Oral Appliance and Pharmacological Agents in the Treatment of Sleep Apnea: A Pilot Clinical Study

BY

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THESIS

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This thesis is dedicated to my parents, for their unconditional love and support.

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RWS

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LIST OF ABBREVIATIONS

2D	Two-Dimensional
3D	Three-Dimensional
A-P	Anteroposterior
AHI	Apnea-Hypopnea Index
C3ai	Anteroinferior Aspect of Third Cervical Vertebra
CBCT	Cone beam computed tomography
CPAP	Continuous positive airway pressure
CSA	Cross-sectional Area
ESS	Epworth sleepiness scale
FH	Frankfort Horizontal
FOSQ	Functional outcomes of sleep questionnaire
MAD	Mandibular advancement device
MAS	Mandibular advancement splint
OA	Oral appliance
ODI	Oxygen Desaturation Index
OSA	Obstructive sleep apnea
PSG	Polysomnography

LIST OF ABBREVIATIONS (continued)

PVT	Psychomotor vigilance test
RERA	Respiratory Effort Related Arousal
SaO_2	Blood-Oxygen Saturation
SBD	Sleep Disordered Breathing
SD	Stand Deviation
UPPP	Uvulopalatopharyngoplasty
VAS	Visual analog scale

SUMMARY

A study of a combination treatment of an oral appliance with drug therapy for obstructive sleep apnea was carried out using a single-blinded placebo case control crossover approach. A custom mandibular advancement device was fabricated, and a combination regimen of fluoxetine and ondansetron was prescribed for 7 patients with severe obstructive sleep apnea (AHI 20-50). Both objective and descriptive measures of treatment effects were obtained from polysomnogram reports, validated surveys, and various logs.

I. INTRODUCTION

1.1. Background

Obstructive sleep apnea (OSA) is a respiratory disorder on the larger spectrum of sleep disordered breathing (SDB). According to the American Academy of Sleep Medicine, SDB is an encompassing term for many different sleep-related breathing disorders during sleep (Kapur et. al., 2017). It is recognized as a major public health issue. Recent prevalence estimates of moderate to severe OSA in the United States among adults are 13% of men and 6% of women (Peppard, 2013).

OSA is primarily characterized by repetitive and transient 10-30 second disruptions of breathing during sleep. These come in two forms: complete cessation and collapse of the upper airway (apnea) and a significant reduction in breathing (hypopnea). Sleep studies quantify these events into an apnea-hypopnea index (AHI), which serves as a key objective outcome measure (Gharibeh and Mehra, 2010). AHI scores of 5, 15, and 30 serve as cutoff points for mild, moderate, and severe sleep apnea, respectively. Extensive biometrics, sleep data, and physiological measurements are routinely obtained through a polysomnogram where the patient is connected to multiple electrodes and monitored during a night of sleep (Patil SP, 2010).

1.2. Obstructive vs. Central Apnea

Obstructive sleep apnea is differentiated from central sleep apnea in that the central form results from problems with the respiratory drive centers of the brain and is often discovered only after the patient is treated for the obstructive form (Thomas et. al., 2007). It can occur independent of the obstructive form, usually in medically compromised patients, those with damage to the brainstem, or can be opioid-induced. Obstructive sleep apnea can be thought of as an anatomical problem where the patency of the upper airway is compromised due to partial or complete airway blockage (Eckert D, Malhotra A, 2005).

1.3. Clinical Presentation

The clinical presentation of OSA includes snoring, daytime sleepiness, which can lead to impaired concentration and mood, increased risk of automobile accidents, job absenteeism, and deterioration of personal relationships (Gharibeh and Mehra, 2010). Direct physiological effects include intermittent drops in blood oxygen saturation, which result in sympathetic nervous system activation and a subsequent increase blood pressure, markers of oxidative stress and inflammation (McEvoy et. al., 2016). It is important to note, however, that objective polysomnogram parameters alone such as AHI and minimum oxygen saturation have not been conclusive in predicting OSA treatment success. Daytime sleepiness and vigilance tests have been shown to be

valuable in assessing and predicting treatment outcome if utilized in combination (Mathis J and Hess CW, 2009) (Batool-Anwar et. al., 2014).

1.4. Risk Factors

Major risk factors for OSA are obesity and patients with metabolic syndrome. It is estimated that 50-60% of these patients have obstructive sleep apnea (Drager et. al., 2013). Numerous studies have shown an independent association between obstructive sleep apnea and hypertension, cardiovascular disease, and metabolic disease (Wolf et. al., 2007). More recently, emerging research is demonstrating an association between sleep apnea severity and degenerative neurological diseases, kidney disease, and cancer (Gildeh et. al., 2016).

Anatomical features, both skeletal and soft tissue, have a role in the predisposition to developing OSA. Hard tissue risk factors include mandibular retrognathia and a narrow or high hard palate. Soft tissue risk factors include narrow airway, macroglossia, tonsillar and adenoid hypertrophy (Eckert D, Malhotra A, 2005).

Age and sex are two major risk factors in the development of obstructive sleep apnea. OSA prevalence increases steadily with age during adulthood, and many studies have found a high prevalence in those age 60 and older. Men are three times more likely to develop OSA than women (Semelka et. al., 2016). It is hypothesized that hormones play a major role in this, which may explain why women are at a higher risk

for developing OSA post-menopause. There is, however, limited research to support this. Anatomical differences in craniofacial structures and fat deposition may also explain prevalence differences between men and women (Young et. al., 2002).

1.5. Pathophysiology

The underlying pathophysiology is multifactorial and varies considerably between individuals. Treatments based on an individual's predominant pathogenic mechanisms is the goal of effective treatment and can prove challenging to identify. While the primary risk factor is obesity, it is important to note that adult obstructive sleep apnea is prevalent in the absence of clinical obesity. Upper airway anatomy plays an important role in the predisposition to airway closure and development of the disease. Increased neck circumference, mandibular retrognathia, macroglossia, decreased pharyngeal muscle tone, and enlarged tonsils and adenoids are all positive predictors of obstructive sleep apnea and contribute to the pathogenesis of OSA (Greenstone M, Hack M, 2014).

Upper airway collapsibility during sleep is one major pathogenic process. This is characterized by passive pharyngeal critical closing pressure (P-crit). It is the estimated nasal pressure at which airflow stops and there is complete upper airway collapse. A higher Pcrit indicates a higher collapsibility. This is most accurately measured while a patient is on continuous positive airway pressure to minimize the influence of airway dilator muscles (Carberry et. al., 2016).

Obstructive sleep apnea follows a cycle which alternates from perpetuating processes that ultimately lead to apneas and hypopneas and protective processes that attempt to restore the body to normal respiration. As breathing effort increases, oxygen saturation decreases and carbon dioxide in the body increases. This ultimately leads to an arousal from sleep due to increases upper airway dilator muscle activity and hyperventilation. After a return to sleep the cycle repeats with decreased upper airway tone, and eventually upper airway narrowing and collapse. (Eckert D, Malhotra A, 2005).

1.6. Rationale for Continued Investigation

The National Institutes of Health acknowledged in their 2011 National Sleep Disorders Research Plan that "many research questions remain unanswered and new questions need to be addressed, therapy for a number of sleep disorders remains suboptimal, and the research workforce addressing sleep science is inadequate." These facts highlight the importance of investigational approaches that transcend traditional disciplinary boundaries to explore innovate solutions for OSA therapy.

The public health consequences of untreated OSA are profound. Patients without treatment are at a much higher risk of being involved in a motor vehicle accidents and work-related injuries. They experience more frequent and longer hospitalizations with increased healthcare-related costs, and an overall decrease in quality-of-life (Greenstone

M, Hack M, 2014).

In this novel series of studies, we hypothesize that the muscle activation or stretching effect of the mandibular advancement device will be additively enhanced by the activation of serotonergic receptors from the drugs ondansetron and fluoxetine acting on the upper airway. This addresses an unmet treatment need for moderate to severe obstructive sleep apnea patients who cannot tolerate the CPAP device. It is the first to combine a dental device and pharmacotherapy.

In 2012 our group was awarded an internal grant – the University of Illinois at Chicago Chancellor's Multidisciplinary Discovery Fund to test the feasibility of our concept in a clinical pilot study. Our last subject completed this study in 2014 and we have presented our preliminary results as a poster format at scientific meetings. That preliminary study (n=12) led by Drs. Galang-Boquiren and Carley established the feasibility of the combined treatment approach utilizing OA and pharmacotherapy in subjects with moderate to severe OSA. A prospective, placebo-controlled, blinded crossover study of 12 subjects with moderate-severe OSA was conducted. Treatment was MAD plus placebo medication for two weeks, followed by a combination regimen of ondansetron (24 mg/day) and fluoxetine (10 mg/day) with continued use of the MAD. The primary outcome measure was Apnea-Hypopnea Index (AHI). Test results indicated

that AHI MAD (19.9±4.5) and AHI MAD + Drug (15.0±2.9) was statistically significantly lower than the AHI baseline (36.1±2.7). Although the results of the two treatment groups (AHI MAD and AHI MAD + Drug) were not statistically significantly different, the combination of pharmacotherapy and oral appliance may be a viable option in treating patients with moderate to severe OSA.

Based on the above findings and feedback we have received in the scientific meetings where our poster was presented, we proposed this follow-up pilot study to administer the same combination intervention but utilize additional robust secondary outcome measures. To be truly competitive for a larger scale federally funded study, this current study builds on our existing pilot data, addressing the variance unaccounted for in our preliminary results by incorporating additional validated outcome measures such as daytime functional testing. Since polysomnogram parameters alone have not been conclusive in predicting OSA treatment success, these sleepiness and vigilance tests have been shown to be valuable in assessing and predicting treatment outcome if utilized in combination. Also, since recent studies have continually shown poor reliability of cephalometric radiograph measures, we are instead utilizing 3D CBCT imaging to capture the three-dimensional anatomy to assess airway volumetric changes in our study subjects. Some obstacles remain to utilizing CBCT imaging such as controlling for the impact of the respiration phase, the influence of tongue position, and the definition

of anatomical boundaries of the upper airway. We chose two respiratory time-points to take the CBCT images, one at end-inspiration of a normal breath, and the second at end-exhalation or functional residual capacity (FRC). One set will be taken with the appliance titrated in place, and the other set will be taken without the appliance. This will allow us to analyze the effect of the oral appliance on airway shape and volume. Anatomical landmark localization and upper airway measurements will be defined following a methodology from a previous study that showed excellent reliability (Guijarro-Martinez R, Swennen G, 2013).

