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PREDICTION OF THE EFFICACY OF A MANDIBULAR ADVANCEMENT SPLINT IN THE TREATMENT OF OBSTRUCTIVE SLEEP APNEA USING VARIOUS DIAGNOSTIC METHODS

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Discipline of Orthodontics
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A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Clinical Dentistry (Orthodontics)

September 2014
DECLARATION

CANDIDATE CERTIFICATION

This is to certify that the candidate carried out the work in this thesis,

in the Orthodontic Department, University of Sydney,

and it has not been submitted to

any other University or Institution for a higher degree.

________________________________________

Anél Blignaut
DEDICATION

To my loving family and close friends.

Thank you for your encouragement to turn my dreams into reality, your support through hardship, for sharing my joyful moments and most of all for all the years of unconditional love.
ACKNOWLEDGEMENTS

My sincerest gratitude is expressed to the flowing people, in no particular order:

Professor Ali Darendeliler, Professor and Chair of Orthodontics, University of Sydney, for his clinical advice and expertise and for providing light during the periods of darkness.

Dr Oyku Dalci, Orthodontic lecturer at the Faculty of Dentistry, University of Sydney, for getting the ball rolling and for her assistance both clinically and in the writing of the manuscript.

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The Australian Society of Orthodontists for their continued financial support of the research of the Sydney Orthodontic Department

And last but definitely not least, all my orthodontic colleagues and friends who offered words of wisdom and encouragement from their own experiences in the past.

Ané Blignaut
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHI</td>
<td>Apnea Hypopnea Index</td>
</tr>
<tr>
<td>APAP</td>
<td>Adjusting Positive Airway Pressure</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CBCT</td>
<td>Cone Beam Computer Tomography</td>
</tr>
<tr>
<td>CT</td>
<td>Computerized Tomography</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous Positive Airway Pressure</td>
</tr>
<tr>
<td>EDS</td>
<td>Excessive Daytime Sleepiness</td>
</tr>
<tr>
<td>ESS</td>
<td>Epworth Sleepiness Scale</td>
</tr>
<tr>
<td>FHP</td>
<td>Frankfort Horizontal Plane</td>
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<tr>
<td>MAD</td>
<td>Mandibular Advancement Device</td>
</tr>
<tr>
<td>MAS</td>
<td>Mandibular Advancement Splint</td>
</tr>
<tr>
<td>MMA</td>
<td>Maxillo Mandibular Advancement</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>nCPAP</td>
<td>Nasal Continuous Positive Airway Pressure</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
<td>------------</td>
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<tr>
<td>OA</td>
<td>Oral Appliance®</td>
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<tr>
<td>OB</td>
<td>Overbite</td>
</tr>
<tr>
<td>OJ</td>
<td>Overjet</td>
</tr>
<tr>
<td>OSA</td>
<td>Obstructive Sleep Apnea®</td>
</tr>
<tr>
<td>OSAHS</td>
<td>Obstructive Sleep Apnea-Hypopnea Syndrome</td>
</tr>
<tr>
<td>PAP</td>
<td>Positive Airway Pressure</td>
</tr>
<tr>
<td>RDI</td>
<td>Respiratory Disturbance Index®</td>
</tr>
<tr>
<td>REM</td>
<td>Rapid Eye Movement®</td>
</tr>
<tr>
<td>RME</td>
<td>Rapid Maxillary Expansion®</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation®</td>
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<tr>
<td>TMD</td>
<td>TemporoMandibular joint Disorder</td>
</tr>
<tr>
<td>TMJ</td>
<td>TemporoMandibular Joint</td>
</tr>
<tr>
<td>TSD</td>
<td>Tongue Stabilising Device®</td>
</tr>
<tr>
<td>UPPP</td>
<td>UvuloPalatoPharyngoPlasty®</td>
</tr>
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*Note: The letters of the words used to make up the acronyms are capitalised*
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1. INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder, which manifests as a reduction (hypopnea) or complete cessation (apnea) of airflow despite ongoing respiratory effort.\textsuperscript{1} The consequences can be severe and even life threatening. The management of OSA should thus focus on facilitating breathing and thereby reducing the risk of increased morbidity. There are several different treatment types, but all focus on preventing collapse of the lumen of the pharynx during sleep.\textsuperscript{2}

Treatment with oral appliances like Mandibular Advancement Splints (MAS) are often preferred by patients, but unfortunately all studies to date have consistently found that not all patients with OSA can be successfully treated with MAS.\textsuperscript{3,4} Being able to predict which patients will respond favorably to certain treatment options ahead of time will maximize health gain, avoid wastage of resources and subsequently increase patient satisfaction.

Clinical studies have suggested that demographic, anthropometric, polysomnographic, physiologic and anatomical characteristics relate to treatment outcome. Unfortunately, these predictors of treatment outcome have not been uniformly reported, thus rendering them useless in clinical practice.\textsuperscript{5,6} Very few studies have been done to assess the use of CBCT for visual assessment of the airway to determine the predominant anatomical site of obstruction. This, in combination with anthropometric, polysomnographic and dentofacial characteristics could improve our understanding of the pathophysiology of OSA and help to select the correct treatment option for different patients.
2. DEFINITIONS

2.1 Apneas & Hypopneas

An apnea is defined as a cessation of breath for at least 10 seconds whilst a hypopnea is characterised by a transient reduction in breathing with a resultant desaturation of 4% or more which lasts for 10 seconds or longer, although hypopneas lasting several minutes may occur in REM sleep.\(^1\)\(^7\) Clinically it is not necessary to distinguish between the two as both types have the same pathophysiology and consequences.\(^1\)

2.2 Apnea-Hypopnea Index (AHI)

The Apnea-Hypopnea Index (AHI) is the average number of apneas and hypopneas per hour.\(^7\) The suggested AHI cut points are 5, 15, and 30 events/hour to indicate mild, moderate, and severe levels of OSA respectively.\(^1\)

2.3 Respiratory Disturbance Index (RDI)

This is also measured as events per hour of sleep and takes into account the average frequency of apneas and hypopneas as well as reductions of airflow with resultant arousal but without meeting the desaturation criteria for a hypopnea.\(^7\)
3. **CLASSIFICATION**

3.1 **Habitual Snoring**

Snoring is an acoustic phenomenon produced by the vibration of the pharyngeal tissues as air passes through a narrow orifice created by the relative positions of the soft palate and the base of the tongue. It is an almost exclusively inspiring noise but can persist on expiration when there is a partial blockage of the airway as is the case with patients with OSA. It initiates when falling asleep, intensifies as sleep progresses to non-REM sleep and then weakens and discontinues during REM sleep.\(^8-10\)

Snoring is one of the cardinal symptoms of OSA, but not all snorers have sleep apnea. It appears to be the milder and initial form of upper airway dysfunction leading to OSA.\(^10\)

3.2 **Obstructive sleep Apnea (OSA)**

Obstructive sleep apnea is a common disorder characterized by disruptive snoring and repetitive episodes of partial or complete upper airway obstruction during sleep. It manifests as a reduction (hypopnea) or complete cessation (apnea) of airflow despite ongoing respiratory effort and results in intermittent hypoxaemia and hypercapnia, cortical arousals and surges of sympathetic arousals.\(^1,11,12\)
Obstructive Sleep Apnea Syndrome (OSAS) is defined as an AHI of more than 5 with associated symptoms such as daytime sleepiness, impaired cognition and fatigue, or an AHI of 15 or greater regardless of associated symptoms.\textsuperscript{7}

### 3.3 Central Sleep Apnea (CSA)

CSA is characterized by recurrent apneic episodes during sleep in the absence of an upper airway obstruction and with minimal or no respiratory effort due to cessation of respiratory drive. Similar to OSA this results in oxygen desaturations, recurrent arousals, and day-time sleepiness.\textsuperscript{17,13–15} Due to the absence of an airway obstruction, CSA is best treated with CPAP.\textsuperscript{15}

### 3.4 Mixed Apneas

Mixed apneas refer to periods of cessation for airflow due to the initial absence of respiratory effort but which persists when respiratory effort resumes due to an upper airway obstruction.\textsuperscript{1,16}
4. PREVALENCE

4.1 Habitual Snoring

Habitual snoring has been reported as occurring in up to 24% of the male population, and up to 14% of the female population\textsuperscript{13}. The prevalence increases with age, reportedly affecting 40% - 60% of the middle-aged population\textsuperscript{14}.

4.2 OSA

Before Measurement Techniques were outlined in 2010 the prevalence of OSA was varied in the literature due to different measurements used in the past.\textsuperscript{1} Using AHI > 5 with no other symptoms gives a prevalence of 24% of men and 9% of women whilst an AHI > 15 may be found in 9% of men and 4% of women. When the second criteria of daytime sleepiness is added as required for OSAS, these figures fall to 4% and 2% for men and women respectively.\textsuperscript{17}

The prevalence of OSA increases as Body Mass Index (BMI) increases. The prevalence of OSA is 41% in overweigh people with a BMI over 28 and as high as 78% in morbidly obese patients.\textsuperscript{7}

4.3 CSA

It has been suggested that CSA occurs at 10% the rate of OSA\textsuperscript{16} but the exact prevalence remains unknown.\textsuperscript{1}
5. PATHOPHYSIOLOGY

The cause of OSA is multifactorial and varies considerably between individuals. The severity of OSA in individuals results from a combination of anatomical and neuromuscular factors including upper airway anatomy, ability of the upper airway dilator muscles to respond to respiratory challenges during sleep, and arousal threshold in response to respiratory stimulation.\cite{1,4,18,19} Defining physiological causes of OSA on an individual basis may be critical to the success of therapeutic approaches.\cite{19}

Upper Airway Anatomy

![Figure 1: Schematic diagram of upper airway\cite{20}](image-url)
The human upper airway contains a collapsible portion that extends from the hard palate to the larynx.\textsuperscript{19} OSA patients have a narrower upper airway compared to normal subjects, which makes them more prone to relapse from an anatomical perspective.\textsuperscript{19,21,22} Obstruction can occur at a single or multiple levels along the upper airway, with the oropharynx or retroglossal airway being the most common site.\textsuperscript{21,23}

**Upper airway muscle activity during sleep**

Upper airway muscle activity decreases during sleep leading to increased collapsibility of the pharyngeal tissues.\textsuperscript{24} Edema or inflammation of pharyngeal tissues due to heavy snoring might not only narrow the upper airway but might also impair normal function of the receptors responsible for initiating protective reflexes.\textsuperscript{18} Furthermore, the neuromuscular responses to upper airway obstruction is impaired in patients with OSA when compared to healthy subjects with similar obstructions.\textsuperscript{25}

These changes result in narrowing of the upper airway, leading to an imbalance between the dilating muscle activity and the collapsing intra-luminal pressure generated during inspiration. When the negative pressure exceeds the force produced by these muscles, the pharynx collapses, occluding the airway.\textsuperscript{26}
Arousal

An apneic or hypopneic episode is often terminated with a brief awakening (arousal) from sleep, however some patients are able to restore ventilation without arousal.24 The reduction in ventilation and subsequent reduction in oxygen saturation stimulate the central nervous system to increase sympathetic neural activity. This results in increased blood pressure, central nervous system arousal, and restoration of upper airway patency. This in turn produces temporary supra-normal ventilation, normalisation of oxygen saturation, and subsequent suppression of sympathetic neural activity.27

6. PREDISPOSING FACTORS

6.1 Unmodifiable factors

Gender

The predominance of OSA in men is much less than previously described with a possible explanation for the underdiagnosis of OSA in women being that women have different presenting symptoms or that their symptoms are often misdiagnosed.28,29 Currently it is estimated that men are twice as likely to have OSA as women with the prevalence of OSA quoted as 4% and 2% respectively in males and females.17 This may be attributed to differences in upper airway shape and genioglossal muscle activity during the awake state, in craniofacial morphology, and pattern of fat deposition around the pharynx.17
Age

The occurrence of OSA in older people is more complex than previously appreciated. OSA prevalence increases steadily with age throughout midlife with a 2- to 3-fold higher prevalence in persons above 65 years of age compared with those between 30-64 years of age. After 65 years it seems to plateau.\textsuperscript{17,29,30} Dimensional changes in the airways related to age, as well as small subtle changes such as the increased size of the soft palate, a more caudally positioned tongue and the inferior repositioning of the hyoid bone, all reduce the airway patency and predispose a patient to OSA.\textsuperscript{19,31}

Genetics

The association of OSA amongst family members may be a reflection of lifestyle, but there are studies supporting a genetic predisposition to OSA in relation to craniofacial structure, body fat distribution and neural control of the upper airway muscles.\textsuperscript{29,32} Although the role of specific genes that influence the development of OSAHS have not yet been identified, current research suggests that several genetic systems may influence the expression of the disorder.\textsuperscript{32,33}

Ethnicity

Genetics may provide an explanation for some differences in OSA epidemiology.\textsuperscript{29} OSA has a greater prevalence in Asian\textsuperscript{34–36} and African-American populations\textsuperscript{37,38} according to some studies, but at present, data from studies of groups other than white subjects are too sparse to determine with confidence if prevalence differs worldwide.\textsuperscript{17}
6.2 Modifiable Factors

Obesity

Obesity has significantly increased over the past few decades in all developed countries and is a common feature of patients with OSA. Obesity is usually determined by Body Mass Index (BMI), which represents an overall increase in body weight for a person’s height. It is estimated that a 10% increase in weight is associated with a 6-fold greater risk of developing OSA among persons initially free of OSA.39 The correlation between OSA and BMI is weak though due to the fat distribution not being homogenous among obese people.40

There is a gradual increase in OSA prevalence with increasing body mass index, neck circumference and waist-to-hip ratio, but OSA is not exclusive to obese people.29 Neck circumference has a stronger correlation due to the regional fat deposition near the pharyngeal airway41-43, but it has been found that waist circumference indicating fat accumulation of the intra-abdominal region is the best predictor of OSA severity.44 Men often have a lower BMI than a woman of the same severity of OSA, however the greater upper-body fat distribution and fat in the neck seen in males make them more susceptible to upper airway collapse and may in part explain the greater prevalence of OSA in males.28,41,45
**Sleeping posture**

Supine-dependent OSA or positional sleep apnea refers to patients who displays a higher AHI when they are sleeping on their back compared to when they are sleeping on their side and comprises of an average of 56% of patients with OSA.46,47 Positional therapy can be used to prevent a patient from sleeping in the worst sleeping position which is usually, but not exclusively, the supine position.46,48

