Jennifer Eriksson
OF 5, Group 13

MANDIBULAR ADVANCEMENT APPLIANCE AS A TREATMENT FOR MILD TO MODERATE OBSTRUCTIVE SLEEP APNEA:
A SYSTEMATIC REVIEW

Master’s Thesis

Supervisor
PhD, Arunas Vasiliauskas

Kaunas, 2017
MANDIBULAR ADVANCEMENT APPLIANCE AS A TREATMENT FOR MILD TO MODERATE OBSTRUCTIVE SLEEP APNEA

Master’s Thesis

The thesis was done

by student ................................................

(signature)

................................................

(name surname, year, group)

........................................ 20....

(day/month)

Supervisor ...........................................

(signature)

................................................

(degree, name surname)

........................................ 20....

(day/month)

Kaunas, 2017
EVALUATION TABLE OF THE MASTER’S THESIS
OF THE TYPE OF SYSTEMIC REVIEW OF SCIENTIFIC LITERATURE

Evaluation: .................................................................................................................................

Reviewer: ........................................................................................................................................

(scientific degree, name and surname)

Reviewing date: .........................................................

<table>
<thead>
<tr>
<th>No.</th>
<th>MT parts</th>
<th>MT evaluation aspects</th>
<th>Compliance with MT requirements and evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>1</td>
<td>Summary (0.5 point)</td>
<td>Is summary informative and in compliance with the thesis content and requirements?</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Are keywords in compliance with the thesis essence?</td>
<td>0.2</td>
</tr>
<tr>
<td>3</td>
<td>Introduction, aim and tasks (1 point)</td>
<td>Are the novelty, relevance and significance of the work justified in the introduction of the thesis?</td>
<td>0.4</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Are the problem, hypothesis, aim and tasks formed clearly and properly?</td>
<td>0.4</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Are the aim and tasks interrelated?</td>
<td>0.2</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Is the protocol of systemic review present?</td>
<td>0.6</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Were the eligibility criteria of articles for the selected protocol determined (e.g., year, language, publication condition, etc.)</td>
<td>0.4</td>
</tr>
<tr>
<td>8</td>
<td>Selection criteria of the studies, search methods and strategy (3.4 points)</td>
<td>Are all the information sources (databases with dates of coverage, contact with study authors to identify additional studies) described and is the last search day indicated?</td>
<td>0.2</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>Is the electronic search strategy described in such a way that it could be repeated (year of search, the last search day; keywords and their combinations; number of found and selected articles according to the combinations of keywords)?</td>
<td>0.4</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>Is the selection process of studies (screening, eligibility, included in systemic review or, if applicable, included in the meta-analysis) described?</td>
<td>0.4</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>Is the data extraction method from the articles (types of investigations, participants, interventions, analysed factors, indexes) described?</td>
<td>0.4</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>Are all the variables (for which data were sought and any assumptions and simplifications made) listed and defined?</td>
<td>0.4</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>Are the methods, which were used to evaluate the risk of bias of individual studies and how this</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>information is to be used in data synthesis, described?</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>15</td>
<td>Were the principal summary measures (risk ratio, difference in means) stated?</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>16</td>
<td>Is the number of studies screened: included upon assessment for eligibility and excluded upon giving the reasons in each stage of exclusion presented?</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>17</td>
<td>Systemization and analysis of data (2.2 points)</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>18</td>
<td>Are the characteristics of studies presented in the included articles, according to which the data were extracted (e.g., study size, follow-up period, type of respondents) presented?</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>19</td>
<td>Are the evaluations of beneficial or harmful outcomes for each study presented? (a) simple summary data for each intervention group; b) effect estimates and confidence intervals)</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>20</td>
<td>Are the extracted and systemized data from studies presented in the tables according to individual tasks?</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>21</td>
<td>Discussion (1.4 points)</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>22</td>
<td>Are the main findings summarized and is their relevance indicated?</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>23</td>
<td>Are the limitations of the performed systemic review discussed?</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>24</td>
<td>Conclusions (0.5 points)</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>25</td>
<td>Does author present the interpretation of the results?</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>26</td>
<td>Are the conclusions based on the analysed material?</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>27</td>
<td>Are the conclusions clear and laconic?</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>28</td>
<td>References (1 point)</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>29</td>
<td>Is the references list formed according to the requirements?</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>30</td>
<td>Are the links of the references to the text correct?</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>31</td>
<td>Are the literature sources cited correctly and precisely?</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>32</td>
<td>Is the scientific level of references suitable for Master’s thesis?</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>33</td>
<td>Do the cited sources not older than 10 years old form at least 70% of sources, and the not older than 5 years – at least 40%?</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Additional sections, which may increase the collected number of points</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Annexes</td>
<td>Do the presented annexes help to understand the analysed topic?</td>
<td>+0.2</td>
</tr>
<tr>
<td>30</td>
<td>Practical recommendations</td>
<td>Are the practical recommendations suggested and are they related to the received results?</td>
<td>+0.4</td>
</tr>
<tr>
<td>31</td>
<td>Were additional methods of data analysis and their results used and described (sensitivity analyses, meta-regression)?</td>
<td>+1</td>
<td>+0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Was meta-analysis applied? Are the selected statistical methods indicated? Are the results of each meta-analysis presented?</td>
<td>+2</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>32</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**General requirements, non-compliance with which reduce the number of points**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Is the thesis volume sufficient (excluding annexes)?</th>
<th>15-20 pages (-2 points)</th>
<th>&lt;15 pages (-5 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td></td>
<td>Is the thesis volume increased artificially? -2 points</td>
<td>-1 point</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td></td>
<td>Does the thesis structure satisfy the requirements of Master’s thesis? -1 point</td>
<td>-2 points</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td></td>
<td>Is the thesis written in correct language, scientifically, logically and laconically? -0.5 point</td>
<td>-1 points</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td>Are there any grammatical, style or computer literacy-related mistakes? -2 points</td>
<td>-1 points</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td></td>
<td>Is text consistent, integral, and are the volumes of its structural parts balanced? -0.2 point</td>
<td>-0.5 points</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td></td>
<td>Amount of plagiarism in the thesis. &gt;20% (not evaluated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td></td>
<td>Is the content (names of sections and sub-sections and enumeration of pages) in compliance with the thesis structure and aims? -0.2 point</td>
<td>-0.5 points</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td>Are the names of the thesis parts in compliance with the text? Are the titles of sections and sub-sections distinguished logically and correctly? -0.2 point</td>
<td>-0.5 points</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td></td>
<td>Are there explanations of the key terms and abbreviations (if needed)? -0.2 point</td>
<td>-0.5 points</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td></td>
<td>Is the quality of the thesis typography (quality of printing, visual aids, binding) good? -0.2 point</td>
<td>-0.5 points</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*In total (maximum 10 points):*

*Remark: the amount of collected points may exceed 10 points.*

Reviewer’s comments:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________
Table of Contents

1. SUMMARY .........................................................................................................................8
   Background ......................................................................................................................8
   Data sources ..................................................................................................................8
   Review method ...............................................................................................................8
   Result ..............................................................................................................................8
   Conclusion ......................................................................................................................8

2. INTRODUCTION ...............................................................................................................9
   AIMS AND OBJECTIVES ................................................................................................11

3. SELECTION CRITERIA OF THE STUDIES. SEARCH METHODS AND STRATEGY ....12
   STUDY ELIGIBILITY ......................................................................................................12
     INCLUSION CRITERIA ..................................................................................................12
     EXCLUSION CRITERIA .................................................................................................12
   LITERATURE SEARCH STRATEGY ...............................................................................12