Finally, since our novel intervention involves medications in the treatment of OSA, we decided to measure treatment acceptability using the validated and widely used Treatment Satisfaction Questionnaire for Medication (TSQM) instrument.

1.7. Specific Aims

1. Establish the feasibility and acceptability of combined treatment by OA+pharmacotherapy.

2. Generate appropriate estimates of the treatment effect sizes for OA and OA+pharmacotherapy in patients with moderate to severe OSA; and

3. Differentiate these effect sizes according to respiratory event frequency (apnea-hypopnea index), upper airway and dental changes (from 3D CBCT data), daytime sleepiness (Epworth Sleepiness Scale and Visual Analog Scale for Sleepiness), functional capacity (Functional Outcomes of Sleep Questionnaire), and daytime performance (Psychomotor Vigilance Task) using well-validated outcome measures.

These objectives are a necessary starting point to establish the feasibility of our approach and to gain effect size information in support of our general hypothesis and essential to appropriately power a future larger-scale clinical study.

1.8. Research Hypothesis

We hypothesize that MAD is not fully therapeutic in moderate to severe OSA and that augmentation of MAD by pharmacotherapy (ondansetron+fluoxetine) will increase therapeutic efficacy in these patients.

II. REVIEW OF THE LITERATURE

2.1. OSA Treatment

Over the past several decades, many therapies have been developed and refined to address the myriad of physiological symptoms and manifestations of obstructive sleep apnea. Apart from conservative approaches such as weight loss, positional changes, and practicing good sleep hygiene, the following are the commonly prescribed treatments for OSA.

2.1.1. Continuous Positive Airway Pressure (CPAP)

Continuous positive airway pressure (CPAP) devices remain the gold standard treatment for obstructive sleep apnea because of their proven efficacy and near 100% success when properly fit and adhered to in numerous studies over the past several decades (Libman et. al., 2017). By introducing pressurized air into the nasal and oral cavity, the upper airway is prevented from collapsing. The benefits provided by CPAP are numerous. It has shown to normalize sleep architecture, reduce nocturnal symptoms of gasping and multiple awakenings, and reduce daytime sleepiness. CPAP treatment often eliminates snoring and has strong evidence linking it to a decreased risk of cardiovascular disease and stroke risk (Libman et. al., 2017). Despite the benefits, adherence to CPAP therapy is poor failure rates ranging from 29-83% and often greater

than 50% (Carberry et. al., 2017). Non-adherence is typically defined as less than 4 hours of usage per night (Rosenberg R, Doghramji P, 2009).

2.1.2. Surgery

A variety of surgical interventions have also been used to treat or cure obstructive sleep apnea. Many are invasive, risky, and therapeutic in only a small percentage of patients. The most commonly performed procedures include skeletal surgeries such as maxillomandibular advancement (MMA), and soft tissue augmentation surgeries to the pharyngeal space such as uvulopharyngopalatoplasty (UPPP), laser assisted uvulopalatoplasty (LAUP), and radiofrequency ablation (RFA) (Caples et. al., 2010). For patients with mandibular insufficiency, surgical intervention to advance the mandible has shown to be beneficial (Noller, et. al., 2017). The most recent Cochrane systematic review on surgical intervention for obstructive sleep apnea concluded that there is still insufficient evidence to recommend surgery as a routine treatment modality (Sundaram et. al., 2008).

2.1.3. Hypoglossal Nerve Stimulation

Upper airway stimulation therapy shows promise as an alternative to traditional surgery. In this approach, an implantable device stimulates the hypoglossal nerve to activate tongue and pharyngeal musculature during sleep which ultimately results in a

more stable airway through a reduction of pharyngeal critical closing pressure (Pcrit) and obstructive episodes (Dedhia et. al., 2015).

2.1.4. Oral Appliances

Oral appliances have become a popular and more patient-friendly alternative to CPAP and surgical intervention. They function by repositioning the lower jaw anteriorly, which displaces oral and pharyngeal soft tissue, including the tongue, anteriorly thus increasing upper airway volume and reducing pharyngeal collapsibility (Marklund, 2017). The changes in airway dimension occur primarily by an increase in the lateral dimension of the velopharynx, elevation of the hyoid bone, and anterior displacement of the tongue (Sutherland et. al., 2017). While OAs are an FDA-approved alternative therapy, they are not universally effective in all patients and have varying degrees of success depending on individual anatomical factors and severity of disease. According to recent clinical practice guidelines issued by the American Academy of Sleep Medicine (AASM), OAs are recommended as a primary therapy in mild forms of sleep disordered breathing (SDB) such as snoring, and as an alternative therapy for patients with obstructive sleep apnea who are intolerant of CPAP therapy (Ramar et. al., 2015). Most patients report subjective improvements in sleep quality and a reduction of daytime sleepiness. Side effects are generally transient and include excessive salivation, muscle and tooth discomfort, and occasionally joint discomfort. These symptoms usually improve over

time. Tooth movement and malocclusion are noted in some patients especially after 1 or more years of treatment. Changes are usually reversible and can be counteracted with a morning repositioner (Ferguson et. al., 2006). The morning repositioner or deprogrammer is a thermoformed upper splint that used the morning after wearing the MAD and helps to restore jaw alignment.

There is emerging data that points to long-term efficacy of mandibular advancement devices. A prospective 1-year study of patients treated with MADs found significant improvements in cognitive and psychomotor performance, as well as an increase in quality of life and a reduction in daytime sleepiness (Galic et. al., 2016). Another study by Wee and colleagues reported positive long-term improvement of daytime sleepiness symptoms from MAD therapy with a mean follow-up duration of 60.5 months (Wee et. al., 2018).

Oral appliances can roughly be divided into three categories: soft palate lifters (SPL), tongue retaining devices (TRD), and mandibular advancement devices (MAD). The first group is no longer in use today. The second group is used only if there are dental contraindications for using a MAD, such as an edentulous state. The MAD is the most common type of oral appliance used today. These devices can be fixed such that the amount of lower jaw advancement cannot be changed, or variable where the amount of

advancement can be adjusted. A systematic review of various oral appliance designs found that no single design was found to be most effective, and that efficacy depends on many factors including patient anatomy, type of materials used, and degree of protrusion (Ahrens et. al., 2010).

Evidence from recent studies suggest that there is no single most effective advancement amount. Aarab and colleagues recommend starting MAD treatment at 50% of the maximum tolerated mandibular protrusive position (Aarab et. al., 2010). Some patients show a significant reduction in AHI scores with as little as 3 mm of mandibular advancement (Anitua et. al., 2017). Response to treatment with MADs varies considerably from patient to patient and there are four main criteria that contribute to overall effectiveness: severity of OSA, amount of mandibular advancement, BMI, and positional-related respiratory events. The best responders to treatment tend to have mild to moderate OSA, a greater amount of mandibular advancement, lower BMI, and have a greater difference in the rate of respiratory events between supine and lateral sleep position (Ferguson et. al., 2006).

2.1.5. Pharmacological Intervention

Considering the poor adherence associated with CPAP, the search for an optimal pharmacotherapeutic agent remains an elusive goal (Randerath et. al., 2011).

Pharmaceutical agents' mechanisms of action are varied and may act through several pathways. These include increasing respiratory drive, reducing the duration of REM stage sleep, increasing upper airway muscle tone, and changing respiratory and cardiovascular reflexes to reduce the collapsibility of the upper airway (Randerath et. al., 2011). Many substances have been tried clinically and reported with optimistic findings. A recent Cochrane systematic review study indicated that, more recently, a more attention has been given to the role of upper airway tone, regardless of respiratory drive (Mason et. al., 2013). Serotonergic drugs are the most promising among those investigated with this goal in mind. Decreased serotonergic facilitation of upper airway motor neurons during sleep may be an important mechanism rendering the upper airway vulnerable to collapse in OSA (Heym et. al., 1982).

Recent studies in rats have shown that apnea-induced long-term facilitation (LTF)/acceleration of respiratory activity of the phrenic and hypoglossal motor neurons is dependent on serotonin (Mahamed S, Mitchell GS, 2008). Endogenous release of serotonin in the brain stem increases the upper airway dilators' drive during the waking state. This primarily occurs via postsynaptic 5-HT2 receptors (Fenik P, Veasey SC, 1999), while the same action at 5-HT3 receptors in the nodose ganglion promotes expression of REM related apnea peripherally (Carley DW, Radulovacki M, 1999). Hypothesizing that combined stimulation of central 5-HT2 and inhibition of peripheral 5-HT3 receptors may

decrease apnea irrespective of the stage of sleep, Drs. Prasad and Carley have successfully tested the effectiveness of a combination of the drugs ondansetron and fluoxetine in reducing sleep apnea through a proof of concept, double blinded, placebo controlled, parallel groups clinical trial. This study is the first to investigate a combined pharmacological approach in humans with OSA, targeting previously examined site and receptor specific serotonin–mediated effects. Combination treatment with a serotonin type-3 receptor antagonist (ondansetron) and a serotonin reuptake inhibitor (fluoxetine) was well-tolerated by OSA patients and reduced the frequency of apneas and hypopneas by an average of 40% even in patients with moderate to severe disease (Prasad et. al., 2011). They have clinically demonstrated potential treatment effects of this drug combination, but future studies are required for definitive evaluation of the responses with high dose combination of these drugs. Despite successes in small short-term studies, there is not enough evidence to recommend drug therapy for obstructive sleep apnea (Mason et. al., 2013).

2.2. Airway Imaging

The development and adoption of three-dimensional airway imaging techniques such as cone beam computed tomography (CBCT) in medicine and dentistry have become commonplace (Abramson et. al., 2010). Due to the lack of norms and published meta-analyses, airway imaging is not yet widely accepted as a diagnostic tool to assess

OSA but its value may lie in assessing predictors for treatment success (Alsufyani et. al., 2013). There is also the possibility that it could be used as a predictive tool to help identify and refer potential high-risk cases of OSA (Momany et. al., 2016). While 2D cephalometric data is readily available, there are conflicting results in the literature – some showing that 2D variables derived from lateral cephalometric radiographs can predict treatment success with OAs, and others that do not show any significant 2D predictors (Alessandri-Bonetti et. al., 2015).

