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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

The effectiveness of different mandibular advancement amounts in OSA patients: a systematic review and meta-regression analysis

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Abstract
Purpose The therapy with mandibular advancement devices (MADs) represents a treatment option for patients with obstructive sleep apnea (OSA). The literature does not provide evidence regarding the most effective mandibular advancement; therefore, the aim of this systematic review with meta-regression was to investigate the effectiveness of different mandibular advancement amounts in reducing apnea-hypopnea index (AHI) in OSA patients.
Methods An electronic search was performed in MEDLINE, Cochrane Database, Google Scholar Beta, ISI Web of Knowledge, Scopus, and LILACS to select randomized controlled trials (RCTs) investigating the efficacy of MADs in reducing AHI in adult OSA patients. Inclusion criteria were the diagnosis of OSA and success evaluation performed with a polysomnography, follow-up of maximum 12 months, and protrusion amount reported as a percentage of the maximum mandibular advancement. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The success rate of each study was computed: [(mean AHI at baseline-mean AHI after treatment)/mean AHI at baseline].
Results Thirteen RCTs performing advancements from 50 to 89 % of maximum mandibular protrusion were included. The meta-regression analysis showed that advancement amounts higher than 50 % do not significantly influence the success rate ($Q = 0.373$, $p = 0.541$). According to the GRADE score system, the quality of evidence resulted to be moderate.
Conclusion The AHI improvement resulted to be not proportional to the mandibular advancement increase. It is plausible that the success of the therapy is influenced by a combination of variables that need closer study.

Keywords Obstructive sleep apnea · Mandibular advancement device · Sleep disorders · Sleep disordered breathing · Temporomandibular disorders

Introduction

Obstructive sleep apnea (OSA) syndrome is a common sleep-related breathing disorder affecting 2–4 % of middle-aged men and women [1–3]. It is characterized by the repetitive obstruction of the upper airway during sleep, which determines snoring, sleep fragmentation and is associated to systemic hypertension, metabolic syndrome, heart failure, neurocognitive impairment [4, 5] and with a significant increased risk of mortality [6, 7].

Forward repositioning of the mandible increases the upper airway volume, widens the lateral dimension of the velopharynx, it stretches tongue muscles counteracting tongue's retrolapse during sleep, and it moves the hyoid bone anteriorly and stabilizes epiglottis and soft palate preventing the posterior rotation of the jaw [8–10]. The therapy with a mandibular advancement device (MAD) represents a treatment option to obtain this anterior jaw repositioning; it is indicated in patients affected by mild to moderate OSA and in the ones with severe OSA who refuse continuous positive airway pressure (CPAP) treatment or surgery [2, 11–14]. The MAD therapy generally improves the Apnea Hypopnea Index

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(AHI) [2], the sleep quality, and also the work performances [8, 12].

Despite many studies investigated the efficacy of the MAD therapy, no consistent data are provided about the most effective mandibular protrusion amount: some authors suggest a mild advancement [15, 16], others prefer a high protrusion [17–19], and while others perform a progressive advancement in order to avoid the masticatory side effects that the MAD therapy brings about [15, 20].

Since a common advancement protocol is lacking [10], the aim of the present systematic review with meta-regression analysis is to investigate which is the effectiveness of different mandibular protrusion amounts in reducing AHI in OSA patients.

Material and methods

The present systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) system [21].

To identify the studies to be considered for inclusion, detailed search strategies were developed for the following electronic databases: MEDLINE, Cochrane Database of Systematic Reviews, Google Scholar Beta, ISI Web of Knowledge, Scopus, and LILACS. Also gray literature was searched in order to find unpublished data. Manual search of selected studies by looking at their references was conducted as well.

Studies from 1 January 1990 to 30 April 2015 were analyzed, without language restrictions.

The search strategy used for MEDLINE including the MeSH and text words was (((Sleep Apnea, Obstructive [Mesh]) OR (Sleep Apnea) OR (Sleep Apnoea)) OR (Sleep breathing disorder OR sleep respiratory disorder))) AND ((Mandibular Advancement Device) OR (Mandibular advancement appliance)).