4. SYSTEMIZATION AND ANALYSIS OF DATA ................................................................13
   DATA EXTRACTION PROCESS ......................................................................................15
   DATA ITEMS ................................................................................................................15
   RISK OF BIAS OF INDIVIDUAL STUDIES ..................................................................15
   SUMMARY MEASURES .................................................................................................16
   STUDY SELECTION .......................................................................................................16
   STUDY CHARACTERISTICS .........................................................................................16
   RESULTS OF INDIVIDUAL STUDIES ..........................................................................17

5. DISCUSSION ....................................................................................................................24

6. CONCLUSIONS ...............................................................................................................27

7. PRACTICAL RECOMMENDATIONS ..............................................................................27

8. REFERENCES ...................................................................................................................27

9. APPENDICES ..................................................................................................................30
TREATMENTS OF OBSTRUCTIVE SLEEP APNEA: A SYSTEMATIC REVIEW

SUMMARY

Background: Obstructive sleep apnea syndrome is a common disorder which is expected to increase in prevalence in correlation with the predicted obesity epidemic. Studies have indicated that if left untreated, it may progress and contribute to more severe morbidities such as growth failure in children, neurologic impairments, pulmonary and systemic hypertension, endothelial dysfunctions, daytime tiredness and concentration difficulties. Oral appliances that advance the mandible forward during sleep have been suggested as an appropriate and non-invasive treatment for mild to moderate obstructive sleep apnea.

The purpose of this systematic review is to research the efficacy of mandibular advancement devices as a treatment for mild to moderate obstructive sleep apnea by assessing the Apnea-hypopnea index values before and after mandibular advancement treatment, and its effect on sleep efficiency. Additionally, predictor factors of treatment success shall also be evaluated.

Data sources: Databases and internet (including MEDLINE/PubMed)

Review method: Searches were performed during January 2016.

Result: Six out of eight studies showed significant decrease of the apnea-hypopnea index. Only two out of eight showed improved sleep efficiency.

Conclusion: Overall, the mandibular advancement device show to be an efficient treatment for mild to moderate obstructive sleep apnea, especially for those with a lower baseline apnea-hypopnea index and after longer periods of usage.

Keywords: Sleep apnea, Obstructive sleep apnea, Mandibular advancement, orthodontic appliance
INTRODUCTION

Over the past decade, there has been a marked increase in the interest of studying sleep quality and sleep disorders, with large numbers of recent studies focusing their research on a sleep disorder deemed to be the most frequent and most relevant—Obstructive sleep apnea (OSA) (1,2).

OSA is characterized by a recurrent complete or incomplete upper airway obstruction which may impede the ability to breathe. OSA occurs during sleep and manifests itself as symptoms such as snoring, daytime tiredness, frequent awakening from sleep, irritability, neurocognitive deficits, depression in adults and behavioral problems in children(1).

The prevalence of OSA is reported to be around 2% for women and 4% for men(3), whilst habitual snoring affects about 3% to 12% of the total world population(4,5). The majority of patients who suffer from sleep apnea are middle aged men, though women and an increasing number of children are also affected by the disease(6). Currently, the prevalence of snoring in children is estimated to be about 0,8% to 24%, with around 1% to 5% suffering from OSA(7).

The etiology of OSA is multifactorial, however it occurs mainly due to a collapse of the upper airway which is a direct result of pharyngeal dilator muscle relaxation, that subsequently causes an upper airway constriction. The three major areas of obstruction include: the nose, palate, and hypopharynx. Additional factors that may contribute this collapse include: soft tissue hypertrophy, obesity, and craniofacial characteristics such as retrognatia. It should be noted that anatomical abnormalities are not always the causative factors of OSA and in fact, in some cases, the etiology is a failure of the central nervous system to signal the pharyngeal dilator muscles to dilate and maintain an open pharynx. The disorder is state related meaning that its manifestation requires sleep to occur. During sleep, there is a reduction of overall neural control and when this occurs in combination with the greater effort required to keep airways open during sleep, OSA may result. Some environmental and genetic factors associated with the syndrome are obesity, increasing age, family history, ethnicity, nasal obstruction, alcohol consumption, smoking, and cranio-facial abnormalities(8).

Despite many possible contributors, OSA remains chiefly an anatomical disorder with all modern treatment options (continuous positive airway pressure, weight loss, oral appliances, and upper airway anatomy) focusing on altering the upper airway anatomy.

OSA usually presents with five or more typical characteristics: apneas, hypopneas, respiratory effort-related arousal, interrupted/paused breathing or snoring, or both. An apnea is defined as a cessation of
airflow for at least 10 seconds whilst a hypopnea is described as a cessation lasting for at least 10 seconds and accompanied with oxyhemoglobin desaturation of 5%, a decreased tidal volume of 50% (3) or an electroencephalogram arousal. The cessation is related with a reduced blood oxygen saturation by 3-4% and may result in an unconscious awakening from sleep and daytime sleepiness. These apneas and hypopneas are counted per hour and will determine the severity of the disease. Currently, an overnight polysomnography (PSG) and apnea-hypopnea index (AHI) are used to diagnose and assess the severity of OSA which may be mild, moderate or severe.

Sufferers of this disorder have a tendency to be unaware of their condition and only acknowledge its existence following observations and comments from people in the sufferer’s life. When left untreated, the patient may come forward with complaints including waking up with a sore throat, morning headaches and a general feeling of fatigue regardless of sleep duration.

Problems linked to long-term untreated OSA include coronary artery disease, arrhythmias, hypertension, stroke, daytime sleepiness, aggressive behavior, attention deficit/hyperactivity disorder, delays in development and a lower IQ(1,7,9,10). A study on early childhood sleep problems predicted behavioral and emotional problems as well as hyperactivity in adulthood if left untreated (7,11).

Currently, the primary treatment option for OSA is a tonsillectomy and/or adenoidectomy, however in some cases, even after this primary treatment, sleep apnea persists. This is likely due to intervention success being largely dependent of any underlying clinical conditions the patient may have. Another common and effective therapy is non-surgical continuous positive air pressure (CPAP). This procedure is most appropriate for adult patients with severe OSA. Despite this treatment showing favorable results, the adherence rate is low and therefore its use in children or uncompliant adults may not a suitable option. The low adherence rate results from the general discomfort it causes and in addition, CPAP carries several possible side-effects such as infection, temporary or permanent numbness in cheeks and chin and malocclusions(12).

Many studies have proven there to be a correlation between sleep apnea and obesity in children, adolescents and adults of all ages. With the increasing obesity epidemic of obesity, the prevalence of OSA is expected to increase(10,13). Investigation into some common features shared amongst non-obese OSA sufferers include: a small retroposed mandible, steep mandibular plane, a narrow posterior airway space, an enlarged tongue, deep soft and hard palate, a inferiorly positioned hyoid bone, uni- or bilateral cross bite and a protruding maxilla(7)

There are two groups of oral appliance treatments available; mandibular advancement devices (MAD), which are attached to the teeth and maintain the mandible in a protruded position, and the tongue retaining device which holds the tongue in an anterior position. MADs have a higher record of adherence rate and
generally more favorable treatment results compared to the tongue retention device(14). Mandibular advancement appliances occur mainly as two distinct types; the monoblock and the two piece appliance(12). Both of these devices are designed to keep the mandible in a protruded and inferior position, consequently widening the pharynx in an anterior-posterior dimension, but even more so in the lateral dimension(15,16). The amount of advancement depends on the anatomy of the individual and it may require a titration procedure, where the advancement would be adjusted over a period of time until a resolution of symptoms is achieved(17).