Regarding 3D images, CBCT has exhibited potential to serve as a tool to assess OA treatment response in OSA patients (Furuhashi et. al., 2013). Some obstacles remain to utilizing CBCT imaging such as controlling for the impact of the respiration phase, the influence of tongue position, and the definition of anatomical boundaries of the upper airway. Chen and colleagues employed a commonly used methodology for obtaining reliable anatomical landmark localization and upper airway measurements from 3-D imaging (Chen et. al., 2016). ANS and PNS were used to define the superior plane. The anterior-inferior point of the second cervical vertebra was used as the most inferior point. Localization of landmarks were done in the axial, sagittal, and coronal views. Reported measurements often include the minimum cross-sectional area (CSA) of the upper airway, total airway volume, and posterior nasal spine and the second cervical vertebrae distance (Momany et. al., 2016)

III. MATERIALS AND METHODS

3.1 Study Design

We conducted a prospective placebo-controlled blinded crossover study of seven (7) subjects with moderate to severe OSA treated initially with MADs and placebo for 2 weeks and then followed by a combination regimen of the drugs ondansetron + fluoxetine in addition to ongoing MAD treatment for another 4 weeks for a total treatment period of 42 days. The rationale behind this design is to assess effect sizes of both modes of treatment to further test the hypothesis of additive or synergistic efficacy of the combined treatment with drugs and oral appliance. We realize that introducing drug therapy only in the 3rd week of study may cause a placebo effect thus we have designed a placebo-controlled blinded crossover, administering placebo drugs with the same dosage instructions together with MADs in the first 14 days and subsequently converting to the study drugs fluoxetine and ondansetron the following 4 weeks.

The primary outcome measures will be parameters derived from polysomnography. These will include treatment related change in Apnea-Hypopnea Index (AHI; number of apneas or hypopneas per hour of sleep), respiratory effort related arousals (RERA index), oxygen desaturation index (ODI), and sleep efficiency. Secondary outcome measures will include: airway volume determined by cone beam CT, the Epworth Sleepiness Scale (a subjective self-assessment of sleepiness), the Functional

Outcomes of Sleep Questionnaire (FOSQ; a self-assessment instrument to evaluate the impact of sleep/sleepiness on daily functioning), the Treatment Satisfaction Questionnaire for Medication (TSQM) to measure treatment acceptability, and the Psychomotor Vigilance Test (PVT) to serve as an objective measure of daytime alertness.

Each eligible, enrolled subject progressed through the following series of procedures, beginning with the initial screening visit. At the initial screening visit, the following tests were performed for determination of study eligibility: routine physical exam, medical history to determine any previous treatments that may exclude subject from study, urine test for drug screening and pregnancy test (if appropriate), dental examination. A baseline polysomnogram test was required to determine eligibility if there has not been any within the past two months. The urine tests were repeated two other times during the study (Study Day 1 – Appliance delivery, and Study Day 14) to confirm that the subjects still meet the inclusion criteria, and to ensure the subject's safety.

3.2. Subject Recruitment

Initial efforts focused on recruiting treatment-naïve individuals using flyers made available at the UIC Sleep Science Center for co-investigator Dr. Prasad for informing potential subjects of the ongoing research. As an additional recruitment strategy,

subjects who were intolerant to CPAP will be were identified at the UIC Sleep Science Center through screening of existing medical records. We have defined CPAP failure less than two hours nightly (mean CPAP hours per night <2 hours for the past 30 days or more). A letter of invitation will bewas sent to subjects who initially meet the inclusion/ exclusion criteria. If they were interested, they were scheduled to come to the UIC Sleep Science Center for an initial selection visit. During that visit, we explained the study in detail, answered any questions, and executed the informed consent document and the HIPAA authorization form.

3.3. Inclusion Criteria

- Patients aged 18-64 yrs. with confirmed diagnosis of OSA defined apnea-hypopnea index (AHI) 20-50 by baseline polysomnography
- Have at least five posterior teeth in each quadrant for retention of the MAD

3.4. Exclusion Criteria

- Patients with very severe OSA warranting immediate care in Dr. Prasad's medical judgment, or whose oxygen saturation is less than 75% for more than 5% of the sleep period time as confirmed by their diagnostic polysomnogram
- Patients with previous chronic use of alcohol, narcotics, or other psychotropic drugs

- Patients who have been treated for OSA by any type of surgery
- Patients who have undergone major surgery within 6 months
- Patients presenting a significant defect in nasal patency due to anatomical abnormalities or uncontrolled or recurrent episodes of rhinitis
- Any clinically significant unstable or progressive medical condition
- Any primary sleep disorder other than OSA (determined by history, physical examination and Screening PSG)
- Presence or history of clinically significant: COPD, cardiovascular disease, gastrointestinal, respiratory, pancreatic, hepatic, renal, hematologic, endocrine (including IDDM), neurological, urogenital, connective tissue, dermatological, thyroid, or other medical disorder
- Presence or history of any clinically significant psychiatric disorder
- Pregnancy demonstrated by positive urine HCG
- Current report or laboratory evidence of drug abuse (urine screening)
- Current orthodontic treatment (braces)
- Active periodontal disease
- Active temporomandibular joint disease
- Individuals who work evening, night, or rotating shifts

3.5. Oral Appliance Fabrication and Delivery

All new patients screened at the Sleep Science Center who meet the inclusion criteria will be made aware of the study. Those who agree to participate and meet the above-mentioned inclusion/exclusion criteria will then be enrolled in the study. Study subjects will report to the orthodontic clinic at the College of Dentistry, where alginate impressions of the upper and lower dental arches will be taken, and bite registration will be recorded and sent to Great Lakes orthodontic laboratory to fabricate the TAP3™ Elite custom made fully adjustable MADs.

The MADs used in this study will be a Thornton Adjustable Positioner - TAP3™ Elite custom suited fully adjustable 2-piece device, fabricated by specially trained dental technicians under the supervision of Dr. Stache. The fabrication procedure involved the following procedures: 1) alginate impressions of the maxillary and mandibular dentition, 2) a protrusive wax interocclusal record at 60-75% maximal protrusion, 3) delivery of two full-coverage clear acrylic appliances that fit onto the dental arches connected by wires extending from the upper arch adjustment of the device for titration of mandibular advancement which allows protrusive movement of up to 7mm. A minimum number of teeth (five per quadrant) is necessary to hold the appliance in place.

Dental assessment was performed at appliance delivery to titrate the appliance to 50% of the maximum protrusion. Patients will be allowed to acclimate to this protrusion

for 1 week, after which we will increase protrusion to 75% of the maximum depending on patient tolerance. Evaluation of patients' oral health and appliance fit were assessed, and appliance wear/ drug intake logs and sleep log questionnaires were also administered.

At visit 3, appliance delivery, after appliance titration, blister cards containing the placebo drugs were distributed and instructions given regarding dosage – one in the morning with breakfast and another in the evening 30 minutes before bedtime. These drugs were encapsulated and packaged in blister cards labeled with dosage day and time (am/ pm) and the returned empty cards serve as an adherence log for the drug regimen. The UIC Investigational Drug Service was responsible for both packaging and providing the over-encapsulated study drugs.

3.6 Titration of MAD with Placebo and Airway Imaging

The MAD advancement level was held in place for 1 week as the patient wore the appliance each night for the duration of their sleep. Any discomfort caused during this period was addressed and corrected as necessary by the principal investigator at the one-week follow-up visit, during which the appliance was further titrated to 75% maximum advancement. Two baseline cone-beam computed tomography (CBCT) radiographs were taken at this time. One without the appliance at end-inspiration and

one at functional residual capacity (FRC). Two images were taken with the appliance in place at the same respiratory time points. The patients were advised to record their number of hours of appliance use and sleep in a log provided at the beginning of treatment.

Our airway imaging was completed at a single time point one week into oral appliance wear. The rationale for this was to wait until the MAD could be titrated to the level most comfortable and effective for each subject. This corresponded to approximately 75% of the subject's maximum protrusion.

Airway measurements were completed using Dolphin 3D imaging software, utilizing previously validated anatomical landmarks and thresholds (Guijarro-Martinez R and Swennen G, 2013). CBCT images were imported into the software using the 3D module. All airway measurements were done by one evaluator (RS). The superior limit was defined as a plane parallel to Frankfort Horizontal (FH) from PNS to the posterior pharyngeal soft tissue wall. The inferior limit was defined as a plane parallel to FH extending from the anterior-inferior point of the third cervical vertebrae (C3ai) to the anterior pharyngeal soft tissue wall. Seed points were placed within the boundaries of the upper airway so that the software could calculate total volume. Sensitivity was set to 70 in order to maximize upper airway volume while minimizing artifacts and noise.

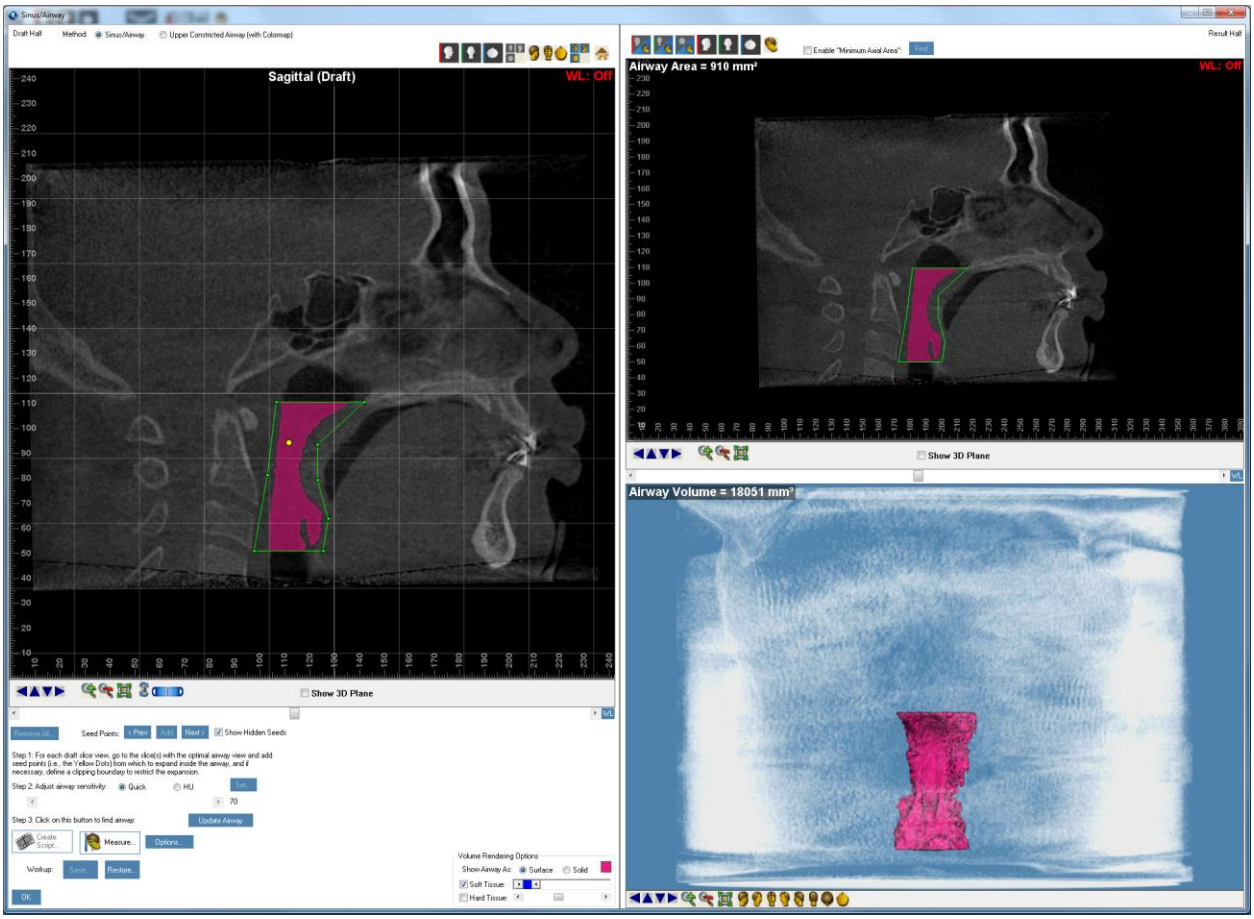

Figure 1. Airway boundary, seed point, and sensitivity setting.

