. Using an oral appliance with CPAP has the potential to reduce required CPAP pressure and, therefore, may make the device more tolerable to wear. The goal of our study is to see if using an oral appliance with CPAP improves people’s ability to tolerate their CPAP device better. There is no cost to participate in this study. All of our study participants will receive an oral appliance at no cost. Your participation in this study may lead to advances in patient comfort with sleep apnea therapy. If you are interested in participating in this study please call Dr. John Harrington at (402) 559-4128.

Sincerely,

John Harrington, MD, MPH - Associate Professor, Sleep Medicine
Jacob Stadler, MA - Matthew Dennis, MD - Fellow, Sleep Medicine

Fig 4.2 Recruitment letter sent out to all prospective subjects.
Fig 4.3 ResMed Airview summary. The report received directly from the CPAP machine. 95th percentile air pressure, usage percentage, AHI, and mask air leaks were recorded from this summary.
Fig 4.4 George gauge. Used to record the subject’s bite registration for MAD fabrication. The numbers on the gauge indicate how far the subject can protrude and retrude their mandible.
Fig 4.5 George gauge being used to record a subject’s mandibular anteroposterior range of motion.
Fig 4.6 George gauge bite forks. The white bite fork (right), which was used in our study, has a 5mm vertical opening in the anterior. The grey bite fork (left) has a 2mm opening in the anterior.
**Fig 4.7 Herbst style mandibular advancement device.** The red dot on the maxillary arch in the anterior indicates to the subject which arch is the top. The red dot on the sides signifies the direction to turn the bolt to increase the protrusion. Sixteen turns is equal to 1mm of advancement.
Fig 4.8 Accu-Fit material in the Herbst style MAD. Accu-fit is a thermal acrylic material that allows you to remold the appliance by heating in a hot water bath. Every appliance was able to be fit on the delivery day.
Figure 4.9 Elastics worn on the Herbst style MAD. The use of the elastics was used to make sure the subject’s mouth did not open during sleep.
Fig 4.10 MAD appliance advanced to 70% of full anteroposterior range. Subjects wore elastics from upper hook mesial to the canine to the lower hook on the same side.
Fig 4.11 Epworth Sleepiness Scale Survey. Used to record subjective daytime sleepiness. Each subject was given the survey before the combination therapy and at the end of combination therapy. (Johns, 1992)
CHAPTER 5: RESULTS

5.1 Patient Acquisition

Forty-eight subjects from the UNMC Sleep Medicine clinic met the initial inclusion and exclusion criteria. After contacting potential subjects, eighteen subjects showed interest in participating in this study. After initial recruitment, two subjects did not have a functional dentition and three subjects decided not to go forward with the project. Thirteen subjects started the study and all thirteen completed the study.

5.2 Demographics

The average age of the subjects at the start of the treatment was 61.6 years old with a range from 45.9 to 73.7 years old. The gender makeup of the study was eight females (62%) and five males (38%). The average AHI score, before any treatment, of the subjects was 40.6.

5.3 Changes in all recorded parameters before and during treatment

There were significant changes and non-significant changes in parameters recorded in this study. This is shown in Table 5.1.

5.4 Compliance percentages

The average pre- and post-treatment for percentage compliance of CPAP wear for all subjects is shown in figure 5.1. Error bars represent the upper and lower 95% confidence limits of each measurement. A box-plot representing the data is shown in figure 5.2. A summary of the paired two-sample T-test is shown in appendix B. P-value for all compliance percentages was set at <0.05. Nine out of the thirteen subjects (69%) showed an increase in compliance percentage, three out of thirteen subjects (23%) exhibited a decrease in compliance percentage, and one out of thirteen subjects (8%) exhibited no change in compliance percentage. An average increase in compliance percentage of 23.0769% with combination therapy was statistically significant (p=0.0154). Males had a 9% larger increase in compliance percentage, but the difference was not significant (p = 0.6024) (appendix B).
5.5 CPAP Air Pressure Levels

The average pre- and post-treatment measurements for CPAP air pressure on all subjects are shown in figure 5.3. Error bars represent the upper and lower 95% confidence limits of each measurement. A box-plot representing the data is shown in figure 5.4. A summary of the paired two-sample T-test is shown in appendix B. P-value for all pressure measurements was set at <0.05. Six out of the thirteen subjects (46%) showed a decrease in pressure, while seven out of thirteen (54%) exhibited an increase in pressure used with the CPAP. An average decrease in pressure of 0.1846 cmH₂O was not statistically significant (p=0.6968). Males had a 1.23 cmH₂O larger decrease in air pressure but the difference was not significant (p = 0.2098) (appendix B).