The Apnea-hypopnea index (AHI) is calculated by dividing the number of apnea events by the hours of sleep. The AHI values are categorized as (for adults):

- Normal: AHI<5
- Mild sleep apnea: 5≤AHI≤15
- Moderate sleep apnea: 15≤AHI<30
- Severe sleep apnea: AHI≥30

For children, an AHI more than 1 is considered abnormal because of their different physiology(18).

AIMS AND OBJECTIVES:

Obstructive sleep apnea (OSA) is the most frequent and important respiratory disorder affecting children and adult during sleep. It can have a big influence on one’s quality of life with effects extending to development of hypertension and/or myocardial infarction and in terms of daytime sleepiness, may even involve the suffer in traffic accidents if left untreated. Treatments with certain orthodontic devices can contribute to the improvement or eradication of these and various other problems. Mandibular advancement devices have the potential to be the primary choice of treatment for adult patients with mild to moderate obstructive sleep apnea.

The objectives of this review are:
- Assessment of apnea-hypopnea index (AHI), before and after mandibular advancement device (MAD) treatment in patients with mild to moderate OSA.
- Assessment of the influence of MAD on the effectiveness of sleep in patients with mild to moderate OSA.
- Assess eventual factors associated with better treatment results.
SELECTION CRITERIA OF THE STUDIES. SEARCH METHODS AND STRATEGY

STUDY ELIGIBILITY

INCLUSION CRITERIA
Following inclusion criteria was applied: (1) adults (<18) with defined presents of mild to moderate OSA based on a polysomnography, (2) mandibular advancement titration appliance as a treatment for OSA, (3) studies conducted on humans, (4) studies available in full-text, (5) Clinical trials, randomized controlled trials, retrospective studies, (6) studies in English language, (7) studies including polysomnographic testing, pre- and posttreatment AH-index recordings.

EXCLUSION CRITERIA
Following exclusion criteria was applied: (1) articles older than 5 years, (2) patients had additional surgical treatment, (3) patients suffering from other untreated oral disease such as periodontal or dental disease, (4) studies that had patients who lost more than 10% of their body weight during the treatment, (5) literature/systematic reviews, debates, (6) studies on animals.

LITERATURE SEARCH STRATEGY
An extensive electronic online search with date and language restriction was performed using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines on PubMed-MEDLINE. Mainly it was PubMed.com that was searched, other databases were searched but findings were either not relevant or duplicates. The search used the MESH key words “obstructive sleep apnea” or “Mild to Moderate obstructive sleep apnea” and “mandibular advancement” or “orthodontic appliance”. It was entered into the data base as: “sleep apnea[MeSH Terms]) OR obstructive sleep apnea[MeSH Terms]) AND mandibular advancement[MeSH Terms]) NOT maxillofacial orthognathic surgery[MeSH Terms]”.
Articles collected from inception of search from November 2016 until January 2017. In addition to the articles retrieved from databases, hand searches in books and journals were performed during the same period of time.

Keywords; Sleep apnoea, Obstructive sleep apnoea, Mandibular advancement, Orthodontic appliance.
Search strategy for databases review, shown in table 1.
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Search strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sleep apnea</td>
</tr>
<tr>
<td>2</td>
<td>Mild to moderate obstructive sleep apnea</td>
</tr>
<tr>
<td>3</td>
<td>Orthodontic appliance</td>
</tr>
<tr>
<td>4</td>
<td>Mandibular advancement</td>
</tr>
<tr>
<td>5</td>
<td>Maxillofacial surgery</td>
</tr>
</tbody>
</table>

(1 OR 2) AND (3 OR 4) NOT 5

(Last search was performed in January 2017)

**SYSTEMORIZATION AND ANALYSIS OF DATA**

The electronic online search is stepwise presented in a flowchart (Figure 1).
The search was conducted on PubMed.com using the advanced search, “sleep apnea[MeSH Terms] OR obstructive sleep apnea[MeSH Terms] AND mandibular advancement[MeSH Terms] NOT maxillofacial orthognathic surgery[MeSH Terms]” was entered and the results gave a total of 717 references. After PubMed filter applied, 142 titles and later abstracts were assessed in a stepwise manner.
to determine if the inclusion and exclusion criteria were achieved. Duplicate records were excluded before the manual review. Relevant studies were selected by the titles in the first step, later the abstract was reviewed as a second step. Finally, the full-text articles were reviewed, the 8 articles with the highest relevance and evidence were retrieved. A hand search of relevant references from primary articles was performed and one other article was identified, evaluated and selected. Other databases were searched but the articles of interested were duplicates. A total of 8 articles were identified and selected as primary articles. The study yields only a small number of studies.

DATA EXTRACTION PROCESS

The primary and hand searched articles was systematically reviewed by one non-blinded independent reviewer by the mentioned inclusion and exclusion criteria. Data regarding mandibular advancement treatment effects on AHI and sleep efficiency of patients with mild to moderate OSA was extracted. In addition, data regarding eventual possible predictors on the treatment outcome was extracted. The outcome data was extracted by one reviewer to validate and control the data. Outcome data was summarized in table 2 in appendix.

DATA ITEMS

Information was extracted from each article: (1) Type of outcome measure (AHI, sleep efficiency, predicting factors), (2) characteristics of patients (age, severity, method of diagnosis), (3) type of innervation (including type of appliance, amount of advancement, duration of use, placebo versus the type). Outcome data was summarized in table 1 in appendix.

RISK OF BIAS OF INDIVIDUAL STUDIES

To assess the validity of the articles the Guidelines for Contributors to American Journal of Occupational Therapy (AJOT)(19) were applied. They were reviewed by one independent author in a non-blinded manner. The author determined the level of bias at outcome level by assessing: randomization and concealment allocating, blinding of patients, health care staff, data collectors, outcome reporters, patient compliance and interference of cross-over studies (shown in table 1, appendices). The effect size of the articles may differ according to the quality of the studies.
SUMMARY MEASURES
Mean AHI reduction and improved sleep efficiency (%) was the primary measure of treatment effect. Quantitative analyses were confined to data extraction prior and post-treatment with MAD.

STUDY SELECTION
Of the 717 records found on the database (www.PubMed.com), 468 was filtered away because they were older than 5 years, studies made on animals, abstract was not available or full-text was not available. The remaining 142 were screened and 104 of them were excluded based on the title and irrelevance to the topic. In the next step abstract was evaluated and included if they had the information required for this study, also research reports, case reports, systematic- and literature reviews were excluded. Thereafter, 25 full-text articles were carefully evaluated for eligibility and out of those a number of 18 was excluded due to lack of PSG data or did met the inclusion criteria in any other way. Other database (www.sciencedirect.com) was searched but only duplicates was found. Reference lists of the primary sources of literature was screened and 2 additional articles was identified. The outcome was 9 primary sources of literature included for the qualitative synthesis. However, after a more thorough review of the primary sources of literature one source of literature was excluded due to it including outcome about severe obstructive sleep apnea which did not fit the inclusion criteria and the final number of studies included is 8. (see flowchart p.10)

STUDY CHARACTERISTICS
Methods: All 8 studies finally selected for the review were various published scientific sources in English. The duration of treatment varied from 3 months to 4 years.
Participants: The included studies involved 288 patients in total. The main inclusion criteria were mild to moderate OSA (5 \leq AHI < 30).
Intervention: Mandibular advancement with orthodontic appliance. Some studies were cross-over studies and included a placebo device.