Minimum cross-sectional area was calculated using the corresponding module. This individual slice was examined for two additional linear measurements, the largest anterior-posterior (A-P) and transverse dimension. From these two measurements, a shape ratio could be determined by dividing the A-P by the transverse measurement.

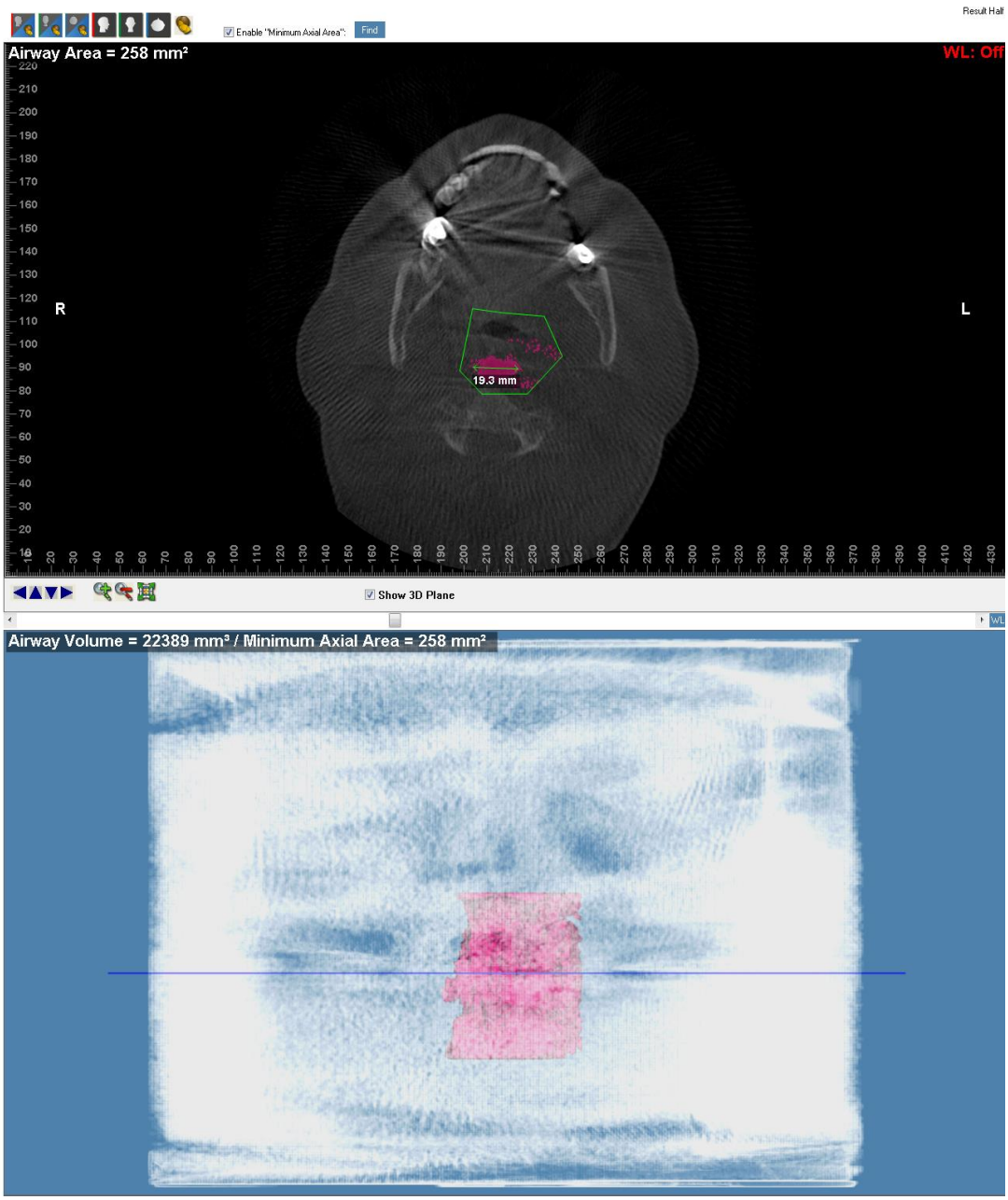

Figure 2. Minimum CSA and airway volume measurements.

At the end of the 2nd week, the patients returned to the Sleep Science Center for a repeat polysomnogram to determine any changes in AHI and sleep architecture. At this time, they returned their empty blister cards.

3.7 Polysomnography

Attended overnight polysomnography is the most precise diagnostic method for diagnosing OSA and involves continuously recording the following: electroencephalograms; right and left electrooculogram; submental and bilateral anterior tibialis electromyograms; electrocardiogram; respiration monitored through nasal pressure transducer, thermocouples at the nose and mouth, and thoracic and abdominal strain gauges; oxyhemoglobin saturation by pulse oximetry; snoring by laryngeal microphone (Punjabi NM, Beamer BA, 2009).

The following variables were recorded by overnight polysomnography at baseline (diagnosis), after MAD-placebo treatment, and at the end of the study after combination drug-MAD treatment: apnea-hypopnea index (AHI), respiratory effort related arousal index (RERA), sleep efficiency, and oxygen desaturation index (ODI). Sleep stages and respiratory events (apneas, hypopneas) were scored according to American Academy of Sleep Medicine criteria by a registered technician and reviewed by board certified sleep specialist, Dr. Bharati Prasad. Our inclusion criteria seek subjects who have an AHI between 20-50 to address the unmet need of providing treatment alternatives for the moderate to severe OSA patient population. The morning after this polysomnogram, subjects were provided with new blister cards containing daily doses of over-encapsulated study drugs.

3.8. Pharmacological Intervention

Patients were prescribed a combination of serotonergic drugs ondansetron and fluoxetine for the next 28 days. Patients were advised to take fluoxetine 10mg with breakfast and ondansetron 24mg at night 30 minutes before going to bed following the same protocol employed by Prasad and Carley. The drugs were over-encapsulated for blinding purposes and packaged in blister cards according to daily dosage schedule, thus the returned empty cards served as an additional adherence log. Another overnight polysomnogram test was conducted at the end of the 42-day treatment period.

Subjects continued to wear the MADs at night and completed daily sleep and treatment adherence logs. Patients returned at Day 28 of the study, two weeks into medication use, to return empty blister card pack and received an additional two-week supply. Giving the patient new blister card packs at each two-week interval aimed to eliminate any bias the patient may internalize as to whether they are receiving placebo or actual medication. A final polysomnogram was performed on the twenty-eighth night of MAD + pharmacotherapy treatment.

3.9. Adjunctive Outcome Measures

Throughout the study, daytime sleepiness, functional status, and daytime

vigilance were assessed using the Epworth Sleepiness Scale (ESS), Functional outcomes of sleep questionnaire (FOSQ), Visual Analog Scale (VAS) for sleepiness, and Psychomotor Vigilance Task (PVT), at baseline (at the time the MAD is delivered to the subject), and again on the morning after each polysomnogram. A modification of the "gold standard" PVT-192 device will be utilized in this study. It has been validated and is capable of measuring response times with a mean delay of less than 10 ms (Khitrov et. al., 2014). The PC-PVT is a freely available software than runs on a computer and uses a left click of the mouse button as the input device. All tests and responses were recorded in the program and analyzed for the subject's mean 1/RT (response speed) and number of lapses. These two variables are most commonly cited in literature and used as objective measures of sleep deprivation because of their high sensitivity (Basner M, Dinges DF, 2011).

Each patient was given the following instructions: The PVT is a simple test where you will be asked to click the left mouse button as soon as you seen a number displayed on the screen. The number will turn on randomly every few seconds for 10 minutes. The purpose of this test is to measure how long you can keep your attention on this task, and to see how sleepy you are.

Medication satisfaction was assessed via the Treatment Satisfaction

Questionnaire for Medications (TSQM) at specified time points.

A follow-up visit 2 weeks after study termination was held to monitor and record any adverse events after the study. At this follow-up visit, a brief assessment of vitals and symptomatic changes, if any, was also conducted. Routine treatment instructions and/or referrals to a sleep medicine physician were given to manage patients accordingly after study termination.

IV. RESULTS

4.1. Subject Characteristics

Baseline sleep study records and past medical history of all patients from the UIC Sleep Science Center were examined for an AHI score of 20-50 over a nearly two-year recruitment period. 1500 patient medical records were filtered based on AHI range and past medical history was reviewed for initial eligibility. Of those records, 228 subjects were initially recruited by mail and phone call to determine study eligibility based on inclusion and exclusion criteria. 15 subjects met inclusion and exclusion criteria and were enrolled in the study. Of the 15 enrolled subjects (8 male and 7 female), 5 were dropped because they did not complete all required study visits. 2 subjects were dropped because of poor treatment response to oral appliance therapy. 1 subject could not tolerate the oral appliance and was dropped. A sample of 7 subjects (5 male and 2 female) was included in the final analysis of this study. All subjects were obese (mean BMI 39.1±6.6) at baseline.

4.2. Statistical Analysis

Test of normality by Shapiro-Wilk indicated that the majority of the study variables are normally distributed. Student's t-test was used. Statistical significance was set at 0.05. IBM SPSS version 22.0 (IBM, Armonk, NY) was used to analyze the data.