**Craniofacial anatomy**

Craniofacial and upper-airway structure have an important role in OSA occurrence. The most frequently reported skeletal and soft tissue abnormalities are a small posteriorly placed mandible (retrognathia), an enlarged tongue and soft palate, and an inferiorly positioned hyoid bone, all of which compromise the pharyngeal airspase.29,49–51 Narrowed nasal cavities and tonsillar hypertrophy during childhood may cause mouth breathing which could lead to abnormal growth patterns and malocclusions and could predispose the individual to OSA in later life.12,53

**Nasal congestion and allergies**

Nocturnal nasal congestion due to allergic rhinitis, acute upper respiratory tract infection, or anatomically narrow nasal cavities may exacerbate snoring and OSA.29
**Alcohol and drug use**

Alcohol and sedatives have an acute inhibitory effect on the genioglossal activity of the tongue & upper airway dilators that leads to an increase in snoring and as well as apnea and hypopnea frequency but the effect of long-term alcohol use on the development or progression of OSA is unknown.\(^{29}\)

**Smoking**

Smoking causes airway inflammation and smoking-related diseases that may contribute to the severity of OSA. \(^{29}\) It has been found that cigarette smokers were three times more likely to have OSA compared to non-smokers, but that the effect is reversible with smoking cessation.\(^{54}\)
7. SEQUELA

Figure 2: Pathogenesis of the consequences of sleep disordered breathing.55

7.1 Clinical consequences

The consequences of OSA are directly related to the recurrent CNS arousals, asphyxia, and subsequent sleep deprivation. These consequences include excessive daytime sleepiness (EDS), neurocognitive impairment, increased motor vehicle and occupational accidents, and diminished quality of life.17,55,56
An OSA patient’s relative risk to have an accident lies between 2.3 to 7.3 times that of non-apneic individuals\textsuperscript{56} and there could therefore be legal implications for both private and commercial drivers if OSA is a significant cause of impaired driving.\textsuperscript{7,17,57} Simulated driving performances have shown that patients with OSA have a significant increase in lapse of concentration when compared to control subjects, but that there is a significant decrease in these lapses with either CPAP or OA.\textsuperscript{58}

Apart from waking up unrefreshed, patients often suffer from nocturnal and morning headaches caused by the increased intracranial pressure secondary to cerebral vasodilatation and increased systemic blood pressure. This can lead to depression, a decreased libido or even impotence, with severe implications on quality of life.\textsuperscript{55}

### 7.2 Morbidity

The morbidity of OSA is primarily related to the cardiovascular system with OSA patients presenting with hypertension, coronary heart disease and congestive heart failure.\textsuperscript{17,55,59} However, the association is confounded by OSA patients also having a high incidence of other cardiovascular risk factors including obesity, age, smoking, and increased alcohol intake.\textsuperscript{56,59}
The prevalence of hypertension is high in patients with OSA, particularly in patients with resistant hypertension. Patients with moderate or severe OSA are at three times greater risk of developing new hypertension.\textsuperscript{29,60}

The high association of hypertension with OSA may be an indirect indication of the risk of congestive heart failure in patients with OSA due to hypertension being a common cause of congestive heart failure.\textsuperscript{27} It has been found that coronary artery disease, particularly in men aged 40–70 years with severe sleep-disordered breathing is associated with high mortality.\textsuperscript{61}

Hypertension also contributes to cerebrovascular morbidity and mortality.\textsuperscript{17} A review of the literature reported a strong relationship between OSA and stroke independent of cofactors.\textsuperscript{7}

A correlation between OSA and epilepsy has also been reported especially in older patients who presents with new-onset epilepsy.\textsuperscript{7}

Fortunately, the use of CPAP has been shown to lessen the morbidity of OSA related diseases and thus emphasizes the importance of early diagnosis and continued management of especially patients with moderate to severe OSA.\textsuperscript{7}
7.3 Comorbidities

There have been reports that OSA might be related to diabetes mellitus, but the overlap of excess body weight and hypertension makes it hard to determine whether these two conditions are simply comorbidities or whether OSA might lead to insulin resistance.\textsuperscript{7,29}

Sleep apnea is associated with a significant increase in peri- and post-operative complications, including difficult intubations, exaggerated respiratory depressions from analgesics and anesthetics leading to increased post-operative reintubations, cardiac dysrhythmias, and longer hospital stays. It is unclear whether pre- and post-operative use of CPAP decreases the incidence of these complications, but the American Society of Anesthesiologists nevertheless advises it.\textsuperscript{7,6,2}

There have been suggestions that there is an association between sleep bruxism and breathing disorders, however their relationship is still controversial. Snoring, breathing pauses and OSA has been found to be more common in bruxers, but this could be due to shared craniofacial dysmorphisms such as mandibular deficiency and temporomandibular abnormalities.\textsuperscript{63} However, when bruxism occurs in accordance to an arousal at the end of an apneic or hypopneic event, treatment with CPAP eliminate most breathing abnormalities and completely eradicates tooth grinding events.\textsuperscript{64}
8. **DIAGNOSIS**

8.1 **Clinical presentation**

The cardinal symptom of sleep apnea is daytime sleepiness,\(^1\,^2\) which is a result from sleep fragmentation related to recurrent central nervous system arousals in response to disordered breathing events. Perception and reporting of daytime sleepiness vary greatly between individuals and can be difficult to quantify as it is often mistaken for fatigue.\(^2\) The problem with daytime sleepiness even when using questionnaires like the Epworth Sleepiness Scale (ESS), is that is subjective. Therefore, there is considerable inter-individual variation in susceptibility to sleepiness resulting from OSA and many patients with severe OSA report minimal daytime sleepiness.\(^1\) Other signs that may be indicative of a sleeping disorder include snoring, witnessed apneas, nocturnal choking and fragmented sleep.\(^6\)

8.2 **Diagnostic Criteria**

Obstructive Sleep Apnea Syndrome (OSAS) is defined as an AHI of more than 5 with associated symptoms such as daytime sleepiness, impaired cognition and fatigue, or an AHI of 15 or greater regardless of associated symptoms.\(^7\) The suggested AHI cutpoints are 5, 15, and 30 events/hour to indicate mild, moderate, and severe levels of OSA.\(^1\)
<table>
<thead>
<tr>
<th>Severity</th>
<th>AHI</th>
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<tr>
<td>Mild</td>
<td>5 – 15</td>
</tr>
<tr>
<td>Moderate</td>
<td>15 – 30</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt; 30</td>
</tr>
</tbody>
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*Table 1: Severity of OSA in adults*¹

### 8.3 Sleep studies

A Polysomnography (PSG) based in an overnight facility remains the gold standard for diagnosing OSA.¹ ² ⁶ ⁶ It is used to determine the amount of apneic and hypopneic episodes as well as sleep time, sleep stages, respiratory effort, airflow, cardiac rhythm, oximetry, and limb movements.⁷ ⁵⁶ ⁶⁷ Overnight PSG is costly though and not always feasible. Apneas and hypopneas often result in oxyhemoglobin desaturation and sleep fragmentation¹ and nocturnal pulse oximetry is widely used to screen for OSA. The findings are not always conclusive though.²⁷

Portable PSG used at home without the need for a technologist to diagnose OSA has recently been approved.¹ ¹ ⁵⁶ The portable monitors can detect respiratory events but cannot determine the actual sleep time, which means that AHI cannot be determined. RDI is used instead as it records the frequency of respiratory disturbances per hour of recording time. The total recording time often exceeds the actual sleep time of the patient and thus the RDI...
is often underrepresents the severity of OSA. For a portable monitor the AHI and RDI needs to be 15 or more to be classified as OSA as opposed to 5 or more when facility based monitors are used. Portable monitors should not be used in patients with congestive heart failure, cerebrovascular disease or respiratory failure.

8.4 Airway assessment

Upper airway constriction is an important contributing factor to OSA and visual assessment of the airway may aid the physician in determining the predominant anatomical site of obstruction. This could improve our understanding of the pathophysiology of OSA and help to select the correct treatment option for different patients.

When choosing a method of airway inspection it is important to choose a procedure that is non-invasive, easy to perform, standardized, accurate, reproducible, cost-effective and readily available. A number of techniques are available, including indirect laryngoscopy, endoscopy during wakefulness, nasendoscopy during sleep, somnofluoroscopy, lateral cephalography, CT scanning, CBCT scanning and MRI scanning.

8.4.1 Indirect laryngoscopy

Although visual inspection is semi-objective, gross anatomical obstructions or malignancies of the nose and pharynx can be ruled out.
8.4.2 Endoscopy

Fiberoptic endoscopy allows for visual inspection of the whole pharynx to locate anatomical anomalies including hypertrophy of the tonsils, uvula and tongue. Once again this is a semi-objective method and the reproducibility is low.68

Endoscopy during wakefulness of patients with OSA is usually performed in the supine position to assess the level of maximum narrowing in the upper airway. The patient can be asked to perform the Müller maneuver, which consists of a forced inspiratory effort against a closed mouth and nose. The retropalatal and retrolingual level of the pharynx can be investigated during this maneuver and may be used to detect collapse in these areas. The predictive value of this maneuver is limited though, as it does not necessarily reflect the obstructions during sleep.68

8.4.3 Nasendoscopy

Fiberoptic endoscopy performed whilst the patient is asleep is known as nasendoscopy. It is a time consuming procedure if sedation is not used, but there is a risk that sedatives may increase OSA due to hypotonia of the genioglossus. A further disadvantage is that various levels of the airway cannot be observed simultaneously and quantifying the cross-sectional area is difficult and once again semi-objective. Videotaped images of the lumen can be digitized and the cross-sectional area calculated, but it is a very time-consuming task.68
8.4.4 Somnofluoroscopy

Fluoroscopy is a dynamic radiographic examination of the upper airway and in combination with PSG is called somnofluoroscopy. A preliminary image is recorded of the patient in the supine position whilst they are awake and then further images are obtained once an obstructive event is witnessed on the PSG. This method is not widely used due to the significant radiation exposure and the airway only being shown two-dimensionally without the possibility to make cross-sectional cuts.68

8.4.5 Lateral cephalography

The lateral cephalogram is a standardized sagittal radiograph of the head and neck that is an easy, readily available, economical, and reproducible way to diagnose upper airway obstruction. It is a common radiograph used by dentists and orthodontists and should serve as a screening tool for enlarged adenoid and tonsils to determine the need for more rigorous ENT follow-ups.69 Unfortunately it is a two-dimensional (2D) image and visualization of changes which occur in the transverse is not possible.70 Single linear measurements as performed on cephalograms does not depict the morphology of the airway when compared to a CBCT 3D analysis.20 Although the AP dimension is that which is most likely to be changed with mandibular protrusion, previous researchers have found that a decreased lateral dimension is often present in patients with OSA2
8.4.6 Computerized tomography (CT)

Sagittal or cross-sectional images of the upper airway can be obtained using a CT scan of a patient in a supine position. The high radiation and cost involved, makes this a less desirable method of assessment though.68

8.4.7 Magnetic resonance imaging (MRI)

This is a non-invasive diagnostic technique to obtain sagittal or cross-sectional images of the upper airway of the patient in a supine position with the added benefit of no radiation exposure. A disadvantage of this technique is the long acquisition time required which could possibly result in motion artifacts due to breathing and swallowing.68 Unfortunately, it is extremely expensive and it might be more cost-effective to trial different treatment options for OSA than to use the MRI to predict effectiveness.2

8.4.8 Cone Beam Computerized Tomography (CBCT)

CBCT devices have become available during the last decade for oral and maxillofacial imaging at reduced radiation and cost. The general CBCT dosimetry is up to 50 times less than a CT scan and uses only minimal radiation, equal to seven panoramic exposures, or approximately 3.5 days of background exposure.2 It is a three-dimensional image that can be used to investigate the anatomical shape and size of the airway, as well as the hard
tissues surrounding it. Unfortunately soft tissue is not clearly delineated from other soft tissue on CBCT.\textsuperscript{20,70}

3D imaging software like Dolphin 3D imaging (Dolphin Imaging/Patterson Dental, Chatsworth, CA) allows for accurate 2D simulations of lateral and anteroposterior cephalometrics, panoramic images, and arthrography without magnification errors as seen in traditional 2D radiographs. In addition, sagittal and cross-sectional images can be obtained to assess the airway in all dimensions.\textsuperscript{2} 3D Dolphin imaging software to analyse the airway volume and dimensions from a CBCT has been proved to be both accurate and reliable.\textsuperscript{71}

\textit{Figure 3: CBCT image of an airway reconstructed with Dolphin software, version 11.1}
9. MANAGEMENT

The management of OSA should focus on facilitating breathing and thereby reducing the risk of increased morbidity. There are several different treatment types due to the multifactorial cause of OSA, but all focus on preventing collapse of the lumen of the pharynx during sleep.²

9.1 Medical

9.1.1 Conservative Measures

Supine dependent

Supine dependent OSA is indicated by a difference of 50% or more in AHI between supine and non-supine positions. Positional therapy can be used to prevent patients from sleeping in the worst sleeping positions, which is usually, but not always, the supine position.² Long term compliance remains an issue, but various techniques are used to prevent patients from assuming the supine position such as positional alarms, tennis balls sown into vests, or special pillows.⁴⁶ A MRI study has found that patients with positional OSA have wider upper airways in the lateral dimension, which may explain the maintenance of pharyngeal airway patency in the lateral sleep position.⁷³ Other factors that will influence the effectiveness of positional therapy include OSA severity, severity in the lateral position, BMI, and patient motivation.²⁷,⁷⁴
Weight loss

Weight loss has been proven to be decrease sleep apnea severity, and should be recommended for all obese patients with sleep apnea. It is not adequate in relieving all respiratory events though and should be used as adjunct rather than curative therapy. In addition, weight loss takes time and only a small percentage of patients successfully maintain it.

Gastric binding

Bariatric surgery is increasingly performed for refractory medically complicated obesity. Due to the improvement in AHI with weight loss, it is thought that bariatric surgery may play a role in the treatment of morbidly obese OSA patients as an adjunct. However, there have been reports of recurrence of OSA after several years even without regaining of weight, so these patients should be followed up long term.

Life-style changes

There is no evidence that simple non-invasive lifestyle changes may improve OSA or its consequences. Exercise has been recommended as a method of losing weight and has been proposed to have an improvement in inflammatory profiles as seen in OSA. Alcohol, tobacco, and respiratory depressant or sedative medications such as opiates or benzodiazepines, should also be avoided since they have been proven to decrease
pharyngeal muscle tone. Improving sleep hygiene may alter the sleep structure and the control of the upper airway during sleep and thus promote its patency. These measures may be tried as they are non-invasive, but it should be done in conjunction with either CPAP or OA therapy.