5.6 Epworth Sleepiness Scale

The average pre- and post-treatment ESS scores for all subjects are shown in figure 5.5. Error bars represent the upper and lower 95% confidence limits of each measurement. A box-plot representing the data is shown in figure 5.6. A summary of the paired two-sample T-test is shown in appendix B. P-value for all ESS scores was set at <0.05. Nine out of the thirteen subjects (69%) showed a decrease in their ESS score, three out of thirteen subjects (23%) exhibited an increase in their ESS score, and one out of thirteen subjects (8%) exhibited no change in their ESS score. An average decrease in ESS score of 1.3846 with combination therapy was statistically significant (p=0.0269). The average decrease in ESS scores for males was 1 point lower than females, but this difference was not significant (p = 0.3992) (appendix B).

5.7 AHI values

The average pre- and post-treatment AHI values for all subjects are shown in figure 5.7. Error bars represent the upper and lower 95% confidence limits of each measurement. A box-plot representing the data is shown in figure 5.8. A summary of the paired two-sample T-test is shown in appendix B. P-value for all AHI values was set at <0.05. Nine out of the thirteen subjects (69%) showed a decrease in their AHI value indicating less obstructive events during sleep. Three out of thirteen subjects (23%) exhibited an increase in their AHI value, indicating more
obstructive events during sleep. One out of thirteen subjects (8%) exhibited no change in their AHI value. An average decrease in AHI value of 0.0692 was not statistically significant (p=0.9075). Females had a mean decrease in AHI value of 0.275 larger than the males, but this difference was not significant (p = 0.8718) (appendix B).

5.8 Air Leaks with CPAP

The average pre- and post-treatment measurements for CPAP mask air leaks on all subjects are shown in figure 5.9. Error bars represent the upper and lower 95% confidence limits of each measurement. A box-plot representing the data is shown in figure 5.10. A summary of the paired two-sample T-test is shown in appendix B. P-value for all leaks measurements was set at <0.05. Six out of the thirteen subjects (46%) showed a decrease in leaks, while seven out of thirteen (54%) exhibited an increase in leaks while using the combination therapy. An average decrease in leaks of 0.8538 leaks/min was not statistically significant (p=0.7542). Females exhibited a mean decrease of 0.54 mask air leaks greater than males, but this difference was not significant (p = 0.9067) (appendix B).
Table 5.1 Mean changes for all subjects

<table>
<thead>
<tr>
<th>Subjects =13</th>
<th>Pre-Treatment Mean</th>
<th>Post-Treatment Mean</th>
<th>Mean Difference</th>
<th>SD</th>
<th>P-Value</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure (cmH₂O)</td>
<td>12.4</td>
<td>12.2154</td>
<td>-0.1846</td>
<td>1.6678</td>
<td>0.6968</td>
<td>NS</td>
</tr>
<tr>
<td>Compliance Percentage</td>
<td>44.3077</td>
<td>67.3846</td>
<td>23.0769</td>
<td>29.4971</td>
<td>0.0154</td>
<td>*</td>
</tr>
<tr>
<td>ESS</td>
<td>7.6154</td>
<td>6.2308</td>
<td>-1.3846</td>
<td>1.9807</td>
<td>0.0269</td>
<td>*</td>
</tr>
<tr>
<td>AHI</td>
<td>2.0615</td>
<td>1.9923</td>
<td>-0.0692</td>
<td>2.1037</td>
<td>0.9075</td>
<td>NS</td>
</tr>
<tr>
<td>Leaks (Leaks/min)</td>
<td>15.2154</td>
<td>14.3615</td>
<td>-0.8538</td>
<td>9.6105</td>
<td>0.7542</td>
<td>NS</td>
</tr>
</tbody>
</table>
Figure 5.1. Pre- and post-treatment mean compliance percentage. CPAP compliance rates were measured three months prior to recruitment with the CPAP only and over a 4-week period with combination therapy. Statistically significant increase in compliance percentage observed (*p = 0.0154).
Figure 5.2. A box-plot diagram comparing compliance percentage pre- and post-treatment. CPAP compliance rates were measured three months prior to recruitment with the CPAP only and over a 4-week period with combination therapy. Black dot represents the mean.
Figure 5.3. Pre- and post-treatment mean 95th percentile air pressure. CPAP air pressures were measured three months prior to recruitment with the CPAP only and over a 4-week period with combination therapy.
Figure 5.4. A box-plot diagram comparing 95\textsuperscript{th} percentile air pressure pre- and post-treatment. CPAP air pressures were measured three months prior to recruitment with the CPAP only and over a 4-week period with combination therapy. Black dot represents the
Figure 5.5. Pre- and post-treatment mean ESS scores. ESS scores were measured at the subject’s first visit with Dr. Stadiem and after a 4-week period with combination therapy. Statistically significant decrease in ESS scores observed (*p = 0.0269).
Figure 5.6. A box-plot diagram comparing ESS scores pre- and post-treatment. ESS scores were measured at the subject’s first visit with Dr. Stadiem and after a 4-week period with combination therapy. Black dot represents the mean.
Figure 5.7. Pre- and post-treatment mean AHI values. AHI values were measured three months prior to recruitment with the CPAP only and over a 4-week period with combination therapy.
Figure 5.8. A box-plot diagram comparing AHI values pre- and post-treatment. AHI values were measured three months prior to recruitment with the CPAP only and over a 4-week period with combination therapy. Black dot represents the mean.
Figure 5.9. Pre- and post-treatment mean mask air leaks. Leaks were measured three months prior to recruitment with the CPAP only and over a 4-week period with combination therapy.
Figure 5.10. A box-plot diagram comparing leaks pre- and post-treatment.Leaks were measured three months prior to recruitment with the CPAP only and over a 4-week period with combination therapy. Black dot represents the mean.
CHAPTER 6: DISCUSSION