4.3. Subjective Outcome Measures

A paired samples t-test indicated that Epworth Sleepiness Scale (ESS) score was on average statistically significant between time point 1 and time point 7. ESS1-ESS7, p-value=0.017, the mean of ESS at T1 is higher than ESS at T7. There was an average decrease in ESS of 3.14 overall. This indicates that subjective daytime sleepiness improved.

TABLES I-IV. EPWORTH SLEEPINESS SCALE RESULTS

T-Test/Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ESS 1	10.4286	7	5.34968	2.02199
	ESS 5	7.7143	7	5.40723	2.04374
Pair 2	ESS 1	10.4286	7	5.34968	2.02199
	ESS 7	7.2857	7	5.85133	2.21160
Pair 3	ESS 5	7.7143	7	5.40723	2.04374
	ESS 7	7.2857	7	5.85133	2.21160

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ESS 1 & ESS 5	7	.823	.023
Pair 2	ESS 1 & ESS 7	7	.901	.006
Pair 3	ESS 5 & ESS 7	7	.951	.001

Paired Samples Test

		Paired Differences				
					95% Confidence Interval of the Difference	
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper
Pair 1	ESS 1 - ESS 5	2.71429	3.19970	1.20937	-.24495	5.67352
Pair 2	ESS 1 - ESS 7	3.14286	2.54484	.96186	.78928	5.49644
Pair 3	ESS 5 - ESS 7	.42857	1.81265	.68512	-1.24785	2.10500

Paired Samples Test

		t	df	Sig. (2-tailed)
Pair 1	ESS 1 - ESS 5	2.244	6	.066
Pair 2	ESS 1 - ESS 7	3.267	6	.017
Pair 3	ESS 5 - ESS 7	.626	6	.555

Paired Samples Statistics

Functional Outcomes of Sleep Questionnaire (FOSQ) and Visual Analog Scale of sleepiness (VAS) tests did not show statistical significance.

4.4. Objective Daytime Sleepiness

A paired samples t-test indicated that Psychomotor Vigilance Test (PVT) Mean Response Time (RT) was on average statistically significant between time point 1 and time point 5 and between time point 1 and time point 7. PVT mean RT 1 – PVT mean RT 5 and PVT mean RT 1 – PVT mean RT 7, p-values = 0.016 and 0.019, respectively. The mean PVT mean RT1 is higher than the mean on PVT mean RT 5 and 7.

Mean PVT response time also indicated a decrease from T5 to T7, but this was not statistically significant.

TABLES V-VIII. PSYCHOMOTOR VIGILANCE TEST RESULTS

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	PVT Mean RT 1	355.2857	7	46.51062	17.57936
	PVT MeanRT 5	303.2857	7	42.68768	16.13443
Pair 2	PVT Mean RT 1	355.2857	7	46.51062	17.57936
	PVT MeanRT 7	300.0000	7	45.14791	17.06430
Pair 3	PVT MeanRT 5	303.2857	7	42.68768	16.13443
	PVT MeanRT 7	300.0000	7	45.14791	17.06430

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	PVT Mean RT 1 & PVT MeanRT 5	7	.573	.179
Pair 2	PVT Mean RT 1 & PVT MeanRT 7	7	.499	.254
Pair 3	PVT MeanRT 5 & PVT MeanRT 7	7	.947	.001

Paired Samples Test

	Paired Differences				
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	
Pair 1 PVT Mean RT 1 - PVT MeanRT 5	52.00000	41.35618	15.63117	13.75192	
Pair 2 PVT Mean RT 1 - PVT MeanRT 7	55.28571	45.86834	17.33660	12.86457	
Pair 3 PVT MeanRT 5 - PVT MeanRT 7	3.28571	14.48809	5.47598	-10.11353	

Paired Samples Test

	Paired Differences 95% Confidence Interval of the Difference Upper	t	df	Sig. (2-tailed)
Pair 1 PVT Mean RT 1 - PVT MeanRT 5	90.24808	3.327	6	.016
Pair 2 PVT Mean RT 1 - PVT MeanRT 7	97.70686	3.189	6	.019
Pair 3 PVT MeanRT 5 - PVT MeanRT 7	16.68496	.600	6	.570

Paired Samples Statistics

4.5. Structural Airway Changes

All subjects showed an increase in total airway volume and minimum cross-sectional area (CSA) from baseline to intervention (MAD + Placebo). The changes were not statistically significant. Mean total airway volume increased by 35%. Minimum CSA increased by 48.8%.

TABLES IX-XII. AIRWAY MEASUREMENTS

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Total Volume (mm3) 4	12958.7143	7	6911.14425	2612.16700
	Total Volume (mm3) 4	17544.0000	7	10002.92679	3780.75095
Pair 2	Airway Shape (AP/TV at minCSA) 4	.4563	7	.16512	.06241
	Airway Shape (AP/TV at minCSA) 4 2	.4386	7	.12805	.04840
Pair 3	Oro Min CSA 41	109.8571	7	82.96069	31.35619
	Oro Min CSA 42	163.4286	7	108.19097	40.89234

Paired Samples Correlations

	N	Correlation	Sig.
Pair 1 TotalVolume(mm3)41&TotalVolume(mm3)42	7	.846	.016
Pair 2 Airway Shape (AP/TV at minCSA)41 & Airway Shape (AP/TV at minCSA) 4 2	7	.181	.698
Pair 3 Oro Min CSA 41&Oro Min CSA 42	7	.765	.045

Paired Samples Test

		Paired Differences			
		Mean	Std. Deviation	Std. Error Mean	95% C.I of Difference Lower
Pair 1	TotalVolume (mm3) 41-Total Volume(mm3)42	-4585.285	5551.40705	2098.23464	-9719.48092
Pair 2	AirwayShape(AP/TVatminCSA)41-Airway Shape(AP/TVat minCSA)42	.01771	.18978	.07173	-.15780
Pair 3	OroMinCSA41-OroMinCSA42	-53.57143	69.62006	26.31391	-117.95924

Paired Samples Test

		Paired Differences 95% C. I. the Difference Upper	t	df	Sig. (2-tailed)
Pair 1	Total Volume (mm3)41- Total Volume (mm3) 42	548.90949	-2.185	6	.072
Pair 2	Airway Shape (AP/TV at minCSA) 4 1- Airway Shape (AP/TV at minCSA) 4 2	.19323	.247	6	.813
Pair 3	Oro Min CSA 41 - Oro Min CSA 42	10.81639	-2.036	6	.088

Paired Samples Statistics

Figure 3. Airway volume without MAD.

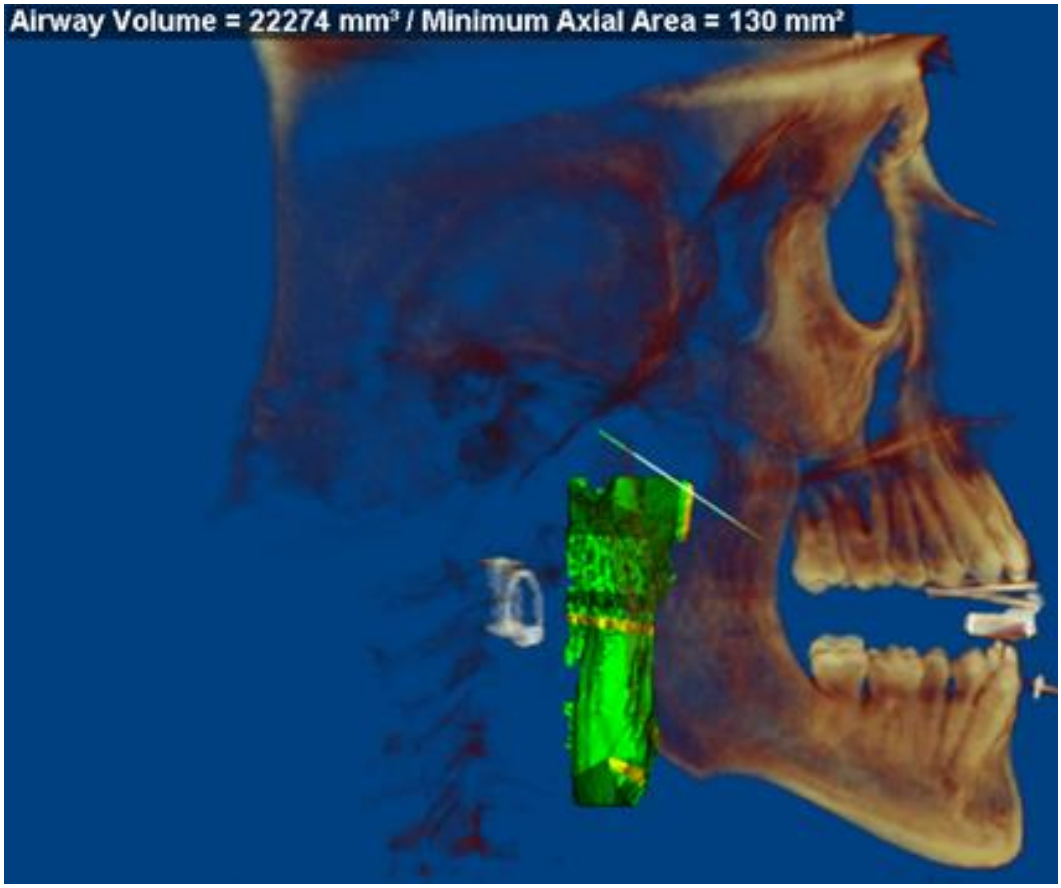

Figure 4. Airway volume with MAD titrated to 75% maximum protrusion.

4.6. Sleep Architecture Changes

Time points 1, 5, and 7 were used for statistical analysis. These time points correspond with the polysomnograms taken at baseline, MAD + placebo, and MAD + drugs, respectively. A paired samples t test indicated that four sleep study variables, on average, were statistically significantly different between their time points:

AHI5-AHI7, p-value= 0.008, the mean on AHI5 is higher than the mean on AHI7. There was a slight increase or worsening of the mean AHI score from baseline to MAD + placebo, but this was not statistically significant. Mean AHI showed a favorable decrease with the combination treatment of MAD + drugs compared to MAD + placebo.