Outcomes
Primary: In all studies, except for one (Otranto de Britto Teixeira et al), the primary outcome assessed was a statistically significant decrease and improvement in the AHI value from baseline till end of treatment. Secondary and additional outcomes: These included the effect on sleep efficiency after using the MAD, which proved to improve in 4 of the studies, but there was only one where the improvement was statistically significant (Zhou et al.). Two studies didn’t specify the sleep efficiency percentage and the
remaining two studies reported a decrease in sleep efficiency, however only one proved to be statistically significant. Additional outcomes included factors associated with better treatment outcomes. The main factors, mentioned in more than one article, implied that patients with a lower baseline AHI and used the device for a longer period had a better treatment result. Furthermore, the type of device had an influence. An individualized appliance and monoblock device showed to have higher success rate. While morphological characteristics such as septum deviation and nasal alterations showed lower success rate. The timing of outcome measures varied widely and includes monthly to yearly interventions.

**RESULTS OF INDIVIDUAL STUDIES**

(See table 1)

**Ballanti. F et al. (2015)**

Twenty-eight patients were elected based on the following inclusion criteria: able to participate in a 48-month long study, mild to moderate OSA, at least 10 teeth for appliance retention, no removable dentures, BMI lower than 40, no pathologies such as periodontal disease or temporomandibular joint disorders, no upper airway disorders or drug induced respiration/sleep. Participants were analyzed by anamnesis, PSG, Epworth Sleepiness Scale (EES) questionnaire and one clinician to avoid recording errors. Recordings and testing were done prior to treatment, 6 months, and 48 months into the treatment. For this treatment, a non-adjustable one-piece device produced by thermoplastic material (Plastulene) was utilized. Impressions of alginate and bite was recorded the protrusion individually, and the devices were constructed to protrude the mandible 75% of the maximal protrusion potential. The breathing opening and vertical height was individually adjusted.

The mean baseline AHI was 12.3 ± 3.6, after 6 months it had decreased to 9.4 ± 3.5, and after 48 months it increased to 10.4 ± 2.1. The authors calculated that 10% of the patients didn’t show much change with the MAD, 20% worsened from the use and 70% improved their PSG score. According to the patient-answered questionnaires only 60% used the device as recommended, whereas the remaining used it carelessly. Over all, the authors conclude that MAD can induce substantial improvement in long term use for patients with mild to moderate OSA. Success rate on treatment depends on the selection of OSA patients, usage protocol and the type of MAD device chosen. It also greatly depends on the commitment of the patient, sleeping position, BMI and status of periodontal tissues(20).

**Durán Cantolla. J el al. (2015)**
Conducted a randomized, placebo controlled, double blinded, and cross over trial of adult patients suffering from chronic snoring. The criteria for a chronic snorer was mentioned by the author as someone who snores more than 5 days per week confirmed by bedmate/roommate and a home polygraphic test that shows snoring more than 30% of the night. Other inclusion criteria were mild to moderate OSA, a roommate/bedmate that could supply information. If the patient didn’t have someone to report information about their night habits, they were excluded as well as if they had: moderate to severe somnolence, high risk professions, respiratory and/or pulmonary disease, temporomandibular joint problems or were pregnant. After screening there 42 randomized patients, they were then assigned one of two possible sequence treatments using the opaque-sealed envelopes. Forty-two patients initiated the treatment and 38 of them completed it, 2 patients left the study due to intolerance or complications from the device. Mean age of patients was 46 ± 9 years and 79% males. During the whole treatment, the patients stay code identified and the only person who knew the identities was not involved in result recording. The treatment lasted for 18 weeks, initiated by two weeks of wash-out period, then 4 weeks of acclimatization, followed by 12 weeks of appliance use. After this the protocol was repeated but with the other device. The MAD that was used for this study was “The commercial device KlearwayTM” and the mandible was protruded 65% of the total protrusion capacity. The placebo device used was the same type, “KlaerwayTM”, adjusted into centric occlusion and no protrusion. The primary outcome, AHI, was measured with polysomnography (3 Healthdyne system). The secondary outcomes; the total sleep time, sleep fragmentation etc. were calculated from the PSG results. No common characteristic could be found so be related to the treatment results. None of the devices, the MAD or the placebo, did not effected the sleep efficiency, intensity or duration of sleep in a statistically significant manner. The AHI was decreased from 15.3 ± 10.2 to 11.9 ± 15.5, this decrease was not statistically significant (p = 0.196), while the placebo device had a total opposite effect and an increased the AHI statistically significant (p = 0.016). The potential carry-over was measured using the mean AHI after the use of both devices and the results showed absents of significant difference. Out of the patients 87.1% of the MAD users and 76.3% of the placebo device users followed protocol and wore the device for more than 5 hours/night. Protocol indicated 6.4 ± 2.4 for the MAD and 6.2 ± 2.0. The main outcome of this study is that the MAD, in comparison with the placebo device, had a positive effect on all parameters measured. For approximately 50% of the patients, that were treated with the MAD, AHI decreased more than 50%. Another puzzling finding was that some patients had a worsening of the AHI value after using the device. There was increase by 50% of the AHI value in 10.3% of the patients that used the MAD compared to the 31.6% of those who used the placebo device. Subgrouping was not achievable due to the sample size, therefore there could be no factors related to good treatment results. Sleep efficiency was not significantly
affected, baseline values: 87.1 ± 7.8% to 88.8 ± 7.8% after the MAD use and 88.9 ± 7.8% for the placebo device(21).

**Galic. T et al. (2016)**

This prospective study was conducted in Croatia, Split, with the inclusion criteria mild to moderate OSA, 6 to 8 teeth healthy teeth and a capacity to protrude jaw at worst 5 mm. Patients with abnormal teeth, TMJ disorders, periodontal disease, psychological, respiratory or neurological disease history, alcohol or drug abuse were excluded from this study. A total of 18 were enlisted but only 15 completed it. During the first appointment recording of anthropometric characteristics were recorded, an EES questionnaire evaluated daytime sleepiness and patients with > 10 were excluded. All participating patients went through an in-laboratory polysomnography (Alice 5LE or PolyMesam) initiation treatment, after a 3-month period and after a 6-month period. The patients were recorded with the same device after treatment as before by a physician who was blind to the aim of the treatment. A Silensor-sl was used in for this examination, it was custom made and produced individually for each participant. One accomplice dentist treated all patients and the MAS was adjusted to 50% of the maximum protrusion capacity as a start, and then increased by the dentist until maximum comfortable protrusion was achieved. The mean advancement set in the end was 7.0 ± 1.6 mm, which is 68.8% ± 56 % of the maximum achievable protrusion. Protocol requested the patients to use the device as much as possible during the night and record the number of hours it was used. The criteria to be defined as a regular user was at least 4 hours/night, 70% of the week. Date from the 3-month follow-up showed a substantial decrease in the index in comparison to baseline values; from 22.9 ± 5.9 to 11.2 ± 4.9 events/h, and after 1 year it decreased from 22.9 ± 5.9 to 9.7 ± 4.5 events/h. The AHI value decrease by 50% or more in 75% and the AHI value was decreased to 10 or less in 53% of the patients and 5 or less in 27% of the patients. As to the sleep efficiency, 60% enhanced from 78.5 ± 17.3% to 85.9 ± 10.5% after the study was completed. Two of the patients wore the device less than 70% days of the week and less than 4 hour, and where not considered compliant with the protocol. Whereas the rest were regarded as regular users(22).