6.1 Relevance of Study

The gold standard for obstructive sleep apnea is still CPAP therapy. The problem associated with CPAP is the high non-compliance rate with CPAP wear. An effective treatment modality that isn’t followed is no more beneficial than an ineffective treatment modality. The main obstacles in achieving increased compliance with CPAP therapy were the side effects of the CPAP. Non-adherence to the CPAP is most commonly due to increased awakenings and dry mouth (Ulander et al., 2014). The goal of our study was to improve the compliance of CPAP wear by delivering a MAD, to go along with the CPAP. The rationale of this thought process was based on two facts. First, a MAD is preferred as an alternative to CPAP by patients (Hoffstein, 2007). Second, studies indicate that a MAD increased the volume of upper airway (Shete & Bhad, 2017). The increased airway volume may be of help in eliminating the discomfort from the increased air pressure, which is needed to provide adequate airflow to treat the obstruction. A MAD may help maintain air pressure at a lower level without compromising comfort for the patient. This study was designed to record the duration of use of the CPAP after the MAD was delivered. If the added MAD didn’t improve the subject’s comfort level, they were likely to stay noncompliant.

6.2 Compliance percentages

The CPAP compliance percentage was measured through the ResMed AirView/SD card and was calculated as the percentage of the 30 days the subject wore the CPAP ≥ 4 hours per night. Our study showed a statistically significant difference in compliance percentage scores (p=0.0154), indicating better compliance with the combination therapy. A person is considered compliant with the CPAP if they wear the CPAP ≥4 hours a night for at least 70% of the nights (Schwab et al., 2013). The average percentage of wear in our study with the CPAP-MAD combination was 67.38%. Although the average percentage of wear was slightly under the 70% mark, six out of the thirteen (46%) subjects eclipsed the 70% mark. Nine out of the thirteen
subjects (69%) showed an increase in compliance percentage, with three subjects exhibiting a 97% compliance percentage. Although there was no significant decrease in air pressure, the increase in compliance could be due to an increase in CPAP comfort with combination therapy. The MADs ability to increase retropalatal and retrolingual spaces (Lee et al., 2009) may reduce the air flow turbulence created during respiration. This decrease in turbulence could result in a higher level of comfort. We only recorded compliance for the first month because it has been shown that the compliance of the CPAP will be determined in the first month (Kribbs et al., 1993). The increase in compliance may lead to a decrease in obstructive sleep apnea co-morbidities. Combination therapy gives the sleep physician and dentist another treatment option before resorting to a surgical therapy.