TABLES XIII-XVI. AHI RESULTS

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	AHI 1	31.7714	7	11.27766	4.26256
	AHI 5	33.9286	7	17.53508	6.62764
Pair 2	AHI 1	31.7714	7	11.27766	4.26256
	AHI 7	21.0571	7	15.36184	5.80623
Pair 3	AHI 5	33.9286	7	17.53508	6.62764
	AHI 7	21.0571	7	15.36184	5.80623

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	AHI 1 & AHI 5	7	.241	.603
Pair 2	AHI 1 & AHI 7	7	.049	.917
Pair 3	AHI 5 & AHI 7	7	.871	.011

Paired Samples Test

		Paired Differences				
					95% Confidence Interval of the Difference	
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper
Pair 1	AHI 1 - AHI 5	-2.15714	18.42198	6.96286	-19.19464	14.88035
Pair 2	AHI 1 - AHI 7	10.71429	18.60694	7.03276	-6.49426	27.92283
Pair 3	AHI 5 - AHI 7	12.87143	8.61331	3.25552	4.90545	20.83741

Paired Samples Test

		t	df	Sig. (2-tailed)
Pair 1	AHI 1 - AHI 5	-.310	6	.767
Pair 2	AHI 1 - AHI 7	1.523	6	.178
Pair 3	AHI 5 - AHI 7	3.954	6	.008

Paired Samples Statistics

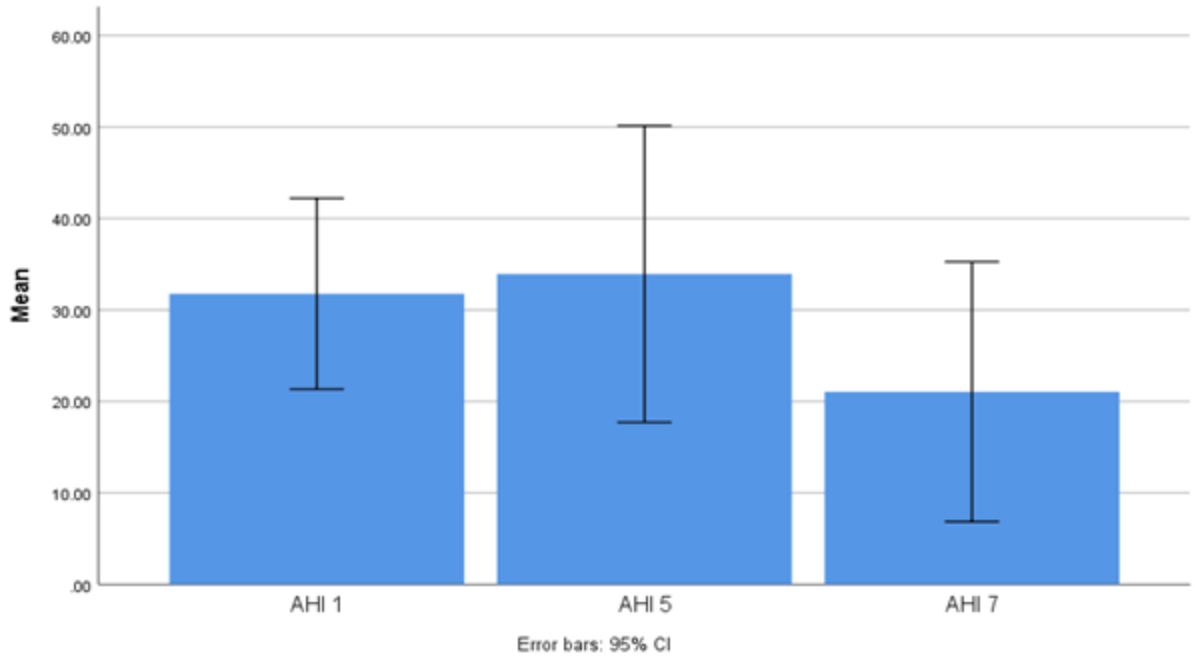

Figure 5. Mean AHI

Respiratory Effort-Related Arousals (RERA) Index 1 – RERA Index 7, p-values= 0.042, the mean RERA Index at baseline (7.1 ± 6.8) is higher than mean RERA Index of MAD + drugs (1.7 ± 1.6). The average RERA index favorably decreased from baseline to both treatment time points, and time point 1 to 7 showed statistical significance.

TABLES XVII-XX. RERA INDEX RESULTS

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	RERA Index 1	7.1429	7	6.84248	2.58621
	RERA Index 5	2.5143	7	1.45308	.54921
Pair 2	RERA Index 1	7.1429	7	6.84248	2.58621
	RERA Index 7	1.7143	7	1.58895	.60057
Pair 3	RERA Index 5	2.5143	7	1.45308	.54921
	RERA Index 7	1.7143	7	1.58895	.60057

Paired Samples Correlations

	N	Correlation	Sig.
Pair 1 RERA Index 1 & RERA Index 5	7	-.246	.595
Pair 2 RERA Index 1 & RERA Index 7	7	.840	.018
Pair 3 RERA Index 5 & RERA Index 7	7	-.649	.115

Paired Samples Test

	Paired Differences			
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower
Pair 1 RERA Index 1 - RERA Index 5	4.62857	7.33592	2.77272	-2.15602
Pair 2 RERA Index 1 - RERA Index 7	5.42857	5.57426	2.10687	.27324
Pair 3 RERA Index 5 - RERA Index 7	.80000	2.76285	1.04426	-1.75521

Paired Samples Test

	Paired Differences 95% Confidence Interval of the Difference Upper	t	df	Sig. (2-tailed)
Pair 1 RERA Index 1 - RERA Index 5	11.41317	1.669	6	.146
Pair 2 RERA Index 1 - RERA Index 7	10.58390	2.577	6	.042
Pair 3 RERA Index 5 - RERA Index 7	3.35521	.766	6	.473

Paired Samples Statistics

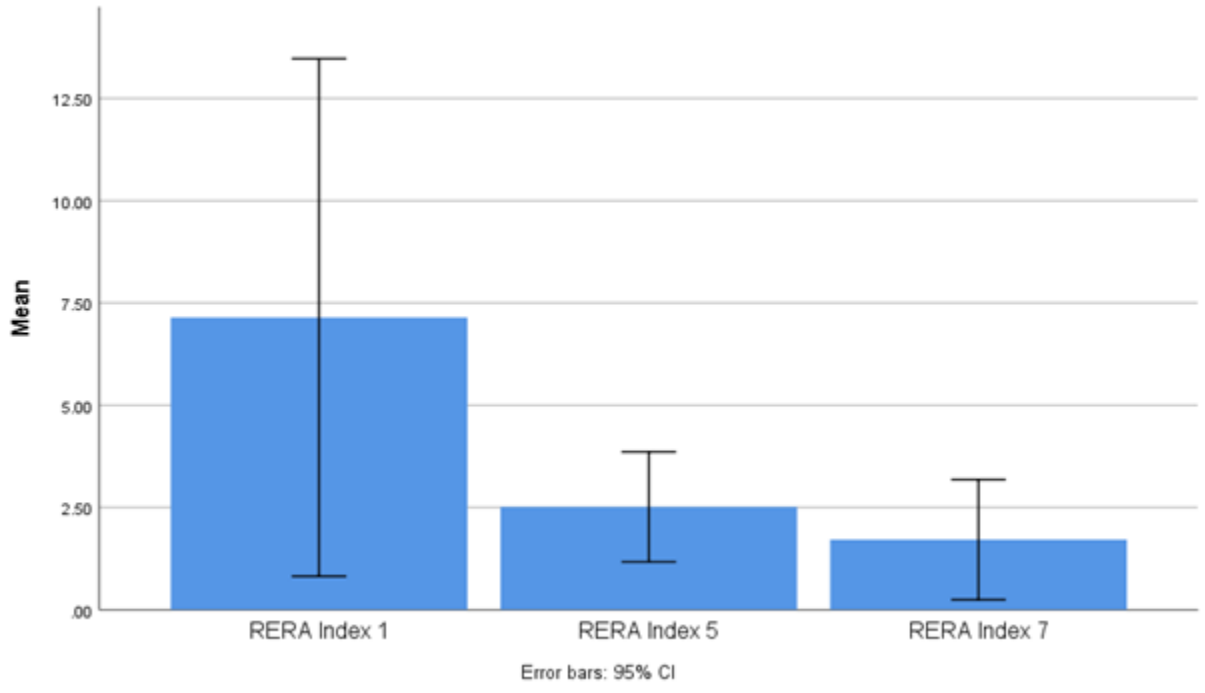

Figure 6. Mean RERA index

Sleep Efficiency % 1 - Sleep Efficiency% 5, P-values=0.019, the mean Sleep Efficiency % 1 is lower than Sleep Efficiency % at time point 5. This was statistically significant and indicated that sleep efficiency improved with MAD + placebo (77.4 ± 11.2) compared to baseline (62.9 ± 19.5). There was a slight, but insignificant increase in sleep efficiency from MAD + placebo (77.4 ± 11.2) to MAD + drugs (77.5 ± 11.3). While sleep efficiency increased overall from baseline to the end of the study, it was not statistically significant.

TABLES XXI-XIV. SLEEP EFFICIENCY RESULTS

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Sleep Efficiency % 1	62.8714	7	19.54514	7.38737
	Sleep Efficiency % 5	77.4143	7	11.23231	4.24541
Pair 2	Sleep Efficiency % 1	62.8714	7	19.54514	7.38737
	Sleep Efficiency 7	77.5286	7	11.26598	4.25814
Pair 3	Sleep Efficiency % 5	77.4143	7	11.23231	4.24541
	Sleep Efficiency 7	77.5286	7	11.26598	4.25814

Paired Samples Correlations

	Correlation	Sig.
Pair 1 Sleep Efficiency% &Sleep Efficiency%5	.825	.022
Pair 2 Sleep Efficiency % 1&Sleep Efficiency 7	.339	.457
Pair 3 Sleep Efficiency %5 &Sleep Efficiency 7	.128	.785

Paired Samples Test

	Paired Differences			
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower
Pair 1 SleepEfficiency%1-Sleep Efficiency%5	-14.54286	12.08785	4.56878	-25.72226
Pair 2 SleepEfficiency%1-Sleep Efficiency7	-14.65714	18.96452	7.16791	-32.19639
Pair 3 SleepEfficiency%5-SleepEfficiency 7	-.11429	14.85939	5.61632	-13.85693

Paired Samples Test

	Paired Differences 95% C.I. of the Difference Upper	t	df	Sig. (2-tailed)
Pair 1 Sleep Efficiency % 1 - Sleep Efficiency % 5	-3.36346	-3.183	6	.019
Pair 2 Sleep Efficiency % 1 - Sleep Efficiency 7	2.88211	-2.045	6	.087
Pair 3 Sleep Efficiency % 5 - Sleep Efficiency 7	13.62836	-.020	6	.984

Paired Samples Statistics

Oxygen Desaturation Index (ODI) 5 – ODI 7, p-values= 0.015, the mean on ODI 5 is higher than mean on ODI 7. Mean ODI showed a statistically significant favorable decrease between MAD + placebo (32.3 ± 17.4) and MAD + drugs (22.8 ± 16.3).