**Fernando. G et al. (2013)**

Fernando G. J et al. performed a study with the aim to measure the effect of an orthodontic mandibular advancement splints (MAS) on a polysomnography (PSG) and the activity of the M.masseter and M.temporalis on a electromyogram. It was a longitudinal cohort study that followed a group of similar
individuals who differ on certain factors. In a total there was 19 participants, 19-70 years, with mild or moderate OSA who were treated with mandibular advancement device during sleep. Patients with temporomandibular joint dysfunctions, wearing braces or removable prosthesis, periodontal disease, patients with other oral or neurological conditions and obesity (with a body mass index - BMI higher than 35) were excluded from this study. All the patients underwent a electromyogram during day time before the treatment and 6 and 12 months after, as well a PSG before and 3 months after treatment. The first PSG showed increased upper airway resistance syndrome (UARS) in 2 individuals (10.5 %), mild OSAS in 10 (52.6 %), and moderate OSAS in 7 (36.8 %).

As a result, the polysomnography showed a decrease in the AH-index (AHI), from 13.8 to 7.8, which is a significant mean decrease. The patients who initially had a lower AHI presented very high rates of success, which indicated that the lower AHI the higher probability of successful results. However, the electromyogram showed no significant change between the before and after results. The criteria for the patient to be considered cured was an improvement of 50% or more in their AHI results and one of the mentioned criteria: Complete cure, which means what previously mentioned criteria and an AHI of 5 when using the appliance; partial cure, which means the first mentioned criteria and an AHI of 10 when using the appliance.

The conclusion that Fernando et al. that the MRS reduced the AHI for the individuals who reported to have enlarged tongue base, sums up to be a good treatment for mild to moderate OSA patients according to the polysomnography, and it does not interfere with the muscle activity of the M.masseter or M.temporalis muscle according to the electromyogram. Note that the milder OSA the higher success rate. The percent of successful cases according to the author was 52.6%, and compared with other studies where the parameter usually is 50% decrease in AHI compared to pre-treatment AHI values and a final index <10, the study has a success rate of 68.4%. The study showed no improved blood oxygen saturation (BOS) values but it should be noted that the BOS values was at a normal level before the treatment was initiated. Furthermore, they mention correlations between AHI and BMI (P<0.01) or age (P<0.01) pre-treatment, but it did not have an effect on improvement of AHI (P>0.05 for both BMI and age). On the basis of the electromyogram, the device does not interfere with the muscle activity and is safe to use as a treatment. No correlation between success rate and age (P>0.05) or BMI (P>0.05) was proven(2).

Marklund. M et al conducted a randomized, single-blinded, parallel study of a MAD compared to a placebo appliance over a 4-month period on 96 patients. A computer randomized patient allocation, patients and recorders were blinded to which device they were given. The patients were included based on inclusion criteria: Mild to moderate OSA, daytime sleepiness, 20-70 years and a BMI less than 35kg/m2. While patients with tonsil hypertrophy, psychiatric disease, dementia periodontal disease, untreated caries, few teeth for appliance retention, occupational drivers, participants in other studies or bias patients were excluded. The two-part appliance (SR Ivo Elastomer Icoclár Vivadent) have a interconnecting screw which gradually can advance the mandible. Starting from a 4 to 5 mm advancement, the mandible was then advance until symptoms ceased or until patient felt uncomfortable. The mean advancement was 6.8 mm finally. The placebo appliance consisting of a one piece bilaminate splint adheres to the palate by suction.

The study was completed by 91 patients, out of these 45 patients used the active appliance, and 76% reported to use it during the whole night and the rest used it for parts of the night. In this group, there was a mean usage of 86% ± 16% of the night. The other group, of 46 patients, reported a mean use pf 82% ± 16% of the night. Eighty-nine percent used it for the whole night.

The mean AHI at baseline was 15.6 ± 9.8 for the group of the active oral appliance and 15.3 ± 10.5 for the placebo group. At the time of the 4-month check-up the AHI was decreased to 6.7 ± 4.9 for the active oral appliance and which is substantially different from the results of the other group where the AHI value increase to 16.7 ± 10.0 (p < 0.001). In the group using the active appliance 49% had an end AHI value lower than 5, compared to the placebo group in which 11% had an AHI lower than 5. Total sleep and sleep efficiency did not show significant difference when comparing active to placebo appliance results. Compared to the placebo appliance, patient slept more supine with the active device (p<0.001).

Overall, a total of 73% felt that the active appliance fully or partially met their expectations and 89% of all the active appliance users were interested in continuing the treatment. The authors conclude that an individualized, adjustable appliance is an efficient treatment for OSA(23).

**Otranto de Britto Teixeira et al. (2013)**

For this double-blinded prospective cross-over study patients were elected by neurologist specialized in sleep medicine based on the belief that they could be treated by an oral appliance. Inclusion criteria was mild to moderate OSA, and primary snorers, patients with less than 8 teeth, severe periodontal disease, temporomandibular disorders were excluded. In total the study included 19 patients, with a mean age of 48.6 ± 9.6. The appliance used in this study was a twin-block, designed from self-cured acrylic resin, producing a incisal opening of 8 mm and the mandible to protrude 75% of the patients maximum
capacity. The placebo device consisted of an acrylic palate plate with a labial wire creating retention, known as wraparound (WRAP). All patients were both devices but allocation order of device was randomized. Patients in both groups and the doctors were not aware of the placebo device. The PGS was made in two different clinics. The protocol indicated the patients to wear it during sleep, regardless of what hour of the day. Placebo device was worn for a mean of $3.8 \pm 0.8$ months and the active device for a mean of $6.5 \pm 2.0$ months, after which a second PGS recorded the outcome. Subsequently, patients were instructed to not wear any device for a period of a week (wash-out period) to bypass any anomalies in the results. The Mann-Whitney test with a significance level of 5% was performed and the result showed no significant difference between the result of the MAS device and the WRAP. The order of use didn’t influence the results; therefore, the two group could be evaluated together. When evaluating the AHI value the patient was considered improved when there was a decrease in the AHI of 50%, and to be counted as healthy the AHI should be below 5. The active twin block appliance induced a decrease of Ahi from $16.3 \pm 7.2$ to $11.7 \pm 9.4$, which had no substantial difference between the AHI prior and post treatment ($p>0.05$). It also decreased the sleep efficiency $84.4\% \pm 7.9\%$ to $78.6\% \pm 12.8\%$. The WRAP device had the opposite effect in reference to AHI and increased it from $16.3 \pm 7.2$ to $19.6 \pm 14.8$ ($p>0.05$). The outcome of this study was the conclusion that mandibular advancement decreased the mean AHI of patients with mild to moderate OSA. However, it did not improve the sleep efficiency, on the contrary, it produced a worsening in sleep efficiency. Finally, the author state that the outcomes worried widely among the patients and although the twin block can be considered a good treatment option it needs close monitoring due to the individual reactions. No possible predictors was mentioned(24).