### 9.1.2 Continuous Positive Airway Pressure (CPAP)

The first reported use of CPAP for OSA in adults was by Colin Sullivan in 1981. Prior to CPAP, OSA patients were almost always treated with tracheotomy. CPAP produces similar results to those of a tracheostomy in reversing excessive daytime somnolence and the sequelae of OSA.

The gold standard for newly diagnosed OSA is CPAP, because no matter where the obstruction in the pharynx occurs, this treatment has been shown to be very effective in most OSA patients. CPAP pneumatically splints the upper airway by means of applying positive pressure to the patient’s airway via an oral or oro-nasal mask that is attached to a machine. The success rate of CPAP is reported to be 95%. Snoring and daytime sleepiness were relieved in more than 65% of the subjects and sleep quality improved in 75%. 

Anel Blignaut
The major limitation of CPAP is poor patient compliance, which ranges from 65 to 80%, with an average usage of less than 50% of the night. Long term compliance is more likely in patients with a history of snoring, high AHI, and severe daytime sleepiness due to the symptomatic relief from CPAP use.

CPAP rarely results in serious side effects. Some of the reported side effects include: nasal congestion with chronic use in about 25% of patients, nasal or oral dryness, sneezing and ulceration of the bridge of the nose. The primary criticism of CPAP is the discomfort associated with its use. Patients complain about the noise from the unit, limited user’s mobility prohibiting them from sleeping on their side or stomach, poor fit of the mask, and feeling hot and claustrophobic with the mask in place. Other complaints about the device pertain to needing to clean the CPAP machine with filtered water as a hassle and its bulk especially with patients who travel frequently.

Several advances have been made to try and reduce the side effects and improve patient comfort. More than a 100 different mask options are now available to patients, including nasal pillows inserted into the nostrils only. The machines are much smaller and quieter, and some have added humidifiers to improve nasal or oral dryness. Adjusting positive airway pressure (APAP) automatically increases and decreases pressure on the basis of identified respiratory events. This facilitates easier respiratory cycles, especially during exhalation, and allows for altered pressure during different body positions. Close follow-up,
intensive education and treatment of nasal congestion is recommended to further increase patient compliance.\textsuperscript{83}

\section*{9.1.3 Pharmacotherapy}

Pharmacological therapies for OSA have been widely discussed, however there is insufficient evidence to recommend the use of drug therapy in the treatment of OSA.\textsuperscript{74,83,86,87} The exception is individuals with hypothyroidism or with acromegaly. Treating the underlying medical condition can have pronounced effects on the AHI.\textsuperscript{86} Better matching of drugs according to the dominant mechanism of OSA may lead to better results in the future.\textsuperscript{74,87}

\section*{9.2 Oral appliances (OA)}

The use of oral appliances (OA) for the treatment of simple snoring and OSA has increased dramatically in recent years and they are now considered an alternative to CPAP.\textsuperscript{11} OA are non-invasive, well-tolerated compared to CPAP, and do not require a power source.\textsuperscript{4} The aim of OA therapy is to improve upper airway patency, thereby preventing pharyngeal collapse during sleep. OA can be divided into two categories based on their mode of action, Mandibular Advancement Splints (MAS), and Tongue Stabilizing Devices (TSD).
9.2.1 Mandibular Advancement Splint (MAS)

A MAS is a removable device that attaches to the dental arches and mechanically protrudes the mandible. Candidates for MAS should have healthy teeth, no periodontal disease, no severe TMJ disorders and an adequate range of jaw movement.65

9.2.1.1 Indications

The most recent report by the American Academy of Sleep Medicine provided indications for MAS use and recommended it as a first-line therapy for mild to moderate OSA patients who prefer MAS to CPAP therapy. It may also be used for severe OSA patients who do not respond to or are unable to tolerate CPAP.6 Until there is higher quality evidence to suggest higher efficacy rates with MAS, CPAP is indicated whenever possible for patients with severe OSA before considering MAS.65

9.2.1.2 Mechanism of action

Two mechanisms of action have been proposed for mandibular advancement splints. The first is that it protrudes the lower jaw forward to thrust the tongue base forward, thereby enlarging the upper airway.2,4,83 Recent studies using imaging modalities and nasendoscopy have found a consistent increase in the cross-sectional area of the velopharynx, especially in the lateral dimension. They also found smaller changes in the
oropharynx and hypopharynx, although this contribution to the therapeutic effect of MAS remains unknown.88–90

Another theory is that it decreases the pharyngeal collapsibility through improved muscle tone.2,4 The lateral wall of the soft palate anatomically connects to the base of the tongue through the palatoglossal arch. Anterior displacement of the mandible and tongue stretches the soft palate, stiffening the velopharyngeal segment and decreasing its collapsibility.91

Figure 4: Schematic illustration of mechanism of action9
9.2.1.3 MAS Appliance Designs & Titration

There are no strict guidelines for the design of a MAS and the appliance can be custom-made or prefabricated, fixed or adjustable, made from soft elastomeric material or hard acrylic, and a one-piece (Monobloc) or a two-piece (Bibloc) design. A custom-made, serially adjustable appliance is more effective than preformed appliances for the treatment of OSA and snoring as is has superior retention and is more comfortable. A Biobloc design is recommended to allow some freedom of mandibular movement thereby reducing the risk of temporomandibular joint pain.

![Figure 5: Variation of MAS designs](image)

Sagittal adjustability is ideal to allow individual titration and greater mandibular advancement as a gradual decline in treatment effect in the long term has been shown previously. A 2mm (20%) increase in the advancement of the mandible can improve the polysomnographic variables by 20%, but success rates are higher if the mandible is protruded at least 50%. The degree of protrusion improves nocturnal oxygenation and prevents pharyngeal collapsibility and this has been shown as an important predictor of
treatment outcome, with greater advancement being associated with greater reductions in sleep-disordered breathing.\textsuperscript{95} Better treatment outcomes have been achieved with 75\% mandibular advancement compared to 50\%.\textsuperscript{96} Generally MAS holds the mandible at 75\% of the patient’s maximal protrusion, though greater protrusion may achieve higher success rates.\textsuperscript{98} The side effects of more protrusion are still unclear from the literature though.\textsuperscript{4} The advantage of adjustable or titratable appliances is that it allows the mandible to be moved forward in increments over weeks to months.\textsuperscript{99} Usually the initial position is set between 50-75\% of the maximum mandibular protrusion.\textsuperscript{100} The amount and rate of advancement should be individualized as the tolerance for advancement may increase with time. Titration should proceed until the maximal comfortable limit is reached\textsuperscript{4,98,101,102} or until the relief of symptoms.\textsuperscript{98,103}

\textit{Figure 6: Titration screw that allows for gradual advancement}
The degree of vertical opening has been shown not to have a significant impact on treatment efficacy. For comfort levels, a decreased vertical opening of 4mm compared to 14mm was preferred by patients.\textsuperscript{104} One study reported a decrease in the airway lumen with increased vertical opening of the MAS most likely due to the posterior rotation of the mandible.\textsuperscript{105}

\subsection*{9.2.1.4 Efficacy}

Self-reported reduction of snoring and witnessed apneas has been reported in 83-90\% of patients treated with MAS.\textsuperscript{98,106} Self-prediction is not accurate though, with randomised controlled studies reporting only a 40-60\% substantial reduction in snoring frequency and intensity,\textsuperscript{98,107} and successful management of OSA varying between 50\% to 80\% depending on the device used, the selection criteria and the parameters for success.\textsuperscript{4} An increased AHI after MAS therapy has been reported in approximately 13\% of patients\textsuperscript{4,108}, therefore a follow-up sleep study should always be conducted following MAS treatment to confirm that the OSA has been adequately managed.\textsuperscript{70}

The literature is conflicting with some studies reporting overall better success rates in patients with lower AHI\textsuperscript{4,91,97}, whilst others found that the baseline OSA severity category did not influence treatment outcome\textsuperscript{94,98}. Generally MAS are not recommended as a first line treatment in patients with severe OSA\textsuperscript{4}, but after review of the American Academy of Sleep
Medicine practice parameters it has also been recommended for use in severe OSA patients who do not respond to or are unable to tolerate CPAP.6

Evidence from a number of recent randomized clinical trials has demonstrated the efficacy of MAS in treatment of OSA. When compared to CPAP, the beneficial effect on blood pressure109 and the modest reduction in daytime sleepiness as measured with the ESS107 are of similar magnitude. CPAP remains superior in reducing AHI and improving oxygen saturation, but not arousal index or sleep architecture.41,1280

9.2.1.5 Compliance

The compliance rates with MAS has been reported as at about 90%96 and usage averages 6.8 hours per night when monitored with an intra-oral device.10. Compared to CPAP compliance rates of 65-80%82 with average usage less than 50% of the night84 it raises the possibility that the superior efficacy of CPAP is mitigated by inferior compliance, resulting in similar effectiveness clinically.6

Patients generally prefer MAS to CPAP,10,2103,111-113 although overweight patients and those with more severe symptoms may favour CPAP most like due to increased improvement of symptoms.81 Patients who do not have the adequate manual dexterity and motivation to insert and remove their MAS may also prefer to use CPAP of a TSD.65
Overall, patients prefer a device that is transportable, discreet and doesn't need a power supply. Matching therapy to patient preferences may help identify the most appropriate treatment, and this may achieve greater likelihood of adherence. Long-term follow-up of compliance found a decrease to 82% after a year and to 62% after 4 years of MAS use. Discontinuation of MAS treatment is generally related to side-effects, complications, or the lack of perceived benefits. The importance of effectiveness shouldn't be neglected and the patient should be fully informed of short and long term side effects of OA therapy.

The durability of OA is estimated at 1.5 to 3 years, although SomnoMed has a guarantee of 5 years for their MAS. The frequency of repairs or replacement of the device and the associated expense and inconvenience proves problematic for some patients.

Follow-up appointments with a dental specialist is recommended at least annually to evaluate the health of the oral structures and integrity of the occlusion, evaluate device deterioration and monitor patient adherence. If there are any signs and symptoms to suggest worsening of OSA, the patient should be referred to a sleep physician for further assessment.
9.2.1.6 Short and long term effects

MAS is well tolerated by most patients as the side effects are mild. Initial side effects tend to last only a few weeks and include dental discomfort, TMJ pain and headaches, salivation, and bruxism. Discomfort is reported mainly at initial wear or infrequent wear, but subsides after getting used to it.

No adverse effects on the TMJ have been reported with long-term use of MAS. On the contrary, a decrease in the frequency and intensity of headaches have been reported.

The primary complaint about the OA is the impact it has on the user's bite with reports of poor occlusion and biting on their cheeks or lips after prolonged use. Long-term studies have reported occlusal changes predominantly characterized by reduced overjet and overbite, and altered molar relationship in conjunction with a posterior open bite. In a seven-year follow-up study, it was found that 14.3% of patients had no occlusal changes, 41.4% had favourable changes, and 44.3% had unfavourable changes. Favourable changes were seen in patients with greater initial overjets and overbites.

Cephalometric changes included retroclination of upper incisors, proclination of lower incisors, and a downwards and forwards position of the mandible with an increased lower face height.
9.2.2 Tongue Stabilizing Device (TSD)

A tongue stabilizing device attaches to the end of the tongue using gentle suction and holds the tongue in a protruding position. It increases the anteroposterior diameter of the velopharynx by displacing the tongue and soft palate anteriorly and the velopharyngeal lateral diameter is extended more with TSD than compared to MAS. The efficacy is similar for both devices, but MAS is associated with better compliance, greater symptomatic improvement and patient preference. TSD have been proposed as an option for patients with a reduced number of teeth, compromised dental health, periodontal disease, gag reflex or those not wanting the dental side effects of a MAS.123

Figure 7: A schematic MRI image showing a TSD holding the tongue forward, preventing it from falling back and obstructing the airway.
9.3 Surgical

The first methods used to treat OSA were surgical.65 Prior to CPAP, patients who suffered from severe OSA were treated with a tracheotomy.89 Although it was highly effective in eliminating OSA, the side-effects of a tracheotomy, including bleeding, infection, excessive secretions, and coughing led to its substitution by less aggressive alternatives when these became available.52,124

The current evidence does not advocate the widespread use of surgical interventions in the management of patients with OSA.125 However, for a select group of patients it can be an effective and definitive form of treatment.126

Primary surgical treatment may be considered in patients with mild OSA who have severe obstructing anatomy that is surgically correctible.65 The most common procedures are adenotonsillectomy and nasal surgery which can be extremely useful, especially in children suffering from OSA.124,127

Surgical procedures may be considered as a secondary treatment for OSA if patients are non-responsive to CPAP, or if they are unable to tolerate PAP therapy or alternative OSA treatments including OA therapy.65,128 The patient should be medically fit, psychologically able to tolerate surgery and be counseled on the risks and benefits of the procedure, as well
as possible side effects, and complications.\textsuperscript{65,126,128} After the surgical team has determined that healing is complete, a final general OSA outcome evaluation is indicated to ensure successful management.\textsuperscript{65,128}

**Soft-tissue surgery**

Soft-tissue surgery has been used the longest and perhaps the most common procedure performed in the past was the uvulopalatopharyngoplasty (UPPP) with an estimated 50% success rate. It was introduced in 1981 and involves the surgical resection of a part of the soft palate and surrounding oropharyngeal tissues to reduce their potential for obstructing the upper airway during sleep.\textsuperscript{2}

**Craniofacial surgery**

The first successful craniofacial surgery reported in the treatment of OSA was in 1983, where a bilateral sagittal split osteotomy (BSSO) was performed to advance the mandible, along with the genioglossus, mylohyoid and anterior digastric muscles.\textsuperscript{129} The downfall of this treatment was that it was only indicated for patients with a retrognatic mandible.

To overcome this problem, maxillary surgery had to be performed as well to re-establish the occlusion modified by the mandibular advancement. The procedure is aggressive, but it has several advantages. The original occlusion can be maintained and the swelling is confined to the soft tissue of the face, preventing the immediate postoperative
period of worsening OSA that is found in soft-tissue pharyngeal surgeries. The best treatment outcome is achieved by advancing the jaw as much as possible, maintaining an acceptable functional and esthetic result. Most OSA patients usually exhibit normal craniofacial skeletal morphology though. For patients who will not benefit aesthetically from MMA, a counter clockwise rotation of the occlusal plane has been proposed. It has shown to produce significant changes to the upper airway by increasing the posterior face height and advancing the mandible with little or no sagittal movement of the maxilla. Results show that MMA can improve PSG parameters comparable to CPAP in the majority of patients whilst preventing deformity.