TABLES XXV-XVIII. OXYGEN DESATURATION INDEX RESULTS

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ODI 1	33.7429	7	14.68717	5.55123
	ODI 5	32.3571	7	17.41004	6.58038
Pair 2	ODI 1	33.7429	7	14.68717	5.55123
	ODI 7	22.8429	7	16.34563	6.17807
Pair 3	ODI 5	32.3571	7	17.41004	6.58038
	ODI 7	22.8429	7	16.34563	6.17807

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ODI 1 & ODI 5	7	-.065	.889
Pair 2	ODI 1 & ODI 7	7	.125	.789
Pair 3	ODI 5 & ODI 7	7	.904	.005

Paired Samples Test

		Paired Differences Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper
Pair 1	ODI 1 - ODI 5	1.38571	23.50081	8.88247	-20.34891	23.12034
Pair 2	ODI 1 - ODI 7	10.90000	20.56186	7.77165	-8.11655	29.91655
Pair 3	ODI 5 - ODI 7	9.51429	7.45418	2.81741	2.62032	16.40825

Paired Samples Test

		t	df	Sig. (2-tailed)
Pair 1	ODI 1 - ODI 5	.156	6	.881
Pair 2	ODI 1 - ODI 7	1.403	6	.210
Pair 3	ODI 5 - ODI 7	3.377	6	.015

Paired Samples Statistics

4.7. Additional Findings

Five out of seven subjects (71%) showed a decrease in AHI of 40% or greater from baseline compared to intervention with MAD + drugs. These subjects were defined as "positive responders" to treatment intervention. Of those five positive responders, four were male and one was female.

TABLE XXIX. DESCRIPTIVE STATISTICS

			Responder V1-7 >40% decrease in AHI-category		
			Yes	No	Total
gender	male	Count	4	1	5
		% of Total	57.1%	14.3%	71.4%
	female	Count	1	1	2
		% of Total	14.3%	14.3%	28.6%
Total		Count	5	2	7
		% of Total	71.4%	28.6%	100.0%

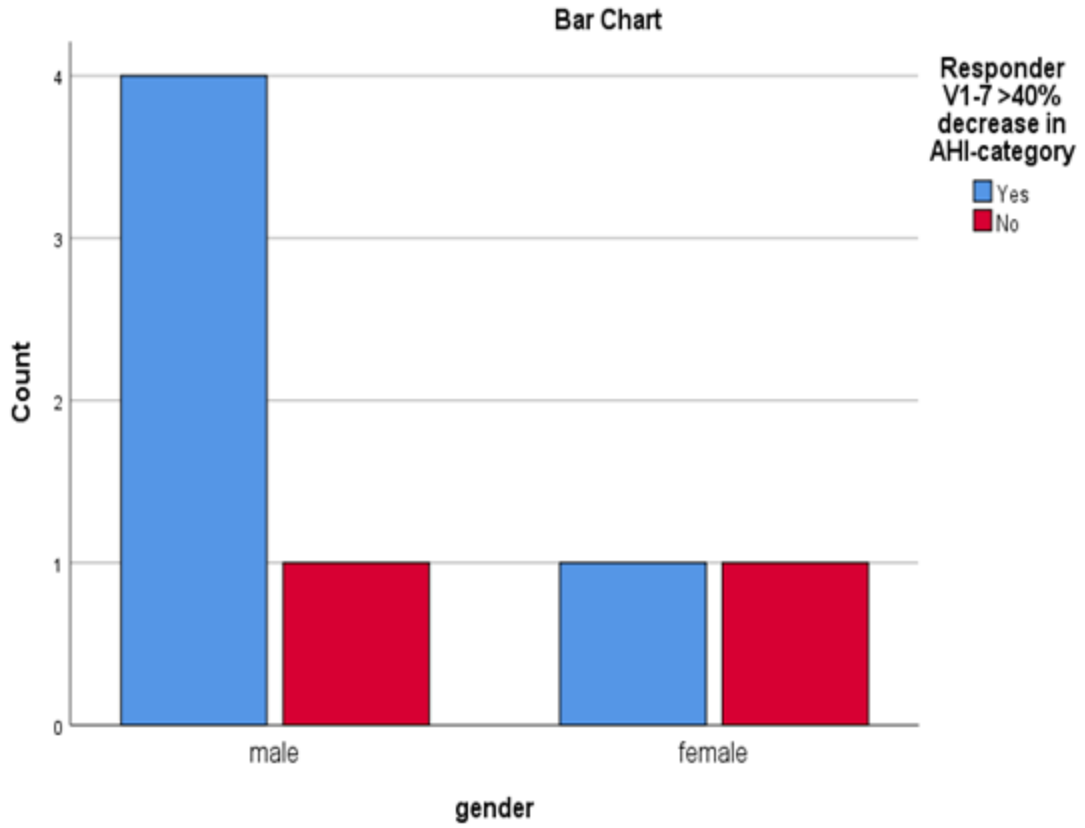

Figure 7. Positive responders by gender

Positive responders had a lower mean BMI (35.6 ± 3.36) than non-responders (48.0 ± 0).

TABLES XXX-XXXI. POSITIVE RESPONDERS BMI

RV17decAHIc = 1- Responder V1-7 >40% decrease in AHI-category
Means/Report

	BMI 1	Responder V1-7 >40% decrease in AHI-%
Mean	35.6000	57.8000
N	5	5
Std. Deviation	3.36155	20.95710

RV17decAHIc = 2	BMI 1	Responder V1-7 >40% decrease in AHI-%
Mean	48.0000	147.0000
N	2	2
Std. Deviation	.00000	56.56854

V. DISCUSSION

5.1. Objective Outcomes

The goal of this pilot study was to determine if combination treatment of oral appliance therapy with pharmacological intervention was effective in moderate to severe obstructive sleep apnea patients. Oral appliance therapy is indicated in cases of mild-moderate obstructive sleep apnea (Ferguson et. al., 2006). It has not been shown to be fully effective in moderate to severe OSA. This study explored the feasibility of treating this patient population with an oral appliance augmented with previously investigated drugs to provide a viable alternative to continuous positive airway pressure.

Night-to-night variability in polysomnogram studies is a well-established phenomenon (Ahmadi et. al., 2009). Stöberl and colleagues followed 77 patients with OSA for two weeks with pulse-oximetry and found significant variability in severity as measured by AHI from night-to-night (Stöberl et. al., 2017). This could explain the increase in AHI for 5 of our 7 subjects from baseline to visit 5 (oral appliance plus placebo). When comparing visit 5 to 7 (oral appliance plus drugs), all 7 subjects showed a decrease in AHI. This suggests that our combination intervention had a positive effect on reducing the number of apneas and hypopneas experienced during sleep.

5 of 7 subjects had a decrease in AHI of 40% or greater from baseline to the end of the study. These subjects were defined as positive responders. No report of adverse drug side effects was recorded from patient study logs, and both oral appliances and medications were well-tolerated. Some subjects reported mild jaw soreness the morning after wearing the oral appliance, but this subsided after 1-2 weeks of wear.

We found that response to treatment varied significantly with all subjects. For oral appliances, the best responders tend to have mild to moderate OSA, have a greater amount of advancement in their appliance, have a lower BMI, and have a greater difference in respiratory events between supine and lateral sleep positions (Ferguson et. al., 2006).

A previously published study followed a 28-day protocol and it is widely accepted that the full therapeutic benefit of fluoxetine is not reached until approximately 4-6 weeks. For this reason, we chose to have the subjects remain on the combination drug treatment for 28 days before undergoing the last polysomnogram of the study.

It is important to note that AHI is not the only important variable recorded during sleep. There are also inherent problems with the Apnea-Hypopnea Index. It is an imperfect outcome measure. There is no quantification of work of breathing. There is

also no differentiation between short and long events. There is currently no consensus on the definition of what is considered a hypopnea. The AASM defines a hypopnea as a 30% drop in nasal pressure for at least 10 seconds when accompanied by a 4% drop in arterial oxygen saturation from baseline. Other authors define a hypopnea as a 50% reduction in ventilation with a ≥4% drop in arterial oxygen saturation, while some define it as a ≥3% decrease in arterial oxygen saturation. (Won et. al., 2018). AHI may or may not be the optimal metric to evaluate sleep-disordered breathing. Additionally, some patients may experience a greater proportion of apneas and hypopneas during specific stages (REM-related OSA) or positions of sleep such as during supine sleep (Duce et. al., 2018). All subjects showed improvement in AHI from OA + placebo to OA + meds, and from baseline to OA + meds. Severity was reduced from severe to moderate in 6 subjects and to mild in 1 subject. Because treatment was not fully effective, subjects were referred to their sleep physician for follow-up evaluation and treatment.

Respiratory effort-related arousals (RERA) can be thought of as a milder form of an apnea or hypopnea. It defined as a subtle fluctuation in airway of 1-2%, lasting 10 seconds or longer, and leads to an arousal or decrease in oxygen saturation (Tsara et. al., 2009). The significance of this is that these are not captured in the AHI score. They are an important outcome measure that can affect overall sleep quality and restfulness. Our data showed a statistically significant decrease in RERA index from baseline, despite not

showing the same with AHI. This highlights the fact that AHI may not be the only important outcome measure to assess when evaluating treatment efficacy of an intervention.

Sleep efficiency is a measure of time spent sleeping compared to the time spent in bed and an increase in sleep efficiency indicates that the patient is falling asleep faster after getting into bed (Dautovich et. al., 2008). Our results indicate that mean sleep efficiency improved with MAD + meds intervention from the baseline by 23%. This indicates that despite some subjects not showing a decrease in the severity of their obstructive sleep apnea, they still benefited from less time spent falling asleep.

Oxygen desaturation index (ODI) is another important sleep variable, which measures the number of drops in blood oxygen levels throughout the night. It is generally defined as a decrease in oxygen saturation of ≥4% for 10 seconds or more (Termirbekov et. al., 2018). This may or may not be correlated with the number of sleep arousals and can be predictive of long-term cardiovascular risks such as hypertension, stroke, and heart attack. (Temirbekov et. al., 2018). We found a statistically significant relationship between MAD + placebo and MAD + meds. ODI decreased marginally from baseline to MAD + placebo as well, but this was not statistically significant.