Prescinotto. R et al. (2014)

Thirty adult patients with mild to moderate OSA, age 25-65, both sexes were recruited. Patient who had previous surgical or clinical treatment for OSA, an alcohol abuse, drug abuse, sedatives, suffered from periodontal disease or lacked enough dentition to support the device were excluded. All patients in this prospective study were evaluated with a sleepiness questionnaire (Epworth Sleepiness Scale [EES]), PSG (EMBLA™ S7000), anthropometric, skeletal and BMI evaluation initially and at the termination of the 120 days of treatment. A daily questionnaire about the MAS usage was filled by the patients during the whole treatment, this data made it possible so subgroup the patients by good and poor assessment of protocol, and between good and poor treatment outcome. Maximum mandibular advancement was measured and device was adjusted to protrude the mandible 50% of the maximum protrusion, thereafter patients were asked to come and adjust the device in increments, 0.5mm once a week, until maximum comfortable protrusion was identified. The device that was employed was the Brazilian Dental Appliance
(BRD), this device allows lateral movements and a small mouth opening even when mandible is protruded. Of a total 30 patients, 28 of them were included in the study. The mean age of the included patients were 48.8 ± 11.3 years, 32.1% males and 67.9% females. Mean BMI 27.4 ± 3.6kg/m2, mean neck circumference was 38.3 ± 3.3 cm. The result showed a significant difference in the AHI value, it decreased from 17.5 ± 8.8 to 8.8 ± 6.0 events/hour. Out of the 28 patients 60.7% of the them had a good treatment response and counted in the subgroup for good response to the treatment. Comparing the good and poor outcome subgroups, it was found that patients with a lower baseline AHI, smaller neck circumference and younger age had better response to the MAD. Over all, 64.3% of the patients filled the criteria for a successful treatment (a 50% reduction and ≤10 events/h), but the best results were seen in patients with mild OSA where complete resolution of symptoms is easier to achieve. There was only one variable that showed to have significance when comparing the successful group to the unsuccessful and it was age; 44.8 ± 9 vs 56 ± 10 years (p < 0.001). Furthermore, this study found a substantial number of patients with obstructive nasal septal defects (grade II or III) and nasal alterations in the failure group, such high prevalence was not observed for the other variables. The successful group and the unsuccessful group consisted of 18 and 10 patients respectively, the successful group has one patient (5.5%) with grade II/III nasal septum deviation while the other group had 4 (40%) (p 0.04). Number of patients with nasal alterations in the successful group was 7 (38.9%) while the unsuccessful group had 8 (80%) (p 0.04). Both variables were statistically significant. Regarding the sleep efficiency in the two subgroups, neither of the groups indicated a significant increase; baseline value for the successful group was 89.0 ± 5% to 89.3 ± 5%. The unsuccessful group went from a baseline value of 85.0 ± 9% to 82.8 ± 8%(25).

**Zhou J (2012)**

A study comparing two different types of appliances the polysomnography was conducted on 16 patients. They were all diagnosed with mild to moderate OSA, dental and periodontal problems were treated and CPAP treatment had been rejected by patients. The BMI of the patients ranged between 22.3 to 29.8 km m² and their average age was 45.23. The two appliances that were being used for this study was SILENT NITE® and an activator mono-block. Before the construction of the appliances there was a night mandibular titration recording to optimize the distance of mandibular advancement for each individual. The patients used the first appliance for 3 months, followed by a period of two-week wash-out period, and then the other appliance was used for 3 months. Both appliances were claimed to be worn 8 hours per day, every day of the week. After every stage data was collected and evaluated by questionnaires and PSG. Few patients complained about muscles and dental discomfort, 7 in total, but all of the patient finished the treatment as planned. According to the data acquired, the activator was more effective than
the SILENT NITE®, but not to a significant amount. All the patients snored less while they were being treated with MAS (P<0.05). There was not a statistical difference in total sleeping time pre- and post treatment and both appliances showed an improvement on AHI, specially the monoblock appliance (P<0.05). The AHI decreased from 26.38 ± 4.13 to 8.87 ± 2.88 for the SILENT NITE® and 7.58 ± 2.28 by monoblock appliance. Nine of 16 patients (56.3%) using the SILENT NITE® and 11 of 16 patients (68.9%) with the monoblock had an absolute solution (AHI <10 and a AHI reduction of 50%). It was concluded that both appliances were effective in reducing symptoms of OSA, but the monoblock reduced the AHI more effectively and was voted the most preferred one by the patients.(12)

**DISCUSSION**

Overall, the evidence seems to be sufficient enough to determine the MAD as an effective as well as primary treatment for mild to moderate OSA. Data of only a single primary source reported a statistically insignificant improvement (Marklund et al) in OSA following MAD treatment. Similar findings were reported in several non-primary sources of literature utilized in the writing of this review (22,26).

In regards to the effect of this device on sleep efficiency, evidence suggests that the MAD does not have a significant effect, with results of two results indicating that it even led to a decreased sleep efficiency. These results could be explained by poor adherence to the appliance and a need for an acclimatization period. The studies that were of a longer duration showed an increase in sleep efficiency, although not significant(21,22).

Several patient characteristics have been suggested to have an impact on the treatment outcome. The characteristics most frequently mentioned were the baseline AHI and a longer period of use. Patients with a lower baseline AHI in different studies had a much higher success rate and lower resulting AHI values. These characteristics can therefore be used as a predictor of MAD treatment outcome. Copious studies have been made on the prediction of MAD treatment, and the majority of them support the idea and provided additional evidence to a lower baseline AHI being closely related to treatment success(17,25,27–29). Nevertheless, it has been shown that a higher baseline AHI may result in a larger overall decrease of AHI percentage-wise(17). There also exists a general consensus that younger patients, patients with a lower BMI, patients with a smaller neck circumference and female patients have a higher success rate(17,30,31).

Two primary articles indicated that a long-term use had an effect on the treatment outcome(22,24). This was supported by several other studies, which suggests that it takes a longer time for the neurocognitive functions to become altered in unison with MAD compared to CPAP, however the improvements are similar with both devices after a long-term period of use(32). Other authors suggest that trials shorter
than 6.5 months create immediate but short-lived results. After a long period of use the results may last longer due to the muscles stretching and enlarging the airway more permanently meaning that there would be a reduction in upper airway edema(24). Currently, most research has been done over a shorter intervention period. More long-term research is needed to detect the potential improvements and determine the full significance of MAD in OSA patients. An adequate period for acclimatization of around 2-3 months should be allowed, since it is only after this period can the true effects be observed. MAD is therefore not recommended for patients who suffer from severe daytime sleepiness, who are recommended to opt for the CPAP device instead(26). Along with this, it must be noted that this disorder is multifactorial and a single predictor factor does not automatically determine the outcomes.