Maxillary constriction has been found to be a common feature in patients with OSA compared to normal subjects with OSA patients having narrower, shorter, more tapered arch forms. Rapid maxillary expansion (RME) in children has proved to be effective in resolving OSA in the majority of cases. Orthopedic expansion with RME widens the nasal fossa and releases the septum, restoring normal nasal airflow with concurrent reduction of obstructive sleep-disordered breathing. Similar expansion of the maxillary and nasal complexes occurs with surgically-assisted RME (SARME) in adults. Limited reports on expansion in adults show that this may be a useful treatment alternative for selected patients with OSA, significantly improving AHI and reducing symptoms.
10. TREATMENT OUTCOME

It is insufficient to use resolution of symptoms like snoring to diagnose elimination of OSA and a medical follow-up with a PSG is recommended to confirm adequate management.\(^7\) Most patients report a reduction of snoring and witnessed apneas when using OA. However, successful treatment of OSA is only achieved in about two thirds of these patients with as many as 13% of patients showing an increase in AHI with OA treatment.\(^4,98,106,108\)

In the scientific literature, the definition of a successful treatment of OSA can be variable.\(^138\) Generally, a complete response can be defined as a resolution of symptoms plus a reduction in AHI to less than 5 as is stipulated by the definition of OSA\(^1\). Partial response is defined as improved symptoms plus a 50% or greater reduction in AHI, but remaining at 5 or more. Treatment failure is defined as ongoing clinical symptoms and/or a reduction in AHI of less than 50%.\(^80,98\) Another definition used to indicate a response to MAS include ≥50% reduction and residual AHI less than 10/h\(^139\). Another study simply classified responders as those with a ≥50% improvement in AHI, and non-responders as those with <50% improvement in AHI as it reflects clinical practice, with patients obtaining clinical benefit from MAS despite incomplete resolution of their OSA.\(^140\)
11. PREDICTORS OF TREATMENT OUTCOME

To date, all studies have consistently found that not all patients with OSA can be successfully treated with a MAS.3,4 The optimal goal is to predict which patients will respond most favorably to certain treatment options ahead of time. 5,19 Being able to predict the treatment outcome will maximize health gain, avoid wastage of resources and subsequently increase patient satisfaction. Clinical studies have suggested that demographic, anthropometric, polysomnograhpic, physiologic and anatomical characteristics relate to treatment outcome. Unfortunately, these are not uniformly reported and predictors of treatment outcome have not been clinically validated to evaluate its accuracy, thus rendering them useless in clinical practice.5,6

11.1 Clinical predictors

Demographic studies have reported a better treatment outcome of MAS in association with younger age138,141 due to the significant functional and structural changes in the upper airway dimensions with increased age, and female gender138,142 most likely due to a difference in fat distribution143.

Anthropometric characteristics points to better treatment outcome in patients with a lower body mass index5,141, smaller neck circumference98, smaller waist circumference144, supine-dependent OSA97, and lower AHI4,97,98,142.
11.2 Imaging Modalities

11.2.1 Photography

Craniofacial phenotype has been assessed using a simple quantitative photographic technique from coordinates of surface landmarks on frontal and profile digital photographs, capturing phenotypic information about both skeletal and soft tissue anatomy. This technique identifies differences in craniofacial structure between patients with and without OSA, but has not been used to predict treatment outcome.

11.2.2 Cephalometry

Skeletal cephalometric variables with a negative predictive value includes an increased MP angle, a steep occlusal plane, over-erupted posterior dentition with backwards rotation of the mandible, an increased gonial angle, an anterior open bite, a shorter maxilla associated with a smaller nasopharynx, an increased ANB angle indicating an intermaxillary discrepancy, a decreased SNB indicating a mandibular deficiency, an increased OJ and OB, an increased anterior facial height, a decreased cranial base angle, and an increased linear distance from the mandibular plane to hyoid bone. Soft tissue factors that positively correlate to responsiveness with MAS includes a smaller oropharynx, larger ratio of vertical airway length to the cross sectional area of the soft palate, a shorter palate length, a small tongue, and a shorter soft palate length.
The relationship between soft and bony tissue dimensions is one of potential importance and has been implicated in the pathogenesis of OSA. The difference ratio of tongue to oral enclosure area between responders and non-responders with MAS treatment suggests that the larger tongue area for a given oral cavity size may help to correct anatomical imbalance by increasing dimensions of the bony enclosure to better accommodate upper airway soft tissue improving airway patency.

It appears that the more abnormal the skeletal and soft tissue dimensions, the poorer the treatment outcome. However, predictive cephalometric measurements for successful or unsuccessful oral appliance therapy outcomes are conflicting and inconclusive. Furthermore, cephalometric measurements are taken in an upright position. Analysis with patients in a supine position, which mimics the position when OSA occurs, may be more clinically suitable. Finally, although a cephalogram can be used to estimate the volume of the tongue, soft palate and nasopharynx, it cannot be used for volumetric measurements of the collapsible velopharynx or oropharynx, which is the most common site for airway obstruction.

11.2.3 Magnetic resonance imaging (MRI)

Sanner et al conducted an MRI study with and without MAS during rest and during the Müller maneuver to locate the area of pharyngeal obstruction in patients with OSA. Their findings during the Müller maneuver were that all patients had pharyngeal obstruction without MAS. Non-responder showed obstruction in the velopharynx only,
whereas responders had obstructions in the oropharynx only or both the oropharynx and velopharynx. With the MAS in place, non-responders showed obstruction mainly at the velopharynx and to a lesser degree at the glossopharynx, whilst most responders showed no significant pharyngeal obstruction.

Another MRI study done by Chan et al.\textsuperscript{140} illustrated changes of the upper airway anatomy between responders and non-responders. The study was done during wakefulness with and without MAS. Without the MAS they found no differences between responders and non-responders in regards to airway volume, cephalometric measurements and skeletal Class. With the MAS they found responders to have an increase in the total airway volume as a result of an increase in the lateral dimensions, mainly in the velopharynx and to a lesser extend in the hypopharynx.

11.2.4 Computerized tomography (CT)

Kyung et al.\textsuperscript{155} studied the pharynx during wakefulness in non-obese patients who responded to treatment with MAS using CT scans. They found that the cross-sectional area of the velopharynx and oropharynx increased significantly with a greater degree of enlargement in the lateral than the sagittal plane.
11.2.5 Cone Beam Computerized Tomography (CBCT)

The airway dimensions change according to head posture. The velopharynx reduces significantly in the anterioposterior dimension from an upright to a supine position which can be attributed to gravity, the relaxation of the soft palate and tongue, and the positional change of the hyoid bone.\(^{156}\) This advocates for taking CBCT images in a supine position, but unfortunately it still does not truly reflect the upper airway during sleep.\(^{70}\)

Several measurements have been made from previous CBCT studies with the most common parameters including: total airway volume, minimal cross-sectional area (MCSA), and linear measurements in the lateral and anteroposterior dimensions at certain anatomical locations.\(^{70}\)

A comparative study of the airway size with and without a mandibular advancement device in place found that there was an increase in the total airway volume of the oropharynx. The biggest changes were evident in the lateral dimension at the level of C2, indicating that the airway acquires a more elliptical shape in cross-section.\(^{2}\) This correlated with a study done on obese patients where they found that the shape of the pharyngeal airway in patients with severe OSA was oriented more in the AP than in the lateral dimension. This orientation of the airway may place the pharyngeal dilator muscles at a relative mechanical disadvantage making it difficult to maintain pharyngeal airway patency.\(^{157}\)
11.2.6 Nasendoscopy

Nasendoscopy during wakefulness and sleep has been proposed as a valuable prognostic indicator of successful MAS treatment. Baseline soft tissue and upper airway volume does not systematically differ between treatment responders and non-responders when examined during awake supine nasendoscopy. However, airway changes consequent to mandibular advancement do differ with larger volume increases in the velopharynx, specifically in the lateral dimension, of responders. Furthermore, a greater extent of collapse of the whole pharynx of non-responders is observed during the Müller maneuver with and without mandibular advancement. This may be useful in predicting responsiveness, but the low specificity suggests that, as a single measure, it is not ideal for reliable clinical assessment. Improved airway patency with simulated mandibular advancement during sleep nasopharyngoscopy have been found to accurately predict treatment success with a MAS.

11.3 Functional Predictors

A remotely controlled device represents another promising prediction method for MAS treatment, since the use of this device during an initial night at the sleep laboratory showed high sensitivity and specificity for the assessment of treatment success or failure in a small sample of OSA patients. However larger clinical trials and assessment of cost effectiveness are needed.

For patients who have already tried CPAP, an optimal pressure of 10 mmHg or less were related to a higher chance of success with a MAS.
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11. MANUSCRIPT

PREDICTION OF THE EFFICACY OF A MANDIBULAR ADVANCEMENT SPLINT IN THE TREATMENT OF OBSTRUCTIVE SLEEP APNEA USING VARIOUS DIAGNOSTIC METHODS

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Prediction of the Efficacy of a Mandibular Advancement Splint in the Treatment of Obstructive Sleep Apnea using Various Diagnostic Methods

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11.1 Abstract

**Background:** Mandibular Advancement Splints (MAS) for the treatment of Obstructive Sleep Apnoea (OSA) is often preferred by patients, but unfortunately all studies to date have consistently found that not all patients with OSA can be successfully treated with MAS.\(^1\),\(^2\) Clinical studies have suggested that demographic, anthropometric, polysomnographic, physiologic and anatomical characteristics relate to treatment outcome. Unfortunately, these predictors of treatment outcome have not been uniformly reported, thus rendering them useless in clinical practice.\(^3\),\(^4\) Being able to predict which patients will respond favorably to certain treatment options ahead of time will maximize health gain, avoid wastage of resources and subsequently increase patient satisfaction.

**Aim:** The purpose of this study was to identify reliable, clinically applicable predictors that will allow the clinician to identify those patients who will respond favourably to MAS treatment in order to maximize health gain, avoid wastage of resources and subsequently increase patient satisfaction.

**Hypothesis:** The anatomical shape and size of the airway as measured on a CBCT can be used in conjunction with anthropometric data and clinical dento-facial examinations to predict the efficacy of MAS used to treat patients with OSA.
Subjects and Methods: Forty one adult patients (25 males, 16 females) with newly diagnosed OSA (AHI>10/hr) as demonstrated by a recent diagnostic nocturnal polysomnograph (PSG) were recruited from sleep disorder clinics for treatment with MAS. Demographic information, anthropometric measurements, polysomnographic data and clinical dento-facial records were obtained including a CBCT image of the head and upper airway in a supine position. Dolphin 3-D software was used to make linear, surface area and volumetric measurements of the reconstructed velopharynx and oropharynx.

All patients were fitted with MAS and after successful acclimatization and titration they underwent a repeat sleep study to determine treatment outcome. Two criteria were used to define clinical response; criteria 1 grouped patients as responders indicating an AHI < 5/hr, partial responders indicating >50% reduction in AHI but still AHI > 5/hr, and non-responders with less than <50% reduction in AHI; whilst criteria 2 grouped patients as responders with residual AHI <10/hr and non-responders ≥ 10/hr.

Results: According to the post treatment AHI results with MAS using criteria 1, there were 14 responders (34.1%), 16 partial responders (39%), and 11 non-responders (26.9%) of which 4 (9.8%) actually got worse. Using criteria 2 there were 26 responders (63.4%) and 15 non-responders (36.6%). Univariate logistic regression models were constructed to examine the relationship between subject response status and various demographic, anthropometric, clinical and radiographic phenotypes. Cross-references were run to detect any possible traits that may indicate the treatment outcome for individuals prior to commencement of MAS treatment. Several trends were observed, but none of these were statistically significant. Treatment success declined as
OSA severity increased. Age and gender had no predictive value of treatment outcome. Obese patients tended to have a poorer treatment outcome as well as an increased waist and neck circumference, especially for women. Both skeletal and dental Class I patients had better treatment outcomes than Class II and Class III. Furthermore, patients with an overjet within the norm (1-4mm) had better success with MAS treatment. Non-responders had a higher amount of titration, most likely due to the lack of relief of symptoms. None of the CBCT measurements had any predictive value.

**Conclusion:** No clinically significant phenotypic traits from various assessments and clinical examinations were predictive of MAS treatment outcome, neither were the inter-relationships between them. The limited data, however, makes any firm recommendations difficult to make. Further research using larger sample sizes is likely to improve its clinical utility.

**Key Indexing Terms:** Mandibular Advancement Splint, MAS, Cone Beam Computed Tomography, CBCT, Obstructive Sleep Apnea, OSA, OSAS, Responder, Non-responder, Treatment Outcome, Treatment Success.
11.2 Introduction

Background

Obstructive sleep apnea (OSA) is a common disorder characterized by disruptive snoring and repetitive episodes of partial or complete upper airway obstruction during sleep.\cite{5} It manifests as a reduction (hypopnea) or complete cessation (apnea) of airflow despite ongoing respiratory effort and results in intermittent hypoxaemia and hypercapnia, cortical arousals and surges of sympathetic arousals.\cite{5, 6, 7} OSA patients have a narrower upper airway compared to normal subjects\cite{9, 10} and obstruction can occur at a single or multiple levels along the upper airway, with the oropharynx or velopharynx being the most common site.\cite{8, 11}

The sequelae of OSA are directly related to the recurrent CNS arousals, asphyxia, and subsequent sleep deprivation. Excessive daytime sleepiness (EDS), neurocognitive impairment, increased motor vehicle and occupational accidents, and diminished quality of life are some of the consequences of OSA.\cite{12, 13, 14} The morbidity of OSA is primarily related to the cardiovascular system with OSA patients presenting with hypertension, coronary heart disease and congestive heart failure.\cite{12, 13, 15} Hypertension also contributes to cerebrovascular morbidity and mortality.\cite{12} Other comorbidities have been reported and include diabetes mellitus\cite{16, 17} and peri- and post-operative complications\cite{17, 18}. 
Polysomnography (PSG) based in an overnight facility is recommended for diagnosing OSA. The severity of OSA is determined by the Apnea-Hypopnea Index (AHI), which indicates the average number of apneas and hypopneas per hour. The suggested AHI cut points are 5, 15, and 30 events/hour to indicate mild, moderate, and severe levels of OSA.

The gold standard for the management of newly diagnosed OSA is Continuous Positive Airway Pressure (CPAP), because no matter where the obstruction in the pharynx occurs, this treatment has been shown to be very effective in most OSA patients. The major limitation of CPAP is poor patient compliance, which ranges from 65 to 80% with an average usage of less than 50% of the night.