6.3 CPAP Air Pressure Levels

CPAP air pressure levels were measured through the ResMed CPAP machine. Each machine automatically adjusted the pressure on a breath by breath basis to keep the airway open. The auto-titrating CPAP was set by the sleep medicine doctors at a pressure range of 6-20 cmH₂O. The average pressure used with the CPAP therapy alone was 12.40 cmH₂O. With the combination treatment, the average pressure recorded was 12.22 cmH₂O, indicating a mean difference of -0.18 cmH₂O. Although the mean value decreased with the combination therapy, the decrease was not statistically significant (p=0.6968). The reduction in air pressure could be non-significant due to a varied location of the upper airway minimal cross sectional area between people. The oropharyngeal area has been reported as the most affected part of the pharynx in OSA patients (Yucel et al., 2005), but the mandibular advancement device may not have affected the exact location of the minimal cross sectional area. Our results vary from the pilot study reported by El-Solh, et al. who found a significant difference of a 2.1 cmH₂O decrease when using the combination therapy (El-Solh et al., 2011). They compared the combination therapy with an auto-titrating CPAP (APAP) to CPAP therapy alone with a fixed pressure CPAP. A meta-analysis showed that APAP pressures were on average 2.2 cmH₂O less than fixed CPAP
machines (Ayas et al., 2004). A reduction of 2.2 cmH₂O would put their average change in air pressure from CPAP alone to CPAP-MAD combination therapy at an increase of 0.1 cmH₂O. Therefore, we cannot compare our results directly to their results. Also, in their study, they included subjects with mild, moderate and severe obstructive sleep apnea, and their subjects had a much lower starting CPAP air pressure. Again, these parameters varied between our study and their study, which would lead to differences in the results obtained. Furthermore, variations exist between the mask types used by the subjects. In our patient pool, there were subjects using oronasal, nasal, and nasal pillow masks. Their pilot study used only nasal masks on their subjects. Oronasal masks have been shown to result in higher air pressures than nasal masks (Bettinzoli et al., 2014). Mask types may influence the outcome of this study in terms of compliance, air-leakage and pressure values. We did not have a large sample size to evaluate the outcome related to mask type.

6.4 Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) survey was administered at the subjects’ MAD fabrication visit and again at the end of the combination therapy. The average ESS score with CPAP therapy alone was 7.62 and the average ESS score after combination therapy was 6.23, a mean difference of -1.39. The difference in ESS scores showed statistical significance (p=0.0269). The decrease in ESS score shows that subjectively the subjects felt less sleepy during the day with the combination therapy compared with the CPAP therapy alone. The pilot study from El-Solh, et al. showed an average decrease in ESS score from 12.7 to 7.5 when comparing no therapy to the combination therapy, but they did not record an ESS score for the CPAP alone. The ESS test-retest reliability has been shown to be reliable with no statistically significant changes when there is no treatment between the first time the test is administered and the second time. The ESS has also been shown to be reliable in reporting a reduction of daytime sleepiness with OSA treatment (Johns, 1992). The ESS has also been proposed as a tool for identifying OSA. For detecting mild OSA, the ESS was shown to have a sensitivity of 54% and a specificity
of 65%. For moderate OSA, the ESS was shown to have a sensitivity of 47% and a specificity of 62%. For severe OSA, the ESS was shown to have a sensitivity of 58% and a specificity of 60% (Chiu et al., 2016). The ESS is not the best tool for detecting sleep apnea, but it does seem reliable when measuring a change in daytime sleepiness with OSA treatment. Our study indicated, the patients were significantly compliant to the combination therapy compared to CPAP alone.

6.5 AHI values

All of the subjects in our study had AHI scores in the therapeutic level (AHI < 5) with the CPAP therapy alone. The average AHI before CPAP therapy, diagnosed from polysomnography, was 40.6. The AHI scores ranged from 20.1 to 93.8. This again reinforces the fact that the gold standard for the treatment of obstructive sleep apnea is CPAP therapy. The average AHI score with the CPAP alone was 2.1 and with the combination therapy was 2.0, a mean difference of -0.1. Although there was a decrease in AHI score, this value was not significant (p=0.9075). There was one outlier that had an increase in AHI of 6.1 with the combination therapy. With this outlier removed the AHI score was reduced on average by 0.6, but still did not show statistical significance (p = 0.07781). This outlier is likely due to an error in the machine reading. A larger sample size could reveal whether a MAD in certain individuals may not be effective in changing the airway. The AHI scores for our study were taken from the auto-titrating CPAP instead of doing an HST or PSG. A study by Desai, et al. showed that the estimate of residual AHI by an Auto-CPAP showed good agreement with the AHI determined from PSG (Desai et al., 2009). Our subjects all showed a successful reduction in AHI (AHI < 5) with the CPAP alone. It was not surprising that the combination therapy did not significantly reduce the AHI when these subjects were already in the therapeutic range. While the reduction in AHI with combination therapy wasn’t significant, when you combine a therapeutic AHI with an increased compliance percentage, the combination therapy can be seen as a clinically successful.
6.6 Air Leaks with CPAP