Furthermore, it has been stressed by various researches that the design of the device is of vital importance. There exists a multitude of designs of adjustment mechanisms and retention types in the market today and clinician has much room for choice. Most studies advocate the adjustable individualized designs(20,23,33), rather than the off-shelf pre-fabricated ones(26). The ability to adjust the device is important in order to be able to find the individuals most beneficial degree of advancement. Maximized mandibular advancement it not always the most optimal and might cause more discomfort than relief. There is a non-linear phenomenon the requires titration to find the ideal advancement for the individual patient(26). Movable devices are favorable for the patients comfort since it gives some mandibular freedom, the patients do not have to feel like their mouth is locked and it gives a low degree of mandibular joint movement considering that advancement of the mandible itself can create substantial discomfort(24). The vertical opening should also be considered, a wide opening has shown to have a reverse effect on the upper airway(17) and reported to be less comfortable for patients, although it does not affect the AHI results(26). More studies must be carried out to determine which type of device is the most useful and for which kinds of patients. So far, most researchers dismiss the older immovable designs and promote the newer adjustable ones. Nevertheless, there are many new designs to choose from. Several studies have shown that a monoblock device achieved better results in terms of lowered AHI and increased patient satisfaction when compared to the twinblock device(1,9,33). Though both appliances were able to improve the AHI, patient compliance was often better for the twinblock device rather than monoblock(1). K. Sutherland et al. found that a twin block increased comfort and compliance as it allowed for some mandibular movement, whilst the monoblock device was cheaper and easier to manufacture. The comparisons between the two devices made in this study found no differences in terms of AHI reduction or sleep efficiency. Patients in this study however preferred the mono block appliance(34).
A recent cohort study by Dort L et al found that combining mandibular advancement with tongue protrusion reduces AHI greater than advancement of mandible alone(35). Many studies have also shown the importance of the positioning and the musculature of the hyoid bone in the regulation of the pharyngeal airway and the use of an orthodontic appliance can improve this by increasing the distance between the mandibular plane and the hyoid bone(27,30,33,36).

It is difficult to determine the best choice of appliance because the criteria of success differs between studies and the reported compliance often varies according to type of MAD, the specific definition of compliance, the duration of usage and the patient’s morphology(1).

Modern research indicates that MAD can be useful for some patients with severe as well as mild to moderate sleep apnea(36). A recent study that compared CPAP and oral appliances indicated that they have the same effect on the mild form of the disease, whilst CPAP is superior in more severe cases(37). MAD showed a higher compliance rate with a median use of 77% of the nights per year, which was significantly higher than the compliance rate of CPAP(16). Phillips CL et al confirmed in their study that CPAP self-reporting has been overestimated compared to objective monitoring(32). Since the outcomes of CPAP are partially based on self-reporting and most studies are conducted on the effect of CPAP compared to MAD, the reliability may be questionable. Sutherland K et al summarized a wide number of studies and concluded that the health outcomes were equal between CPAP and MAD, even in severe OSA. Although CPAP has a greater immediate reduction of AHI, an oral appliance showed higher compliance and percentage of usage during the nights(34).

In the authors opinion, the results suggest that MAD could be considered as a primary choice of therapy for patients with mild to moderate OSA showing a possibly bad adherence to the CPAP device in the future. With strict monitoring and a well-developed protocol, mandibular advancement devices can be continually optimized and achieve good treatment results. Compared to the CPAP device or a surgical intervention an orthodontic appliance is less invasive and easy manufactured. As OSA is growing to become a global health issue it’s important to find a cost-efficient treatment than can be available in great extent. From this perspective, a MAD is to be preferred over other treatments.

This systematic literature review was written with several existing limitations. This includes a limited number of primary sources of literature. In general, much of the available literature was deemed unsuitable due to them not containing all the required measurements. A meta-analyses was not attempted due to the heterogeneity of indices, differences in methodology and cut-off values. There also exists a lack of consensus around the definition of a successful treatment.
CONCLUSIONS

The majority of scientific literature used in the writing of this systematic review suggests that a mandibular advancement device leads to a significant improvement in the apnea-hypopnea index value. Sleep efficiency was not improved and factors such as apnea-hypopnea index baseline, period of usage and type of device show to have an influence on the success rate of the treatment.

An oral appliance that is individualized, adjustable and movable can effectively reduce apnea-hypopnea values and occurrences of snoring. More studies should be conducted in order to assert which type of device is maximally tolerated and is accompanied by the lowest rates of secondary effects.

PRACTICAL RECOMMENDATIONS

1. A sleep therapist and a dentist should consult to prescribe an oral appliance for adult patients who primary complaint is snoring.
2. The oral appliance should be an individualized, adjustable appliance.
3. A oral appliance should be prescribed to patients who are intolerant to CPAP treatment, rather than no treatment.
4. A sleep physician should closely monitor and follow-up the treatment to improve or adjust the device.

REFERENCES


35. Dort L, Remmers J. A Combination Appliance for Obstructive Sleep Apnea: The Effectiveness of Mandibular Advancement and Tongue Retention. 2012;8(3).

36. Shen H, Wen Y, Chen N, Liao Y. Craniofacial morphologic predictors of oral appliance


APPENDICES

Table 1 summarizes the evidences collected in the sources of literature.