Patients generally prefer oral appliances (OA) to CPAP as they are non-invasive, well-tolerated compared to CPAP, do not require a power source, and have minimal side-effects. A mandibular advancement splint (MAS) mechanically protrudes the mandible and the degree of protrusion improves nocturnal oxygenation and prevents pharyngeal collapsibility. Better treatment outcomes have been achieved with 75% mandibular advancement compared to 50%. Generally MAS holds the mandible at 75% of the patient’s maximal protrusion, though greater protrusion may achieve higher success rates. The side effects of more protrusion are still a unclear from the literature though.
Adjustable or titratable appliances allow the mandible to be moved forward in increments over weeks to months.\textsuperscript{33} Usually the initial position is set between 50-75\% of the maximum mandibular protrusion.\textsuperscript{34} The amount and rate of advancement should be individualized as the tolerance for advancement may increase with time. Titration proceeds until the maximal comfortable limit is reached\textsuperscript{2,27,32,35} or until relief of symptoms is experienced\textsuperscript{26,32}.

Successful management of OSA with MAS varies between 50\% to 80\% depending on the device used, the selection criteria and the parameters for success.\textsuperscript{2} An increased AHI after MAS therapy has been reported in approximately 13\% of patients\textsuperscript{2,36}, therefore a follow-up sleep study should always be conducted following MAS treatment to confirm that the OSA has been adequately managed.\textsuperscript{37}

In the scientific literature, the definition of a successful treatment of OSA can be variable.\textsuperscript{38} Generally, a complete response can be defined as a resolution of symptoms plus a reduction in AHI to <5/hr as is stipulated by the definition of OSA\textsuperscript{5}. Partial response is defined as improved symptoms plus \(\geq 50\%\) reduction in AHI, but remaining at \(\geq 5\)/hr. Treatment failure is defined as ongoing clinical symptoms and/or a reduction in AHI <50\%.\textsuperscript{32,39} One study defined a response to MAS as \(\geq 50\%\) reduction and a residual AHI <10/h\textsuperscript{40}. Another study simply classified responders as those with a \(\geq 50\%\) improvement in AHI, and non-responders as those with <50\% improvement in AHI as it reflects clinical practice where patients obtain clinical benefit from MAS despite incomplete resolution of their OSA.\textsuperscript{41}
**Predisposing Factors**

Currently it is estimated that men are twice as likely to have OSA as women with the prevalence of OSA quoted as 4% and 2% respectively in males and females.\textsuperscript{12} The occurrence of OSA in older people is more complex than previously appreciated. OSA prevalence increases steadily with age throughout midlife with a 2- to 3-fold higher prevalence in persons above 65 years of age compared with those between 30-64 years of age. After 65 years it seems to plateau.\textsuperscript{12,16,42}

The prevalence of OSA is 41 % in overweight people with a Body Mass Index (BMI) over 28 and as high as 78% in morbidly obese patients.\textsuperscript{17} There appears to be a gradual increase in OSA prevalence with increasing BMI, neck circumference and waist-to-hip ratio, but OSA is not exclusive to obese people.\textsuperscript{16} The weak correlation between OSA and BMI is due to the fat distribution not being homogenous among obese people.\textsuperscript{43} Neck circumference has a stronger correlation due to the regional fat deposition near the pharyngeal airway\textsuperscript{44-46}, but it has been found that waist circumference indicating fat accumulation of the intra-abdominal region is the best predictor of OSA severity.\textsuperscript{47} Men often have a lower BMI than women of the same severity of OSA, however the greater upper-body fat distribution and fat in the neck seen in males make them more susceptible to upper airway collapse and may in part explain the greater prevalence of OSA in males.\textsuperscript{44,48,49}
Craniofacial and upper-airway structure have an important role in OSA occurrence. The most frequently reported skeletal and soft tissue abnormalities are a small posteriorly placed mandible (retrognathia), an enlarged tongue and soft palate, and an inferiorly positioned hyoid bone, all of which compromise the pharyngeal airspace.\textsuperscript{16,50–52} Narrowed nasal cavities and tonsillar hypertrophy during childhood may cause mouth breathing which could lead to abnormal growth patterns and malocclusions and could predispose the individual to OSA in later life.\textsuperscript{21,53}

**Airway Assessment**

Visual assessment of the airway may aid the physician in determining the predominant anatomical site of obstruction. This could improve our understanding of the pathophysiology of OSA and help to select the correct treatment option for different patients.\textsuperscript{54,55} When choosing a method of airway inspection it is important to choose a procedure that is non-invasive, easy to perform, standardized, accurate, reproducible, cost-effective and readily available.\textsuperscript{54} A number of techniques are available, including indirect laryngoscopy, endoscopy during wakefulness, nasendoscopy during sleep, somnofluoroscopy, lateral cephalography, Computerized Tomography (CT), Magnetic Resonance Imaging (MRI) and Cone Beam Computed Tomography (CBCT).\textsuperscript{54}

The lateral cephalogram has been used historically to try and predict treatment outcome with MAS. Skeletal cephalometric variables with a negative predictive value includes an increased mandibular plane angle\textsuperscript{32,56,57}, a steep occlusal plane\textsuperscript{56}, over-erupted posterior dentition with backwards rotation of the mandible\textsuperscript{56,58}, an increased
gonial angle \textsuperscript{56}, an anterior open bite \textsuperscript{56}, a shorter maxilla associated with a smaller nasopharynx \textsuperscript{56}, an increased ANB angle indicating an intermaxillary discrepancy \textsuperscript{3}, an increased SNB indicating a mandibular deficiency \textsuperscript{3,59}, an increased overjet and overbite \textsuperscript{3}, an increased anterior facial height \textsuperscript{3,57}, a decreased cranial base angle \textsuperscript{38,59}, and an increased linear distance from the mandibular plane to hyoid bone \textsuperscript{57,60}. It appears that the more abnormal the skeletal and soft tissue dimensions, the poorer the treatment outcome \textsuperscript{57}. However, predictive cephalometric measurements for successful or unsuccessful oral appliance therapy outcomes are conflicting and inconclusive \textsuperscript{61}.

CBCT devices are now readily available at reduced radiation and cost compared to CT and MRI respectively. Cephalometric measurements that are taken in an upright position do not depict the airway dimension changes brought on by a change in head posture. The velopharynx reduces significantly in the anterio posterior (AP) dimension from an upright to a supine position which can be attributed to gravity, the relaxation of the soft palate and tongue, and the positional change of the hyoid bone \textsuperscript{62}. This advocates for taking CBCT images in a supine position, but unfortunately it still does not truly reflect the upper airway during sleep \textsuperscript{37}.

Furthermore, single linear measurements as performed on cephalograms do not depict the morphology of the airway when compared to a three-dimensional analysis \textsuperscript{63}. Although the AP dimension is that which is most likely to be changed with mandibular protrusion, previous researchers have found that a decreased lateral dimension is often present in patients with OSA, especially in obese patients \textsuperscript{55,64}. They also found that the
biggest changes in the airway were evident in the lateral dimension\textsuperscript{11}, especially in the velopharynx.\textsuperscript{65–67}

Three-dimensional imaging software allows for sagittal and cross-sectional images to be obtained for assessment of the airway in all dimensions. In addition, accurate 2D simulations of lateral and anteroposterior cephalometrics, panoramic images, and arthrography without magnification errors as seen in traditional 2D radiographs can be created.\textsuperscript{55} Dolphin 3D Imaging (Dolphin Imaging/Patterson Dental, Chatsworth, CA) has been proved to be both accurate and reliable to analyse the airway volume and dimensions from a CBCT.\textsuperscript{68}

The optimal goal is to predict which patients will respond most favorably to certain treatment options ahead of time.\textsuperscript{3,9} Being able to predict the treatment outcome will maximize health gain, avoid wastage of resources and subsequently increase patient satisfaction. Clinical studies have suggested that demographic, anthropometric, polysomnographic, physiologic and anatomical characteristics relate to treatment outcome.\textsuperscript{3,4} In this study, we hope to find clinically applicable indicators from anthropometric data and visual airway analysis by means of CBCT to successfully predict the treatment outcome and thus the efficacy of MAS used in the treatment of patients with OSA.
11.3 Subjects & Methods

11.3.1 Patient Selection

This prospective clinical trial recruited patients from two tertiary referral sleep clinics in Sydney, Australia. Adult patients with newly diagnosed OSA (AHI ≥ 10/hr) as demonstrated by a recent diagnostic nocturnal polysomnograph (PSG) were deemed eligible and were given the opportunity to undergo MAS treatment and take part in the study. Patients with periodontal disease or evidence of temporomandibular disorders (TMD), including pain or limited opening of less than 40mm, were excluded from the study. The study was approved by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health Network. Written informed consent was obtained from all participants after adequate time was given to consider enrollment. Details of the trial are provided in the APPENDIX.

Between January 2012 and June 2013, 56 patients were screened for the study. Fourteen patients were excluded on the basis of declination to participate (n=5), withdrawal from the study (n=4), and incomplete data due to inability to contact patients for follow-up appointments (n=5). Of the four withdrawals, 2 patients were unable to wear the MAS, one had nasal issues and one patient gave no reason for his withdrawal. Consequently 41 adult patients participated in the study.
11.3.2 Study Design

Demographic, anthropomorphic, polysomnographic and dento-facial measurements as well as CBCT scans were obtained on all patients at baseline. CBCT scans were reconstructed and analyzed with the author (AB) blinded to the treatment outcome. Following an average acclimatization period of 6 weeks, a second PSG was performed with the MAS to determine treatment outcome.

Polysomnography (PSG)

The baseline PSG was used to obtain each patient's AHI so that they could be classified into categories as having mild, moderate or severe OSA at cutpoints of 5, 15, and 30 events/hour respectively.5

Demographic and anthropomorphic measurements

Gender and age were noted at baseline as demographic variables. Anthropometric data collected included body mass index (BMI) calculated as Weight / (Height)^2, waist circumference with the norm as recommended by the WHO to be less than 80 cm for women and 94 cm for men69, and neck circumference with previously proposed norms as less than 42 cm in men and 37 cm in woman.70
Dento-facial measurements

Dental variables collected included profile classification, dental classification, overjet (OJ) and overbite (OB). The maximum mandibular advancement at baseline was determined with a George-Gauge™ (H Orthodontics, Michigan City, IN, USA) and the amount of expected titration was calculated to be 25% of the maximum protrusion as the adjustable MAS was made at 75% of maximum advancement.

Cone Beam Computed Tomography (CBCT)

CBCT scans were taken of all patients prior to treatment with MAS using a NewTom 3G (QR, Verona, Italy) with a 12” field of view (FOV) at 110kV with an exposure time of 5.4s. The scans were obtained with the patient in a supine position37,62 using adjustable head support to prevent over extension of the neck and to ensure that the Frankfort horizontal plane was perpendicular to the floor.

After the raw data was checked to ensure that the patient had not moved during the image acquisition, the obtained images were reconstructed and imported as DICOM (digital imaging and communications in medicine) data files into Dolphin Imaging Premium® software (version 11.0 Dolphin Imaging and Management Solutions, Chatsworth, California).
Mandibular Advancement Splint (MAS)

The MAS used was a two-piece, custom-made adjustable device (SomnoMed® Ltd, Australia) (Fig 1), the design features and effectiveness of which have been previously published. The appliance was fabricated at 75% of the maximal advancement, as recommended in the literature, using a George Gauge TM (Great Lakes Orthodontics Ltd, New York, America). Acclimatization occurred over a period of approximately 6 weeks, during which the appliance was incrementally advanced by 0.2mm bilaterally on a daily basis until the maximum comfortable limit of mandibular advancement was reached. Patients were given verbal and written instructions and a diary to complete daily during the titration period. A copy is provided in the APPENDIX.

Airway Analysis

Dolphin Imaging Premium® software (version 11.0 Dolphin Imaging and Management Solutions, Chatsworth, California) was used to analyse all CBCT scans. All images were first oriented in a similar method (Fig 2) by starting with a lateral view and superimposing the right and left zygomatic processes & orbits to ensure that the roll and the yaw of the head is correct. The pitch was corrected by ensuring that the axial plane was parallel to the Frankfort Horizontal Plane (FHP), which is a line that connects the inferior border of the orbit with the superior border of Porion. In the frontal view the mid-sagittal plane was positioned to pass through Nasion and the anterior nasal spine (ANS).
Using the sinus/airway analysis tool a clean segmentation of the airway can be produced due to the lower CT value exhibited by air space compared to the denser surrounding soft tissue. A threshold range of 45 units were used for most CBCT analysis after observing consecutively that this unit provided the most comprehensive airway selection without adding or leaving out upper airway space. The threshold had to be decreased for 1 patient and increased for 6 patients due to the opacity of the soft tissue present.

The anatomical velopharynx and oropharynx (Fig 3) stretching from the hard palate to the tip of the epiglottis were selected to be analysed as these tend to be the most common sites of obstruction\textsuperscript{41,74,75} and shows the biggest response to MAS treatment\textsuperscript{8,55}. The parameters of the airway were demarcated using the following limits: anteriorly by the posterior wall of the soft palate and base of the tongue, posteriorly by the posterior pharyngeal wall, superiorly by a plane traced through the posterior nasal spine (PNS) that is parallel to the FHP (as determined during the CBCT orientation), and inferiorly by a plane passing through the most superior point of the epiglottis traced parallel to the FHP (Fig 4).

Once the airway had been demarcated, the seed points placed and the threshold selected, Dolphin 3-D software was used to calculate the volume and minimal cross sectional area (MCSA) (Fig 5). Linear measurements were taken to determine the length of the combined velo-and oropharynx.
An axial slice of the MCSA was used to make linear measurements of the transverse (TV) and antero-posterior (AP) dimensions. The AP dimension was made through the center of the airway whilst the TV measurements were taken at the widest part of the airway (Fig 6). These measurements were repeated three times by the same operator and the average was used. The shape of the airway was also noted and described as convex or non-convex depending on whether the AP and TV lines intersected each other.

Right lateral skull cephalometric radiographs were extracted and analysed to attain linear and angular measurements (Fig 7). The measurements included SNA, SNB, ANB, Jarabak’s Ratio, SN-MP, Co-Gn, Co-A and are defined in Table 1. A single assessor who was blinded to the apneic status of the patients made all cephalometric measurements. The measurements were compared to the norms as outlined in Table 2.