The psychomotor vigilance test (PVT) was used to measure daytime function. This is used as an objective measure for sleep deprivation and can assess daytime wakefulness and alertness. Mean response time (1/RT) and number of lapses are most commonly cited in literature due to their high sensitivity (Basner M and Dinges DF, 2011). We found that mean response time improved. Subjects did not complete the test at the same time of day during each session. This is a significant limitation because hormone levels that affect alertness fluctuate throughout the day, which would affect their performance on the test.

Airway imaging data was obtained with and without MAD at two respiratory time points. The rationale behind this was to attempt to control for the variability in the airway shape and size that is seen during different stages of the respiratory cycle. While changes in upper airway size and shape were seen between the two respiratory phases, we chose to limit the scope of our data analysis to end-inspiration phase with and without MAD. This respiratory phase was found to have more consistent results in our study. We found an increase in total airway volume and minimal cross-sectional area in all subjects with the MAD in place. However, the changes were not statistically significant. The positive change in airway volume and shape did not correlate with an equally positive change in objective outcome measures such as AHI. Our observations must be interpreted with caution given our sample size of seven.

Our subject pool had a very high initial average body mass index (39.1±6.6). Mandibular advancement devices have been shown to decrease in effectiveness as BMI and neck circumference increases (Sutherland et. al., 2014). Our subjects with the highest BMI showed a negative response to treatment and were worse than at baseline. One patient that was dropped from our study had an initial BMI of 61 because of poor treatment response.

5.2. Subjective Outcomes

Subjective outcome measures included the Epworth Sleepiness Scale, Functional Outcomes of Sleep Questionnaire, Visual Analog Scale, and Treatment Satisfaction Questionnaire for Medication. These results must be interpreted with caution. We found statistical significance only with the Epworth Sleepiness Scale, which is a well-validated outcome measure.

Interestingly, all our subjects reported feeling improvements in daytime sleepiness and increased energy level with our combination intervention of MAD + drugs. This is contradictory to some of our observed sleep data. This sleep data was recorded at two time points during our study four weeks apart, and only provides short term picture of the response to treatment. A much longer follow up period would be

ideal to determine how patients adapt to the treatment modality.

5.3. Study Limitations and Future Considerations

We collected data on 21 robust variables and successfully established the feasibility of our intervention. However, the scope and funding of our pilot study was limited. Additional funding and a comprehensive research team is needed to properly run a large-scale study.

Our biggest limitation was the small sample size of our study. We had 7 subjects included in our data analysis. We found it difficult to find suitable subjects that fit all our inclusion and exclusion criteria and were willing to complete the entire study. We recruited subjects from a single sleep center, which may have reduced the diversity of our subject pool. Airway imaging was performed while the patient was upright. The i-CAT Next Generation machine does not allow for supine positioning. It has been shown that treatment response can still be correlated from upright airway imaging.

The concern with taking airway images (using any methodology) in supine awake subjects is that observations depend very heavily on muscle activity within the upper airway muscles. To know that this is true, simply consider that even patients with severe obstructive sleep apnea maintain patent airways even while supine during wakefulness.

This changes dramatically when during sleep and upper airway muscle activity diminishes. However, this muscle activity during wakefulness is not the result of conscious effort or intent – it results from involuntary reflexes. Trying to get someone, even healthy volunteers, to fully relax their upper airway muscles while supine during wakefulness is difficult and leads to inconsistent results. Thus, imaging the upper airway during supine wakefulness will do little to predict the state of the airway during supine sleep (Sittitavornwong S, Waite PD, 2009).

On the contrary, the shape and state of the upper airways during seated (upright) breathing while awake is much less dependent on muscle activity – which is lower in this posture. Thus, imaging the upper airway in a seated awake individual may give information about the "relaxed" state of the airway and how this may respond to the MAD. This still may not be highly predictive of how the upper airway will perform during supine sleep with or without the MAD, but it seems to be a better candidate measure than supine wake measurements.

In order to minimize radiation exposure, we obtained the radiographs using the quick scan setting. This resulted in lower image resolution and reduced the accuracy of our airway measurements.

Our results highlight the complexity of obstructive sleep apnea and illustrate the importance of identifying traits that may predict treatment response to MAD therapy. Future studies need to be adequately powered to draw conclusions about the effectiveness of combination MAD and pharmacotherapy.

5.4. Conclusions

This study determined that augmentation of MAD by pharmacotherapy (ondansetron + fluoxetine) may increase therapeutic efficacy in these seven patients. Combination of pharmacotherapy and oral appliance may be a viable option in treating patients with moderate to severe OSA. Subjects generally reported sleeping better with the oral appliance and having increased alertness during the day on their follow-up appointment. Further larger scale studies will help to provide more understandable relationships among the outcome measures of interest in this type of therapy for sleep apnea.

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APPENDIX A

1. IRB Approval from University of Illinois – Chicago

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Approval Notice
Amendment to Research Protocol and/or Consent Document – Expedited Review
UIC Amendment # 7

November 7, 2016

Maria Therese S. Galang-Boquiren, DDS,MS
Orthodontics
801 S. Paulina
Rm 131, M/C 841
Chicago, IL 60612
Phone: (312) 413-3022 / Fax: (312) 996-0873

RE: Protocol # 2011-0629
"Oral Appliance and Pharmacologic Agents in Treatment of Sleep Apnea: A Follow-Up Pilot Clinical Study"

Dear Dr. Galang-Boquiren:

Members of Institutional Review Board (IRB) #1 have reviewed this amendment to your research and/or consent form under expedited procedures for minor changes to previously approved research allowed by Federal regulations [45 CFR 46.110(b)(2) and 21 CFR 56.110(b)(2)]. The amendment to your research was determined to be acceptable and may now be implemented.

Please note the following information about your approved amendment:

Amendment Approval Date: November 2, 2016
Amendment:

Summary: UIC Amendment #7, dated June 16, 2016 (received July 6, 2016; response to deferral received on August 8, 2016), is an amendment to amend the initial IRB submission because funding for this study from the UIC Chancellor's Interdisciplinary Fund has expired, and the investigator has obtained some new funding from the American Association of Orthodontists Foundation to conduct a follow-up pilot study. It will based on an entirely new

APPENDIX A (continued)

set of subjects, which means the investigator is re-opening this study for enrollment. None of the previous subjects will be contacted.

The majority of the protocol will remain the same aside from the addition of a few more outcome measures to better explain preliminary data (Questionnaires: Treatment Satisfaction Questionnaire for Medicaiton, Visual Analog Scale for Sleepiness; Psychomotor Vigilance Task/Test, Osler Sleep Resistance Test to determine daytime vigilance of the subjects; Conebeam Computed Tomography skull images to obtain airway imaging data). Also, the study medications will be given two weeks longer in order to reach their full therapeutic effect and to assess possible time-dependent effects of the intervention. The study medications are fluoxetine and ondansetron.

The informed consent document has been amended to include the additional outcome measures and protocol changes mentioned above, as well as to address improvements suggested by a recent (2015) IRB audit. Specifically, these were addressed:
1. More clearly specify duration, procedures, and indication of experimental procedures.
2. Specify that the FDA and State of Illinois Auditors may inspect records.
3. Update contact information for research subjects' rights to reflect current template language.
4. Specify the regulatory status of the device.

There are some additions and deletions in study personnel, which are reflected in a revised Appendix P. Dr. James Herdegen, Chad Ratsamy, and Henry Arantes were removed from the study. Joseph Deek was added to the study.

Also, the title of the study was modified to indicate that this is a follow-up of a previous study.

Approved Subject Enrollment #: 50
Performance Sites: UIC
Sponsor: American Association of Orthodontists
PAF#: 2016-03674
Grant/Contract No: Not available
Grant/Contract Title: AAOF Biomedical Research Award
Research Protocol(s):

a) ORAL APPLIANCE AND PHARMACOLOGICAL AGENTS IN TREATMENT OF SLEEP APNEA: A FOLLOW-UP PILOT CLINICAL STUDY; Version #8, 10/06/2016

Investigational Device: TAP III Elite Anti-Snoring Device [510(k): K160239]

Recruiting Material(s):

a) Patient Letter, Version #2, 07/05/2016
b) Recruitment Screening Script for Study Protocol: Oral Appliance and Pharmacological Treatments in Treatment of Sleep Apnea: A Follow-Up Pilot Clinical Study, Version #3, 09/06/2016
c) Flyer for Sleep Apnea Patients, Version #3, 09/06/2016

APPENDIX A (continued)

Informed Consent(s):

a) Short Form - Spanish; Version #2, 08/03/2016
b) Combined Consent/Authorization: Oral Appliance and Drug Treatment of Sleep Apnea; Version #14, 11/01/2016
c) Waiver of informed consent granted [45 CFR 46.116(d)] for the identification of potential subjects in the recruitment phase of the research
d) Alteration of Informed Consent granted [45 CFR 46.116(d)] for the Telephone Screening
e) Waiver of Documentation of Informed Consent granted [45 CFR 46.117(c)] for the Telephone Screening

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
07/06/2016	Amendment	Convened	07/20/2016	Deferred
08/08/2016	Response To Deferred	Convened	08/17/2016	Deferred
09/12/2016	Response To Deferred	Convened	09/21/2016	Modifications Required
10/21/2016	Response To Modifications	Expedited	11/02/2016	Approved

Please be sure to:

→ **Use only the IRB-approved and stamped consent document(s) and/or HIPAA Authorization form(s) enclosed with this letter when enrolling subjects.**

→ Use your research protocol number (2011-0629) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure,
"**UIC Investigator Responsibilities, Protection of Human Research Subjects**"
(*http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf*)

Please note that the UIC IRB #1 has the right to ask further questions, seek additional information, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact the OPRS at (312) 996-1711 or me at (312) 413-7323. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

APPENDIX A (continued)

Sincerely,

Jennifer Joaquin, MPH, CIP
Assistant Director, IRB # 1
Office for the Protection of Research Subjects

Enclosure(s):

1. **Informed Consent Document(s):**
   a) Short Form - Spanish; Version #2, 08/03/2016
   b) Combined Consent/Authorization: Oral Appliance and Drug Treatment of Sleep Apnea; Version #14, 11/01/2016
2. **Recruiting Material(s):**
   a) Patient Letter, Version #2, 07/05/2016
   b) Recruitment Screening Script for Study Protocol: Oral Appliance and Pharmacological Treatments in Treatment of Sleep Apnea: A Follow-Up Pilot Clinical Study, Version #3, 09/06/2016
   c) Flyer for Sleep Apnea Patients, Version #3, 09/06/2016

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	The American Institute of Orthodontics Research Award, 2016
	Best Clinical Science Award, Omicron Kappa Upsilon, Sigma Chapter, 2016
	Clinic and Research Day Best Clinical Science Award, Illinois State Dental Society, 2015
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