<p>| Table 1 [Table of evidence] | | | | |
|---|---|---|---|
| <strong>Author/Year</strong> | <strong>Level of evidence/Study design/Participants/Inclusion criteria</strong> | <strong>Intervention and Control groups</strong> | <strong>Outcome Measures (AHI - events/h, mean)</strong> | <strong>Results</strong> |
| <strong>Ballanti. F et al. (2015)</strong> | Level III Clinical study n = 38 22 male, 6 female Mean age: 52.2 ± 6.8 Incl: MAS for at least 48 months, OSA; 5 ≤ AHI &lt; 30, at least 10 teeth, no dentures or oral diseases, BMI &lt;40, no upper airway abnormalities, no medication that could influence. | Intervention: Patients used the MAS device during 48 months. Control: PSG | AHI: Baseline: 12.3 ± 3.6 After 6 months: 9.4 ± 3.5 After 48 months: 10.4 ± 2.1 | Statistically significant improvement over long-term (48 months). Influential factors; election of patients, appropriate therapeutic protocol, the device should be individual, non adjustable. Position during sleep and other systemic disease. |
| <strong>Durán Cantolla. J et al. (2015)</strong> | Level I RCT, Cross-over trial n = 42 [adults] 78% males, 22% female Mean age: 46.5 ± 9.3 | Intervention: Randomly assigned to receive two possible sequences of treatment (MAS) or placebo device (PD). 4 w of adaptation &amp; 12 w of treatment. 2 w wash-out period. Control: Overnight PSG | KlearwayTM 75% protrusion of mandible | AHI Baseline: 15.3 ± 10.2 MAD: 11.9 ± 15.5 PD: 25.9 ± 26.0 | Baseline: 87.1 ± 7.8% Follow-up: 88.8 ± 7.8% MAD intervention not statistically significant. Sample size did not allow subgrouping to identify factors associated with good treatment results Sleep efficiency improvement not significant. |</p>
<table>
<thead>
<tr>
<th>Study Description</th>
<th>Intervention</th>
<th>Control</th>
<th>AHI: Baseline</th>
<th>Follow-up (1 yr)</th>
<th>AHI was improved significantly.</th>
<th>The mean AHI improved significantly.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Galic. T et al. (2016)</strong></td>
<td><strong>Intervention:</strong> 1 yr and 3 month follow up occasions.</td>
<td><strong>Control:</strong> PSG</td>
<td>AHI: Baseline: 22.9 ± 5.9 3 months: 22.9 ± 5.9 to 11.2 ± 4.9 (p &lt; 0.05) 1 year: 22.9 ± 5.9 to 9.7 ± 4.5 (p&lt;0.001)</td>
<td>Baseline: 78.5 ± 17.3 %</td>
<td>Follow-up (1 yr): 85.9 ± 10.5% (p = 0.437).</td>
<td>Sleep efficiency improvement not significant.</td>
</tr>
<tr>
<td><strong>Fernando. G et al. (2013)</strong></td>
<td><strong>Intervention:</strong> Patient wore device during sleep for 3 months.</td>
<td><strong>Control:</strong> Overnight PSG</td>
<td>AHI: Baseline: 13.8 ± 6.6 3 month follow-up: 7.8 ± 6.9 (P &lt; 0.05)</td>
<td>-</td>
<td>Significant improvement in AHI.</td>
<td>Patients with lower AHI baseline showed greater success rate.</td>
</tr>
<tr>
<td><strong>Marklund. M et al (2015)</strong></td>
<td><strong>Intervention:</strong> An oral appliance vs an intraoral placebo device. 4 month intervention.</td>
<td><strong>Control:</strong> Overnight PSG</td>
<td>AHI: Baseline 15.6 ± 9.8 4 month follow-up: 6.7 ± 4.9</td>
<td>Baseline: 90.7 ± 8.1% 4 month follow-up: 90.8 ± 9.3%</td>
<td>Total sleep time, sleep efficiency, and sleep stages did not differ between the groups (P &lt; .001)</td>
<td>AHI was improved significantly. Sleep efficiency did not improve significantly.</td>
</tr>
<tr>
<td>Table 1 [Table of evidence]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Otranto de Britto Teixeira et al. (2013)</strong></td>
<td><strong>Intervention:</strong> Cross-over study, with one week wash out period. MAS follow-up after a mean period of 6.5 month. Placebo group follow-up after a mean of 3.8 months. <strong>Control:</strong> Overnight PSG</td>
<td><strong>AHI:</strong> Baseline: 16.3 ± 7.2 Follow-up: 11.7 ± 9.4 (P&gt;0.05) <strong>Placebo follow-up:</strong> 19.6 ± 14.8 <strong>Influencing factors of treatment results:</strong> Long-term use, likely to induce airway enlargement and reduction of upper airway edema. <strong>Cross-over study:</strong> Significance level of 5%</td>
<td><strong>Sleep efficiency</strong> to drop from 84.4 ± 7.9% to 78.6 ± 12.8% Placebo: Sleep efficiency was reduced from 84.4 ± 7.9% to 78.5 ± 10.9% No significant difference in AHI values. Sleep efficiency was decreased with the twin block. Long term use give better results.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>Twin-block. Mandibular advancement device was modified.</td>
<td><strong>Sleep efficiency</strong> to drop from 84.4 ± 7.9% to 78.6 ± 12.8% Placebo: Sleep efficiency was reduced from 84.4 ± 7.9% to 78.5 ± 10.9% No significant difference in AHI values. Sleep efficiency was decreased with the twin block. Long term use give better results.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective controlled longitudinal study. Double-blind, cross-over study</td>
<td><strong>Incl:</strong> OSA; 5 ≤ AHI &lt; 30</td>
<td><strong>Sleep efficiency</strong> to drop from 84.4 ± 7.9% to 78.6 ± 12.8% Placebo: Sleep efficiency was reduced from 84.4 ± 7.9% to 78.5 ± 10.9% No significant difference in AHI values. Sleep efficiency was decreased with the twin block. Long term use give better results.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 19 42.1% male, 57.9% female Mean age: 48.6 ± 9.6 yrs</td>
<td><strong>Intervention:</strong> Cross-over study, with one week wash out period. MAS follow-up after a mean period of 6.5 month. Placebo group follow-up after a mean of 3.8 months. <strong>Control:</strong> Overnight PSG</td>
<td><strong>Sleep efficiency</strong> to drop from 84.4 ± 7.9% to 78.6 ± 12.8% Placebo: Sleep efficiency was reduced from 84.4 ± 7.9% to 78.5 ± 10.9% No significant difference in AHI values. Sleep efficiency was decreased with the twin block. Long term use give better results.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prescinotto, R et al. (2014)</strong></td>
<td><strong>Intervention:</strong> 120 days of MAS use. <strong>Control:</strong> overnight PSG</td>
<td><strong>AHI:</strong> Baseline: 17.5 ± 8.8 to 8.8 ± 6.0 <strong>Influencing factors of treatment results:</strong> Septal deviation degree II/III (5.5% of successful patients vs 40% of unsuccessfully treated patients) and septal deviation degree II/III Nasal alterations (38.9% vs 80%)</td>
<td>Successful group: Baseline: 89.0 ± 5% Follow-up: 89.3 ± 5% Unsuccessful group: Baseline: 85.0 ± 9% Follow-up: 82.8 ± 8% Significant improvement of AHI. Sleep efficiency decrease, not statistically significant. Patients with nasal alterations and septum deviations have lower success rate. Patients will lower baseline AHI showed higher success rate.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level I</td>
<td>Brazilian Dental Appliance</td>
<td><strong>Sleep efficiency</strong> to drop from 84.4 ± 7.9% to 78.6 ± 12.8% Placebo: Sleep efficiency was reduced from 84.4 ± 7.9% to 78.5 ± 10.9% No significant difference in AHI values. Sleep efficiency was decreased with the twin block. Long term use give better results.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective study</td>
<td><strong>Incl:</strong> 25-65 years, both genders, OSA; 5 ≤ AHI &lt; 30.</td>
<td><strong>Sleep efficiency</strong> to drop from 84.4 ± 7.9% to 78.6 ± 12.8% Placebo: Sleep efficiency was reduced from 84.4 ± 7.9% to 78.5 ± 10.9% No significant difference in AHI values. Sleep efficiency was decreased with the twin block. Long term use give better results.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 28 [adults] 32.1% Males, 67.9% female Mean age: 47.9 ± 10</td>
<td><strong>Intervention:</strong> 120 days of MAS use. <strong>Control:</strong> overnight PSG</td>
<td><strong>Sleep efficiency</strong> to drop from 84.4 ± 7.9% to 78.6 ± 12.8% Placebo: Sleep efficiency was reduced from 84.4 ± 7.9% to 78.5 ± 10.9% No significant difference in AHI values. Sleep efficiency was decreased with the twin block. Long term use give better results.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1 [Table of evidence]

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Intervention:</th>
<th>Monoblock and SILENT NITE®</th>
<th>AHI: Baseline:</th>
<th>Monoblock:</th>
<th>SILENT NITE®:</th>
<th>Baseline:</th>
<th>Both appliances showed significant improvement in AHI values.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou. J et al. (2012)</td>
<td>Patients divided into two groups. 3 months one appliance, two week wash-out period followed by 3 months using the other appliance.</td>
<td></td>
<td>6.58 ± 2.28</td>
<td>6.58 ± 2.28</td>
<td>9.87 ± 2.88</td>
<td>80.68 ± 12.47</td>
<td></td>
</tr>
<tr>
<td>Incl: OSA; 5 ≤ AHI &lt; 30, total count of 20 teeth, all premolars and molars preserved.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Monoblock appliance had a significant improvement to the mean sleep efficiency.</td>
</tr>
</tbody>
</table>

Table 2, Table of bias.

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Selection bias</th>
<th>Performance bias</th>
<th>Detection bias</th>
<th>Attrition bias</th>
<th>Reporting bias</th>
<th>Cross-over study bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durán Cantolla. J et al. (2015)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Galic. T et al. (2016)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fernando. G et al. (2013)</td>
<td>?</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Otranto de Britto Teixeira et al. (2013)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Prescinotto. R et al. (2014)</td>
<td>?</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Zhou. J et al. (2012)</td>
<td>+</td>
<td>?</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

ABBREVIATIONS
AHI – apnea-hypopnea index
CPAP – continuous positive air pressure
MAD – mandibular advancement device
OSA – obstructive sleep apnea
PSG – polysomnography

GUIDELINES
For this systematic review, the *Handbook for Systematic Reviews of Interventions* Version by Higgins JPT, were used. Available from http://handbook.cochrane.org.