11.3.3 Treatment Outcome

Patients were grouped according to their AHI measured during a second (after MAS titration) nocturnal PSG whilst using their MAS. Due to the variation in the literature to define clinical response two different criteria were used (Table 3). The first criteria represents a more scientific approach with a complete response defined as a resolution of symptoms plus a reduction in AHI to less than 5/hr, a partial response defined as improved symptoms plus a 50% or greater reduction in AHI, but remaining 5/hr or more, and treatment failure defined as ongoing clinical symptoms and/or a reduction in
AHI of less than 50%. The second criteria was used to reflect a more practical classification with responders defined as having residual AHI < 10/hr and non-responders ≥ 10/hr. This reflects the cutoff point at which patients were selected for this study. Patients who showed an increase in AHI were also grouped as non-responders for statistical analysis.

11.3.4 Statistical Analysis

Data was analysed using a statistical package (IBM SPSS Statistics Version 21). All descriptive statistics are presented as mean±SD. The \( \chi^2 \) test (for categorical data) and the ANOVA (for quantitative outcome) were used to compare the similarities and differences between outcome categories (i.e. responders and non-responders). Levene Statistics was used to test of homogeneity of the variances for ANOVA. For post-hoc test where appropriate, we used Bonferroni adjustments or Tamhane tests to correct the significance level for multiple comparisons. A p value <0.05 was considered significant.

11.4 Results

Descriptive statistics of all patients, responders, partial responders and non-responders are given in Tables 4-7 respectively.

Treatment Outcome

Using criteria 1, 34.1% (14 patients) had a complete response, 39% (16 patients) had a partial response, and 26.9% (11 patients) were non-responders (Chart 1). Of the non-responders 9.8% (4 patients) had an increase in their AHI when using a MAS. Using
criteria 2, 63.4% (26 patients) were responders and 36.6% (15 patients) were non-responders (Chart 2).

A quantitative treatment response was measured as a percentage to determine the degree of AHI reduction. The mean reduction was -58% with a maximum reduction of -95.8% that reflected a drop in AHI of 60/hr. The worst response was +63.4% with an increase in AHI of 19/hr.

**Baseline Polysomnography**

The baseline AHI ranged from 10 to 74.9 with a mean of 25.8/hr. 24.4% (10 patients) had mild OSA, 41.5% (17 patients) had moderate OSA, and 34.1% (14 patients) had severe OSA.

Criteria 1 (Chart 3) showed that of the patients who started with mild OSA 70% (7 patients) had a complete response and 30% (3 patients) were non-responders. In the moderate OSA group, there were 30% (5 patients) non-responders as well, but with complete responders and partial responders distributed equally as 35% (6 patients) per group. The severe OSA group had the smallest amount of complete responders of 7% (1 patient), with 70% (10 patients) partial responders and 21% (3 patients) non-responders. Using criteria 2 (Chart 4), patients who were initially diagnosed with mild OSA had 80% (8 patients) complete responders and 20% (2 patients) non-responders. In the moderate OSA group, there were 64.7% (11 patients) complete responders and
35.3% (6 patients) non-responders. The severe OSA group had 50% (7 patients) complete responders as well as 50% (6 patients) non-responders.

**Demographic Analysis**

Patients had a mean age of 53.4 years, ranging from 36.5 – 73.3 years. Of the 41 patients, 25 (61%) were males and 16 (39%) were females. The distribution of age and gender were equally distributed amongst all treatment outcome groups using both criteria 1 and 2.

**Anthropometric Analysis**

The mean BMI was 29.58 with 9.8% (4 patients) falling within the normal weight category (BMI < 25), 48.8% (20 patients) being classified as overweight (BMI 25 – 30) and 41.5% (17 patients) considered being obese (BMI ≥30).

When BMI was compared to treatment outcome according to criteria 1 (Chart 5), patients in the normal BMI category showed a 50% (2 patients) complete response, 25% (1 patient) had a partial response, and 25% (1 patient) were non-responders. Of the overweight group 45% (9 patients) had a complete response, 30% (6 patients) had a partial response, and 25% (5 patients) were non-responders. The obese group of patients had 17.6% (3 patients) complete responders, 52.9% (9 patients) partial responders and 29.4% (5 patients) non-responders.
Using criteria 2 to compare BMI to treatment outcome (Chart 6), patients in the normal BMI category showed a 75% (3 patients) complete response and 25% (1 patient) were non-responders. Of the overweight group 70% (14 patients) had a complete response and 30% (6 patients) were non-responders. The obese group of patients had 52.9% (9 patients) complete responders and 47.1% (8 patients) were non-responders.

The waist circumference for males ranged from 76-128cm with 72% (18 males) considered having a normal waist circumference below 94cm and 28% (7 males) considered to have an increased waist circumference. For women the waist circumference ranged from 84.5-130cm, with 100% (16 females) having an increased waist circumference of 80cm or more.

The neck circumference for men ranged from 37-47cm, with 64% (16 males) considered having a normal neck circumference less than 42cm and 36% (9 males) having an increased neck circumference. For women the neck circumference ranged from 33-43.5cm, with 25% (4 females) considered having a normal neck circumference less than 37cm and 75% (12 females) having an increased neck circumference. (Chart 7)

BMI, waist and neck had statistically significant correlations with each other both for males (p < .001) and females (p < .050) and were positively correlated. (Chart 8)
Comparing waist circumference to treatment outcome using criteria 1, the men who were considered to have a normal waist circumference of 94cm or less had 57.1% (4 males) responders, 28.6% (2 males) partial responders, and 14.3% (1 male) non-responders. The men who had an increased waist circumference had 22.2% (4 males) complete responders, 44.4% (8 males) partial responders, and 33.3% (6 males) non-responders. None of the women had a normal waist circumference of 80cm or less and were all considered to have an increased waist circumference. 37.5% (6 females) were complete responders, 37.5% (6 females) were partial responders, and 25% (4 females) were non-responders. Using criteria 2 to determine treatment outcome for waist circumference, the men with a normal waist circumference had 85.7% (6 males) responders and 14.3% (1 male) non-responders whilst those with an increased waist circumference had 50% (9 males) responders and 50% (9 males) non-responders. The women, who were all considered to have an increased waist circumference, had 68.8% (11 females) responders and 31.3% (5 females) non-responders. (Chart 9)

Comparing neck circumference to treatment outcome using criteria 1, men with a normal neck circumference of 42cm or less had 43.8% (7 males) responders, 37.5% (6 males) partial responders, and 18.8% (3 males) non-responders. The men with an increased neck circumference had 11.1% (1 male) responders, 44.4% (4 males) partial responders, and 44.4% (4 males) non-responders. Of the women who had a normal neck circumference of 37cm or less 25% (1 female) were complete responders, 75% (3 females) were partial responders, and 0% were non-responders. The women with an increased neck circumference had 41.7% (5 females) complete responders, 25% (3 females) partial responders, and 33.3% (4 females) non-responders. Using criteria 2 to
determine treatment outcome for neck circumference, the men with a normal neck circumference had 68.8% (11 males) responders and 31.3% (5 males) non-responders whilst those with an increased waist circumference had 44.4% (4 males) responders and 55.6% (5 males) non-responders. The women with a normal neck circumference had 100% (4 females) responders whilst those with an increased neck circumference had 58.3% (7 females) responders and 41.7% (5 females) non-responders. (Chart 10)

**Dento-facial Analysis**

Skeletal classification was determined by the ANB angle measured from on a reconstructed lateral cephalometric radiograph. 34% (14 patients) were classified as having a skeletal I base, 58.5% (24 patients) had a skeletal II base and 7.5% (3 patients) had a skeletal III base. Due to the small sample size for class III both skeletally and dentally, this was not further analysed.

Using criteria 1, skeletal I patients had a 50% (7 patients) complete treatment response, 35% (5 patients) had a partial response and 14.3% (2 patients) were non-responders. The treatment outcome for skeletal II patients was 29.2% (7 patients) for complete responders, 37.5% (9 patients) for partial responders and 33.3% (8 patients) were non-responders. Using criteria 2, skeletal I patients had 78.6% (11 patients) responders and 21.4% (3 patients) were non-responders. Skeletal II patients had 54.2% (patients) responders and 45.8% (11 patients) non-responders.
Dental classification was determined according to the molar and canine relationship. 73.2% (30 patients) had a class I dental relationship, 24.4% (10 patients) were classified as class II and 2.4% (1 patient) were class III.

The treatment outcome using criteria 1 for class I patients was 43% (13 patients) for responders, 33.3% (10 patients) for partial responders and 23.3% (7 patients) for non-responders. Class II patients had 10% (1 patient) responders, 50% (5 patients) partial responders and 40% (4 patients) non-responders. Using criteria 2, dental class I patients had 66.7% (20 patients) responders and 33.3% (10 patients) non-responders. Dental class II patients had 50% (5 patients) responders and 50% (5 patients) non-responders.

The overjet measurements ranged from 0 to 9mm with a mean of 2.61mm. The overbite ranged from -3 to 10mm with a mean of 2.5mm. The maximum protrusion measured ranged from 6 to 15mm with a mean of 9.6mm.

When overjet was compared to treatment outcome using criteria 1, all complete responders had a fairly normal overjet range of 1 to 4 mm with a mean of 2mm. Partial responders ranged from 0 to 8mm and non-responders from 1 to 9mm, both with a mean of 3mm. Overbite (p= 0.62) and maximum protrusion showed no trends and had no predictive value.
The expected amount of titration was calculated as 25% of the maximum protrusion and ranged from 1.5 to 3.5mm with a mean of 2.4mm. The actual titration ranged from 0.4 to 6mm with a mean of 3.7mm. The difference between the expected titration and actual titration was calculated to determine the discrepancy between the true amount of advancement and the initial amount of maximum protrusion measured at 100%. The difference ranged from -3.9 to +2.9mm with a mean of -1.35mm. Using criteria 1, the complete responders had a mean difference of -0.74mm, the partial responders had a mean difference of -1.66mm and the non-responders had a mean difference of -2.01mm. The reverse responders had a mean difference of -1.05mm. This was statistically significant with a p value of .042. When criteria 2 was used, responders had a mean difference of -1.22mm and non-responders -1.56mm which was not statistically significant.

**CBCT Analysis**

The combined volume of the velopharynx and oropharynx was measured and ranged from 3901.2 to 21014.3mm³ with a mean of 9694.8mm³. Both the minimum and maximum volume fell in the complete response group. The minimal cross sectional area (MCSA) ranged from 32.9 to 269.7mm² with a mean of 81.8mm². Once again the minimum and maximum MCSA fell in the complete response group.

The MCSA anatomical position was situated in the velopharynx for 33 patients (80.5%), on the border of the velo- and oropharynx for 5 patients (12.2%) and in the
oropharynx for 3 patients (7.3%). Using criteria 1, the treatment outcome for the patients with the MCSA in the velopharynx was 33% (11 patients) responders, 36.4% (12 patients) partial responders and 30.3% (10 patients) non-responders; on the border of the velo- and oropharynx it was 60% (3 patients) responders, 40% (2 patients) partial responders and 0% non-responders; and in the oropharynx it was 0%

responders, 66.7% (2 patients) partial responders and 33.3% (1 patient) non-responders. The treatment outcome using criteria 2 for patients in whom the MCSA fell in the velopharynx was 57.6% (19 patients) for responders and 42.4% (14 patients) for non-responders; on the border of the velo- and oropharynx it was 100% (5 patients) for responders and 0% for non-responders; and in the oropharynx it was 66.7% (2 patients) for responders and 33.3% (1 patient) for non-responders.

The combined length of the velopharynx and oropharynx ranged from 39.8 to 65.7mm with a mean of 51.4mm. The transverse of the MSCA as measured across the widest part on the airway on an axial slice ranged from 6.4 to 30.7mm with a mean of 16mm. The antero-posterior width measured in the center of the airway ranged from 1.6 to 11.1mm with a mean of 4.1mm. The ratio between AP and TV ranged from 1.2 to 19.6mm with a mean 4.7mm.

Upon subjective visual inspection of the airway shape, 70.7% (29 patients) had a convex shaped airway and 29.3% (12 patients) had a non-convex shape. The convex group had 41.4% (12 patients) complete responders, 31% (9 patients) partial responders and 27% (8 patients) non-responders in regards to criteria 1 and 58.6% (17
patients) responders and 41.4% (12 patients) non-responders using criteria 2 as a treatment outcome. The non-convex group had 16.7% (2 patients) complete responders, 58.3% (7 patients) partial responders and 25% (3 patients) non-responders using criteria 1 and 75% (9 patients) responders and 25% (3 patients) non-responders using criteria 2.

**Cephalometric Analysis**

No statistical findings or trends were found for any cephalometric measurements when compared to treatment outcome using both criteria 1 and 2.

**11.5 Discussion**

Numerous studies have been conducted to try and predict the treatment outcome for patients who prefer oral appliances to CPAP for the treatment of OSA. In the scientific literature, the definition of a successful treatment of OSA can be variable. One of the strengths of this cohort prospective study is that we used two different types of treatment outcomes to validate the efficacy of a mandibular advancement splint. The first criterion was used for scientific comparison to other studies whilst the second criterion was focused on a more clinically applicable treatment outcome. Treatment outcome was determined using a laboratory based PSG and all other data was quantitative rather than qualitative or subjective as is often the case with questionnaires such as the Epworth Sleepiness Scale (ESS). Another strength is that the CBCT scans were taken in a supine position. Even though it does not truly reflect the upper airway during sleep, it reflects the gravitational changes that occur within the velopharynx
which reduces significantly in the anterioposterior (AP) dimension from an upright to a supine position.62

As in other studies5-76, non-response ranged from 27-37% for treatment outcome criteria 1 and 2 respectively. An increase in AHI was found in 9.8% of patients which compares to previous findings of 13%2,36 and reinforces the need for a follow-up PSG to confirm treatment success.

The percentage of responders decreased as the baseline OSA increased when criteria 2 was used to determine treatment outcome. This confirms previous findings in the literature that reported overall better success rates in patients with lower AHI2,77,78, although there were others who found that the baseline OSA severity category did not influence treatment outcome32,79. This could be due to different treatment outcomes used as the non-responders were fairly equally distributed amongst the three OSA categories when criteria 1 was applied. Focusing on the complete and partial responders for criteria 1, there appeared to be a trend for patients with initial mild OSA to be complete responders, those with moderate OSA had a 50% chance of being a complete responder whilst the other 50% were partial responders, and of the severe OSA group most of the responders were partial responders with only 10% showing a complete response. It could be concluded that complete treatment response decreases as initial AHI severity increases.
Demographic studies reported a better treatment outcome of MAS in association with younger age\textsuperscript{38,80} due to the significant functional and structural changes in the upper airway dimensions with increased age, and female gender\textsuperscript{38,81} most likely due to a difference in fat distribution\textsuperscript{70}. This study found neither age nor gender to be an indicator of treatment success.