One potential problem with adding a MAD to an existing CPAP setup is the chance that the mask won’t fit properly. Ideally, you would want the subject to be fit for a new mask with the appliance to make sure the appliance isn’t causing the mask to leak. In our study we had the subject continue wearing the mask they were currently using with the CPAP. The average mask leaks with the CPAP therapy alone was 15.2 leaks/min and the average mask leaks with the combination therapy was 14.4 leaks/min, a mean difference of -0.8 leaks/min. Although there was a decrease in leaks, this difference was not significant (p=0.7542). Mouth opening, mean CPAP pressure, sleep position and REM sleep have been shown to be factors that increase unintentional leakage (Lebret et al., 2017). The use of elastics with the appliance to keep the subjects mouth from opening in this study may have helped avoid unwanted leaks in our study. Mask air leaks have been associated with poor adherence to CPAP and has been associated with side effects such as oral dryness or nasal congestion (Borel et al., 2013, Valentin et al., 2011). Oronasal masks have been shown to exhibit more mask leaks than nasal masks (Teo et al., 2011). This implies that if patients use nasal masks along with CPAP-MAD therapy, a significant reduction in leakage is possible, which could lead to a further improvement in air pressure and compliance.

6.7 Study Limitations and Future Studies

All subjects in this study were advanced to a 70% of the maximum anteroposterior range. A titration of each appliance using HSTs could have possibly made these appliances more effective because we would have the appliances at each subject’s most therapeutic position.

Our original power analysis based on the previously published pilot study showed that we needed 12 subjects to show significance in the change of pressure and compliance (El-Solh et al., 2011). From the results that we obtained, power analysis indicates we would actually need a sample size of 641 to show significance level of 0.05 for a change in air pressure. This study population is far from being able to reach this number. A larger sample size would also help in seeing if there is a significant difference in the response to combination treatment by males and
females, any influence with mask designs, and whether MAD has deleterious effects on certain individuals with OSA.

Again, we would like to emphasize the difficulty in recruiting patients for this type of study, due to their lack of knowledge regarding an oral appliance and its effectiveness in improving their sleep related problems. Not only patient’s unawareness leads to not utilizing the available more effective therapy, the medical professional needs scientific evidence regarding this approach of combination therapy and its effects on compliance of CPAP wear along with other advantages discussed in this chapter, for a multidisciplinary approach in treating OSA patients. Oral appliances are increasing in popularity with recent years, but randomized control clinical trials are needed to further prove the effect to the scientific community and medical professionals. Only after the medical professionals give their approval of this type of treatment can the lay people truly grasp its contribution. Even with the small sample size, this study proves that there is hope for the combination therapy and a multidisciplinary research approach is needed to exhibit the results seen.

A randomized controlled trial with half of the subjects receiving a MAD and the other half receiving a sham appliance would be an ideal study design for a meaningful result. The chance of not receiving a MAD made many subjects very hesitant to participate.

A future addition to the study is to have each of these subjects go through an HST to see how effective their MAD is as a single treatment. This will also give us the ability to compare the effectiveness in reducing the AHI with the MAD alone to its ability to change the air pressure during combination therapy.

Another future study option could be using CBCT to look at the effects of vertical versus anteroposterior advancement of MADs on airway dimensions. There is a disagreement in the literature on which direction the appliances should be adjusted to be more effective. Whether more vertical opening of the jaw or more forward movement of the jaw would improve airway dimensions needs to be answered. A CBCT measuring volumetric changes of the airway with
vertical versus horizontal adjustment could help to better understand how to more effectively construct the MAD.
CHAPTER 7: CONCLUSION

In this study five variables regarding the CPAP-MAD combination therapy were compared to CPAP therapy alone. The null hypothesis was rejected for two variables and accepted for the other three. Compliance and ESS scores were changed significantly with the combination therapy, whereas the air pressure, AHI scores, and mask air leakage did not show any significant changes. Compliance percentages increased by an average of 23%, while ESS scores decreased by an average of 1.4. A decrease in pressure, AHI, and leaks was observed as well but this decrease was not statistically significant. Further studies, with improvements in study design, are needed to fully assess the clinical efficacy of combination CPAP-MAD therapy.
BIBLIOGRAPHY


### Appendix A: Experimental Data

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## Appendix A: Experimental Data

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APPENDIX B: t-Test Data
### t-Test: Paired Two Sample for Means

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### t-Test: Paired Two Sample for Means

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### Comparing Male Vs Female

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**Statistical Test**

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