The literature also points to better treatment outcome in patients with a lower body mass index\textsuperscript{3,80}, smaller waist circumference\textsuperscript{82}, and smaller neck circumference\textsuperscript{32}. The percentage of non-responders tended to increase as BMI increased when criteria 2 was applied. When the BMI of responders and non-responders in criteria 1 was observed, there appeared to be a trend for obese patients to be partial responders instead of complete responders. Responders tended to have a smaller waist and neck circumference compared to non-responders especially for women. However, none of our anthropometric findings were statistically significant.

Dento-facial analysis comparing dental and skeletal classes to treatment outcome for both criteria indicated that patients with a skeletal I base or dental class I had the best treatment outcome with a fairly low failure to respond. Patients with a skeletal II base or a dental class II had a much poorer complete response rate with an increased partial response rate as well as an increase in failure to respond. All complete
responders from criteria 1 had an overjet ranging from 1 to 4mm with a mean of 2mm, whereas the partial and non-responders had a much bigger range and an increased mean OJ. Although the evidence is not conclusive or statistically significant, this trend might indicate that MAS is better suited for skeletal and dental class I patients with an overjet within the norm (1 to 4mm). This supports previous observations that the more abnormal the skeletal and soft tissue dimensions, the poorer the treatment outcome.57

The amount and rate of advancement was individualized as suggested in the literature and titration proceeded until the maximal comfortable limit was reached2,27,32,35 or until the relief of symptoms was experienced.26,32 Most patients managed to advance the mandible more than the expected advancement of 25% of the maximum protrusion. This is most likely due to muscle adaptation and stretch from slow, incremental advancement of 0.2mm per day. Although it has been hypothesized that there is a positive correlation between the amount of advancement and a decrease in AHI, this study found that for criteria 1 the non-responders had the highest amount of titration with a mean of 4.6mm instead of the expected mean of 2.6mm, thus over-titrating with 2mm. The lack of relief of symptoms may have been a reason to keep advancing the device. It could be speculated that too much advancement has a negative effect on the improvement of OSA, but the analysis when criteria 2 was used as a treatment outcome showed no statistical significance.

Our results concur with previous studies41 that found no predictive value towards treatment outcome in regards to the volume and MCSA of the airway as measured on a reconstructed CBCT. Linear measurements including the length, and transverse and antero-posterior width of the airway as measured on an axial slice across the MCSA did
not have any predictive value either. Most of the patients had the MCSA situated in the velopharynx. For the few who had the MCSA situated on the transition of the velopharynx into the oropharynx, none showed a failure to treatment with MAS. However, the sample size is too small to have any predictive value. The ratio between the AP and TV dimensions of the airway showed a wide range, indicating a variety of airway dimensions with the smaller value indicative of a more spherical (round) airway and the bigger number pointing to a more elliptic (ovoid) airway shape. All the airways were wider in the lateral dimension than in the AP dimension. This ratio had no predictive value towards treatment outcome. A subjective visual inspection of the airway shape was used to describe the airway as convex or non-convex depending on whether the AP and TV lines intersected each other or not, but once again there was no evidence that suggested that airway shape may indicate treatment success with MAS.

A potential limitation of this study is that the first and second PSG was not standardized as to the position in which the patient was sleeping. This could lead to a false positive or negative treatment outcome due to the supine-dependent nature of OSA.\(^{83}\) This might be a standardization to include in future studies to ensure that the two PSG results are of a similar nature. Nevertheless, we believe that our sample and data collection is representative of patients who have OSA and the results can be extrapolated to a general OSA population.
11.6 Conclusion

We have demonstrated that the efficacy of MAS to treat patients with OSA is similar to findings in previous studies and that it can be used as an alternative to CPAP in about two out of three patients, even in patients with severe OSA. Follow-up PSG should be mandatory though as some patients did display an increase in OSA with MAS therapy.

Our study looked at various polysomnographic, demographic, anthropometric, dento-facial and CBCT measurements at baseline to predict the efficacy of MAS. Several trends that were not statistically significant were observed including:

- Treatment success declined as OSA severity increased.
- Age and gender were not predictive of treatment outcome.
- Obese patients had a smaller percentage of complete response with MAS than overweight patients or those with a normal BMI.
- Responders tended to have a smaller waist and neck circumference compared to non-responders especially for women.
- Better treatment success was observed for skeletal and dental class I patients with an overjet within the norm (1-4mm).
- Non-responders over-titrated their appliance possibly due to the lack of relief of symptoms. The influence of over-titration on the success of MAS treatment is unclear though.
None of our findings were statistically significant which reinforces that OSA is multifactorial and that the pathophysiology is more complex than we might think. Furthermore, measurements made from CBCT scans at baseline were not predictive of the treatment outcome individually or when cross-referenced. Other forms of diagnostic tools may yield better results and should be further investigated.

11.7 Acknowledgements

The authors would like to thank the ASO Foundation for Research and Education for their kind financial support, the University of Sydney and the National Health and Medical Research Council for their generous grant.
11.8 References


61. Lowe A. Can We Predict the Success of Dental Appliance Therapy for the Treatment of Obstructive Sleep Apnea Based on Anatomical Considerations? *Sleep* 1993;16(8):S93–95.


11.9 Figure legends

<table>
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<th>Figure</th>
<th>Description</th>
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<tr>
<td>Figure 1</td>
<td>SomnoMed custom-made adjustable two-piece Mandibular Advancement Splint (MAS)</td>
</tr>
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<td>Figure 2</td>
<td>Orientation of CBCT to replicate Natural Head Position</td>
</tr>
<tr>
<td>Figure 3</td>
<td>Anatomical airway parameters</td>
</tr>
<tr>
<td>Figure 4</td>
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</tr>
<tr>
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<td>A, Airway volume (mm³); B, Minimal Cross-sectional Area (mm²)</td>
</tr>
<tr>
<td>Figure 6</td>
<td>A, Axial slice of the airway with two types of airways measured: B, a convex airway; C, a non-convex airway.</td>
</tr>
<tr>
<td>Figure 7</td>
<td>Simulated lateral cephalometric image with superimposed tracing.</td>
</tr>
</tbody>
</table>

**Figure 1:**

![Image of the SomnoMed custom-made adjustable two-piece Mandibular Advancement Splint (MAS)](image)
Figure 2:

Figure 3:
**Figure 4:**

![Image of Figure 4]

**Figure 5:**

![Image of Figure 5]
Figure 6:

Figure 7:
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</tr>
<tr>
<td>Table 7</td>
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## Table 1:

<table>
<thead>
<tr>
<th>Cephalometric Landmarks and Measurements</th>
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<tr>
<td>Sella (S)</td>
<td>Centre of the outline of the pituitary fossa (sella turcica)</td>
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<tr>
<td>Nasion (N)</td>
<td>Interior and anterior point of the frontonasal suture</td>
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<tr>
<td>A point (A)</td>
<td>Point at the deepest midline concavity on the maxilla</td>
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<tr>
<td>B point (B)</td>
<td>Point at the deepest midline concavity on the mandibular symphysis</td>
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<td>Gonion (Go)</td>
<td>Point formed by the tangents to the lower and posterior borders of the mandible</td>
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<td>Menton (Me)</td>
<td>Most inferior point on the mandibular symphysis</td>
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<tr>
<td>Gnathion (Gn)</td>
<td>Most anterior inferior point on the symphysis of the chin</td>
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<tr>
<td>Condyllion (Co)</td>
<td>Most superior point on the head of the condylar head</td>
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<td>SNA</td>
<td>Angle between sella, nasion and A point</td>
</tr>
<tr>
<td>SNB</td>
<td>Angle between sella, nasion and B point</td>
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</table>

[^3]: Reference to page 83
[^4]: Reference to page 84
Table 2:

<table>
<thead>
<tr>
<th>ANB</th>
<th>Angle between A point, nasion and B point</th>
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<tr>
<td>Jarabak’s Ratio (S-Go/N-Me)</td>
<td>The ratio of the distance from sella to gonion compared to the distance from nasion to menton</td>
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<td>SN</td>
<td>Plane formed by sella to nasion</td>
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<td>MP (Go-Me)</td>
<td>Mandibular plane between gonion and menton</td>
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<td>SN-MP</td>
<td>Mandibular plane angle</td>
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<td>Co-Gn</td>
<td>Distance between condyliion and gnathion</td>
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CEPHALOGRAPH MEASUREMENTS NORMS

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<tr>
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<td>≥ 10 /hr</td>
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<td>Table 4: Descriptive statistics for all patients</td>
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<tr>
<td>J (%)</td>
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<td>MP angle</td>
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And Blignaut 123
Prediction of the Efficacy of a Mandibular Advancement Splint in the Treatment of Obstructive Sleep Apnea using Various Diagnostic Methods

| Gonial angle (°) | 40 | 25.20 | 117.90 | 143.10 | 127.75 | 5.94 |
| UFH (%) | 40 | 14.30 | 38.00 | 52.30 | 43.35 | 2.92 |
| LFH (%) | 40 | 11.60 | 50.40 | 62.00 | 56.90 | 2.54 |

**Table 5: Descriptive statistics for responders**

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<tr>
<th>N</th>
<th>Statistic Statistic Statistic Statistic Statistic Statistic</th>
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Table 6: Descriptive statistics for partial-responders

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Prediction of the Efficacy of a Mandibular Advancement Splint in the Treatment of Obstructive Sleep Apnea using Various Diagnostic Methods

| Corpus (mm) | 16 | 15.7 | 70.2 | 85.9 | 75.944 | 4.7914 |
| Ramal (mm) | 16 | 27.1 | 49.0 | 76.1 | 64.506 | 7.9446 |
| J (%) | 16 | 21.7 | 48.9 | 70.6 | 62.438 | 5.9902 |
| MP angle | 16 | 25.3 | 27.1 | 52.4 | 37.650 | 7.5383 |
| Gonial angle (°) | 16 | 24.9 | 118.2 | 143.1 | 129.275 | 6.2333 |
| UFH (%) | 16 | 12.4 | 39.9 | 52.3 | 43.863 | 3.4004 |
| LFH (%) | 16 | 9.7 | 50.4 | 60.1 | 56.763 | 2.5617 |

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### Prediction of the Efficacy of a Mandibular Advancement Splint in the Treatment of Obstructive Sleep Apnea using Various Diagnostic Methods

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### 11.11 List of Charts

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<td>Treatment outcome using criteria 1</td>
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<td>Chart 2</td>
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<tr>
<td>Chart 3</td>
<td>Baseline OSA severity compared to Treatment Outcome 1</td>
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<td>Chart 4</td>
<td>Baseline OSA severity compared to Treatment Outcome 2</td>
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<td>Chart 5</td>
<td>BMI categories compared to Treatment Outcome 1</td>
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<td>Chart 6</td>
<td>BMI categories compared to Treatment Outcome 2</td>
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<tr>
<td>Chart 7</td>
<td>The criteria used for an increased waist circumference was &gt;80cm for women and &gt;94cm for men. Men were considered to have an increased neck circumference if it was &gt;42cm and &gt;37cm in women.</td>
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<td>Chart 8</td>
<td>Correlation between BMI, waist and neck circumference</td>
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<td>Chart 9</td>
<td>Waist circumference measurements for men and women compared to Treatment Outcome using Criteria 2</td>
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<td>Chart 10</td>
<td>Neck circumference measurements for men and women compared to Treatment Outcome using Criteria 2</td>
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<td>Chart 11</td>
<td>Dental and skeletal analysis compared to Treatment Outcome using criteria 1</td>
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<td>Chart 12</td>
<td>Dental and skeletal analysis compared to Treatment Outcome using</td>
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<td>Chart 13</td>
<td>Overjet measurements compared to Treatment Outcome using Criteria 1 with Non-responders included as a separate category.</td>
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<td>Chart 14</td>
<td>Difference between expected amount of advancement (mm) and actual amount of advancement (mm) compared to Treatment Outcome using Criteria 1 with Non-responders included as a separate category.</td>
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<td>Chart 15</td>
<td>Airway shape compared to Treatment Outcome (Criteria 1)</td>
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<tr>
<td>Chart 16</td>
<td>Airway shape compared to Treatment Outcome (Criteria 2)</td>
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Chart 1: Treatment Outcome: Criteria 1

- Responders: 34%
- Partial responders: 39%
- Non-responders: 17%
- Reverse Responders: 10%

Chart 2: Treatment Outcome: Criteria 2

- Responders: 63%
- Non-responders: 37%
Chart 3:

**OSA severity compared to Treatment Outcome 1**

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<th>Moderate</th>
<th>Severe</th>
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Chart 4:

**OSA severity compared to Treatment Outcome 2**

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Prediction of the Efficacy of a Mandibular Advancement Splint in the Treatment of Obstructive Sleep Apnea using Various Diagnostic Methods

Chart 5:

BMI compared to treatment outcome: Criteria 1

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Chart 6:

BMI compared to treatment outcome: Criteria 2

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Chart 7:

**Waist and neck circumference distribution**

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<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist Normal</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Waist Increased</td>
<td>72</td>
<td>100</td>
</tr>
<tr>
<td>Neck Normal</td>
<td>64</td>
<td>25</td>
</tr>
<tr>
<td>Neck Increased</td>
<td>36</td>
<td>75</td>
</tr>
</tbody>
</table>

Chart 8:

**Gender**
- * Male
- * Female
Chart 9:

Chart 10:
Chart 11:

**Dento-facial Analysis (Criteria 1)**

![Chart](Image)

Chart 12:

**Dento-facial analysis (Criteria 2)**

![Chart](Image)
Chart 13:

Chart 14:
Chart 15:

Airway Shape (Criteria 1)

![Chart showing percentage of non-responders, partial responders, and responders for non-convex and convex airway shapes.]

Chart 16:

Airway Shape (Criteria 2)

![Chart showing percentage of non-responders and responders for non-convex and convex airway shapes.]

Prediction of the Efficacy of a Mandibular Advancement Splint in the Treatment of Obstructive Sleep Apnea using Various Diagnostic Methods

Anêl Blignaut
12. FUTURE DIRECTIONS

One of the limitations of this study was that the initial and follow-up PSG was not standardized as to the position that the patient slept in. Due to OSA being supine-dependent, different sleeping positions may result in different treatment outcomes.

In this study we found measurements made from baseline CBCT scans not to be useful in the prediction of the efficacy of MAS to treat OSA. Simulation of MAS by means of wax bite blocks made with the use of a George Gauge may be useful in future, as this will place the mandible in a protruded position. This will still only subject the patient to an initial CBCT and if the simulation proves helpful, it will predict the effect that MAS will have on the airway without incurring the costs of actually making one.
13. APPENDICES

13.1 Information for Participants

Investigators:
- Dr Ané Blignaut (Doctoral degree in clinical dentistry candidate)
- Professor Ali Darendeliler (Head of the Department of Orthodontics)
- Professor Peter Cistulli (Professor of Respiratory Medicine at the University of Sydney)
- Dr Andrew Chan (Woolcock Institute of Medical Research & Royal North Shore Hospital)
- Dr Kate Sutherland (Woolcock Institute of Medical Research & Royal North Shore Hospital)

Introduction

You are invited to take part in a research study which aims to develop a mechanism to predict whether or not a person with obstructive sleep apnoea (OSA) will benefit from treatment with an oral appliance based on a variety of structural and functional measurements of the head, neck and airway.

There are several different types of treatment available for OSA. One of these treatments is an oral appliance of which the most common is a mandibular advancement splint (MAS) and is the device used in this study. The MAS consists of dental plates that hold the lower jaw forward during sleep and stops the airway from collapsing. The MAS has been shown to be clinically successful in approximately 75% of patients, and approximately 50% of these have their OSA completely resolved when using a MAS. The aim of this study is to examine whether or not any simple measurements can predict whether or not the MAS will be a successful treatment for any given patient with OSA (phenotyping).

The study is being supported by a research grant from the University of Sydney and an application for additional funding has been submitted to the National Health and Medical Research Council.
Study Procedures

If you agree to participate in this study, you will be asked to sign the Participant Consent Form. You will then be asked to undergo the following procedures:

- a) Dental assessment by the study dentist to assess your dental eligibility for the MAS and to take impressions used to construct the MAS
- b) Phenotyping assessment visit to the Woolcock Institute of Medical Research or Royal North Shore Hospital (see below for more details)
- c) A period to get used to using the MAS (acclimatisation) (4-8 weeks) and a visit to the study dentist to assess your progress
- d) A sleep study whilst using your MAS to assess how well the MAS is treating your OSA

Steps a) and c) described above are the routine clinical practice for patients who use a MAS to treat OSA. Steps b) and d) are additional procedures specific to this research study.

Description of specific procedures:

**Dental assessments:** the MAS consists of custom-made upper and lower acrylic plates which fit over the teeth. You will undergo assessment by a trained dentist who will make sure that your teeth and gums are healthy enough to wear the device. As part of the dental assessment you will have a cone beam computed tomography (CT) scan of your head to assess the health of your teeth (the CT images will also be used to make measurements of your airway and related structures to use for the phenotyping aspect of the study). Moulds of your teeth will be taken in order to construct the appliance. The device takes approximately two weeks to make and once the device has been received by the study dentists from the manufacturer, you will attend a fitting appointment and your MAS will be issued to you. You will then use the MAS each night at home and get used to using it. You will gradually adjust the lower component of the MAS forward over a period of 4-8 weeks until you reach the maximum advancement that is comfortable. You may need to visit the study dentist during this period to have your progress assessed. When you have reached the maximum advancement, you will have one final visit to the study dentist to ensure that you are at your optimal advancement for treatment of your OSA.

**Phenotyping assessments:** Prior to using the MAS, you will be asked to attend one visit of 2-3 hours at either the Woolcock Institute of Medical Research or Royal North Shore Hospital where you will undergo the following procedures:
a) Collection of information regarding your age, sex, ethnicity, medical history
b) Measurement of your height, weight, neck and waist circumferences

c) Examination of your nose and throat by nasendoscopy. This is a routinely performed clinical assessment for patients with OSA. A small dose of anaesthetic nasal spray is applied into your nose and the lubricated endoscope is inserted into the nose whilst you are lying down. The doctor will asked you to perform certain breathing techniques and will also ask you to insert a bite block to hold your lower jaw forward whilst s/he looks at your airway. The images will be recorded as a video file for later measurements by the investigators.

d) Measurement of your lung function using a portable spirometer. You will be asked to breathe into a tube attached to a machine which will measure the flow and volume of air you breathe out during a specific breathing manoeuvre.

e) Nasal Resistance will be measured. You will be asked to breathe through your nose whilst wearing a nose mask connected to a machine which will measure pressure and flow.

f) Photographs of your head (front view and profile) will be taken to make detailed measurements of various structural features of your face, neck and head. You will have a small maker placed on your face for calibration purposes.

The study team will use all this information to produce and test a prediction model to determine whether or not any of the tests or measurements (or a combination) are able to predict whether or not a sleep apnoea patient will respond to MAS treatment (phenotyping).

**Risks**

All medical procedures - whether for diagnosis or treatment, routine or experimental – involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown and unforeseeable. In spite of all precautions, you might develop medical complications from participating in this study although the risk is considered to be minimal.

The risks of participating in this study are:

**Mandibular Advancement Splint:** The MAS is generally well tolerated after an initial acclimatisation phase. It may produce tooth and jaw discomfort, excessive salivation, and a temporary awareness of bite change on waking. The symptoms tend to be minor and transient, dissipating after 2 to 3 weeks of use. Devices which are in contact with the teeth may be associated with movement of teeth, although when this occurs it is usually minor. Temporomandibular joint dysfunction is a rare complication of treatment. The MAS may dislodge during sleep, but the size of the device minimizes the risk of choking.
In summary the risks include:
- Jaw discomfort
- Salivation
- Bite change
- Teeth movement
- Temporomandibular dysfunction
- Choking
- Aspiration

**Nasopharyngoscopy:** (small telescope inserted in the airway) is a routine clinical procedure that is safe and poses minimal risk. It can occasionally cause gagging, bleeding, a choking sensation, or fainting. Mild nasal discomfort is common, but is usually well tolerated. The topical local anaesthetic agent used may rarely cause allergic reactions and heart rhythm disturbances.

In summary the risks include:
- Mild discomfort
- Skin abrasion
- Bleeding
- Spasm of the vocal cords
- Lightheadedness or fainting
- Gagging
- Allergic reaction
- Abnormal heart rhythms

**Exposure to Radiation:** This research study involves exposure to a very small amount of radiation. The cone beam CT used in this study is routinely used for patients who are being assessed for suitability for MAS treatment. The study does not expose to you any additional radiation than you would receive under standard clinical care.

Please inform us if you have participated in any other research studies using radiation in the last five years. Please keep this form in a safe place for the next five years in case you volunteer for any more studies using radiation, when you should show it to the Investigator.

If you suspect you might be pregnant, we will ask you to take a pregnancy test before having the cone beam CT scan. If the pregnancy test is positive, you will not be able to continue your participation in the study and we will inform your sleep physician who will ensure you receive appropriate treatment for your OSA.
Benefits

If the MAS improves your sleep apnoea you may have some benefit from taking part in this study however, if the MAS does not improve your OSA, you may not benefit. Information learned from the study may help other people in the future.

Compensation for injuries or complications

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

In addition, you may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). You do not give up any legal rights to compensation by participating in this study.

Costs

Participation in this study will not cost you anything, nor will you be paid. However, you will be entitled to keep your MAS if it is deemed clinically suitable for your treatment at the end of the study at no cost to yourself.

Voluntary Participation

Participation in this study is entirely voluntary. You do not have to take part in it. If you do take part, you can withdraw at any time without having to give a reason. Whatever your decision, please be assured that it will not affect your medical treatment or your relationship with the staff who are caring for you.

Sometimes during the course of a study, new information becomes available about the treatment that is being studied. While you are participating in this study, you will be kept informed of any significant new findings which may affect your willingness to continue in the study.
Confidentiality

All the information collected from you for the study will be treated confidentially, and only the researchers named above and other study staff will have access to it. The study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such a presentation. All photographic and/or video images collected for this study will be de-identified.

Further Information

When you have read this information, an investigator will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact the following study investigators:

Prof Peter Cistulli – 02 9926 8673
Dr Andrew Chan – 02 9926 8874
Dr Kate Sutherland – 029926 5542
Ms Amanda Greenwood – 02 9926 5542

This information sheet is for you to keep.

Ethics Approval and Complaints

This study has been approved by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health Network. Any person with concerns or complaints about the conduct of this study should contact the Executive Officer on 02 9515 6766 and quote protocol number X11-0134.

The conduct of this study at Royal North Shore Hospital has been authorised by the *Northern Sydney Health Human Research Ethics Committee*. Any person with concerns or complaints about the conduct of this study may also contact the Research Governance Officer on (02) 9926 7947 and quote protocol number *X1106-211M*. 
13. 2 Participant Consent Form

I, .................................................................................................................. [name]
have read and understood the Information for Participants on the above named research study and have discussed the study with Dr ..................................................

I have been made aware of the procedures involved in the study, including any known or expected inconvenience and discomfort. The risks or potential side effects and their implications as far as the researchers currently know them have been explained and include the following:
- Fracture of the teeth and / or fillings
- Development of pain in the Temperomandibular Joint or exacerbation of an existing Temperomandibular Joint Disorder
- Tooth movement of 1-2mm over a time period of approximately 2 year if the MAS is worn full time.

Any of these side effects will have to be seen to by a private dentist as the Sydney Dental Hospital cannot provide these services.

I freely choose to participate in this study and understand that I can withdraw at any time. I also understand that the research study is strictly confidential.

I hereby agree to participate in this research study.

NAME: ................................................................................................................

SIGNATURE: ......................................................................................................

DATE:..................................................................................................................
I, .............................................................................................................................[name]
of .............................................................................................................................[address]
have read and understood the Information for Participants on the above named research study and have discussed the study with ...............................................................[name]

I have been made aware of the procedures involved in the study, including any known or expected inconvenience, risk, discomfort or potential side effect and of their implications as far as they are currently known by the researchers.

I freely choose to participate in this study and understand that I can withdraw at any time.

I also understand that the research study is strictly confidential.

I understand that the photographs taken of me during the study may be used in the publication of the study results, but that such photographs would be digitally modified to protect my identity, and I agree to this. I hereby agree to participate in this research study.

NAME OF PARTICIPANT: .................................................................
SIGNATURE OF PARTICIPANT: .................................................................
DATE: .................................................................................................................................

NAME OF INVESTIGATOR: .................................................................
SIGNATURE OF INVESTIGATOR: .................................................................
DATE: .................................................................................................................................

NAME OF WITNESS: ....................................................................................
SIGNATURE OF WITNESS: ....................................................................................
DATE: .................................................................................................................................
13.3 Mandibular Advancement Splint Instructions and Sleep Diary

These instructions will guide you through the procedure for advancing your dental splint to bring your lower jaw forward.

How to advance the splint

- The splint can be advanced a maximum of 6mm
- Each screw is turned by the key provided
- Both screws should be turned an IDENTICAL number of winds
- 1 wind consist of a single insertion of the key which is used to turn the screw through 90° in the direction of the arrow until it can turn no further
- 1 wind = 0.1mm advancement
- 10 winds = 1mm advancement

Procedure for Self Titration (advancement) of splint

- You should advance the splint by two turns each day on each screw. This amounts to 0.2mm per day
- It is important to carefully document in the diary provided, both the date and the number of turns made to each screw
- If you forget how many winds you have made on each screw then you should
  1. Wind both screws back to the beginning until they provide a small amount of resistance and will not wind any further (DO NOT continue to wind when there is resistance as you may damage the device)
  2. Wind both screws forward an equal number of turns so that the splint is advanced back to the last known point documented in your diary
- It is also important to document whether there has been any noticeable discomfort such as excessive joint pain. It is not unusual to experience minor pain particularly in the early stage of advancement. If you notice any excessive pain that does not resolve within 1-2 nights then you should try not advancing anymore and retaining the current advancement. However, if the pain persists after 2-3 days, then you can wind back by 2 turns (on each side) per day until discomfort subsides.
- If you continue to have pain, please contact staff at Sydney Dental Hospital at (02) 9293 3388/9 to make an emergency appointment to consult an orthodontist.
- When you reach maximum advancement which is either the maximum limit at which you are comfortable with or at 6mm (60 turns) you need to return to Sydney Dental Hospital so that Dr Ané Blignaut can verify that your acclimatization is complete.
**Titratio Diary:** Write 2 on the turns field or -2 if unwinding
Please return / bring this sheet to your final appointment at Sydney Dental Hospital

<table>
<thead>
<tr>
<th>Date</th>
<th>Turns</th>
<th>Details of any Discomfort</th>
</tr>
</thead>
<tbody>
<tr>
<td>28/03/2012</td>
<td>2</td>
<td><em>No problems</em></td>
</tr>
</tbody>
</table>

**Please note:** If you feel that you can comfortably advance your jaw further, beyond the maximum permitted by the screw, please discuss this with your orthodontist at your last visit.
**13.4 MAS Study Completion Letter**

.../..../........

Dear Dentist

Re: __________________________________________________________________________ DOB: / / .

The above patient agreed to participate in a research study which part of my Specialisation (DClinDent) that is entitled “Multimodal Phenotyping to Predict Oral Appliance Treatment Outcome in Obstructive Sleep Apnoea.” The patient was provided with a Mandibular Advancement Splint (MAS) with the objective to treat their Obstructive Sleep Apnoea (OSA).

Their MAS has been titrated to their need. A follow-up sleep study will be organised by their sleep physician. Their sleep physician will advise the patient on the results of the sleep study.

If this device is unsuccessful in managing their OSA, the sleep physician will discuss with the patient other treatment options. **The patient will no longer wear their MAS.**

However, if this device is successful, this mandibular advancement splint will need to be worn nightly to manage the patient’s obstructive sleep apnea until otherwise indicated by their treating sleep physician.

In order to maintain the successful management of their obstructive sleep apnea, with a mandibular advancement splint, the patient will require the following:

1. **Regular 6 monthly checkups and cleans.** It is essential that the health of their periodontium be emphasised and maintained, as the MAS applies significant pressure on the dentition and periodontium.
2. If any minor restorative work is required, the MAS will need to be adjusted by yourself as required. However if any major restorative work is required, the MAS will need to be adjusted by Somnomed and may incur a fee. Please refer the patient back to an orthodontist or to the Sydney Dental Hospital.
3. If there are noticeable dental changes or jaw pains that concern yourself or the patient, please refer the patient to an orthodontist or contact the Sydney Dental Hospital for management of these concerns. I have advised the patient that there will unfortunately be dental side effects as a result of the MAS, but these are variable between patients.

Ané Blignaut
Should you have any questions regarding this letter of request or the patient’s care please contact the Sydney Dental Orthodontic Department reception desk on (02) 9293 3388.

Kind regards,

Dr Anél Blignaut  
Orthodontic Registrar

CC: ..............................
Prediction of the Efficacy of a Mandibular Advancement Splint in the Treatment of Obstructive Sleep Apnea using Various Diagnostic Methods