Only randomized controlled trials (RCTs) that investigated the relationship between the MAD protrusion amount and the improvement of the AHI were included in the present review. Other inclusion criteria were the diagnosis of OSA performed with a polysomnography (PSG) (AHI≥5) same as the evaluation of the success of the therapy, adult patients (>18 years), follow-up of maximum 12 months to limit the variation of the BMI which could affect AHI's results, and protrusion amount reported as a percentage value of the maximum mandibular protrusion.

Two researchers independently selected the articles (M.L.B. and E.R.). Intra-examiner conflicts were resolved by the discussion of each article to reach a consensus.

Data items and collection

The following data items were collected from each study included: study design, sample size, mean age, mean BMI, MADs' protrusion amount, AHI at baseline, AHI after therapy, follow-up, and authors' main conclusions.

Risk of bias in individual studies and across the studies

To document the methodological soundness of each article, the Quality Assessment Tool for Quantitative Studies by Effective Public Health Practice Project (EPHPP) [22] was used. To evaluate the risk of bias in individual studies, the Cochrane Collaboration's tool for assessing risk of bias in randomized trials was used [23]. To evaluate the quality of body of evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) was performed [24].

Two assessors (F.B. and G.A.B.) independently performed the quality evaluations; when in disagreement, a conjunct evaluation was performed to reach a consensus.

The risk of bias across the studies was evaluated by means of Egger's test and Funnel plot; no information about reporting bias is presented because our evaluations are not based on raw data of individual studies.

Statistical tests of heterogeneity were carried out to assess whether the observed variability in study results (effect sizes) was greater than that expected to occur by chance. The heterogeneity among studies was assessed using a χ^2-based Q statistic test and I^2 index; however, because of the moderate insensitivity of the Q statistic, only an I^2 index greater than 50 % was considered associated with a substantial heterogeneity among the studies. The tau^2 was also calculated for the heterogeneity assessment.

Definition for success rate

Success rate for each protrusion amount was calculated as [(mean AHI at baseline - mean AHI after treatment)/mean

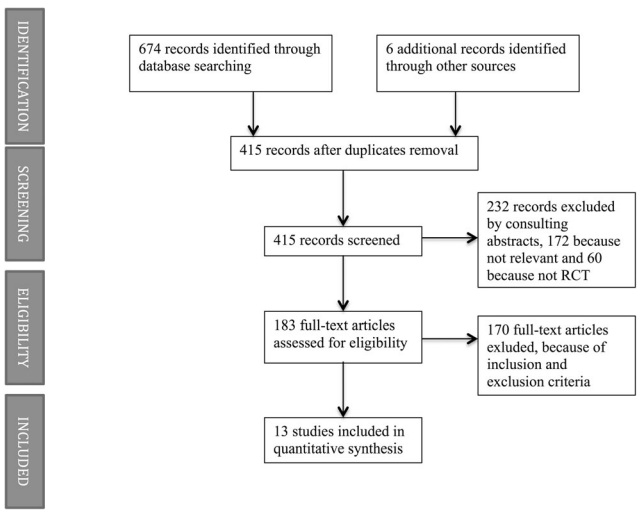

Fig. 1 Flow diagram of the search strategy (PRISMA)

Table 1 Description of the studies included in the systematic review

Study	Study design	Control	Sample size	Age (Mean ± SD)	BMI (Mean ± SD)	Protrusion amount	AHI baseline (Mean ± SD)	AHI after therapy (Mean ± SD)	Follow-up	Authors' main conclusion
Bloch 2000 [28]	RCT crossover	Different type of MAD	24	50.5 ± 1.5	27.4 ± 0.6	75 %	22.6 ± 3.1 22.6 ± 3.1	7.9 ± 1.6 8.7 ± 1.5	156 ± 14 days	Both the Herbst and the monobloc are effective
Walker-Engstrom 2002 [26]	RCT	UPPP	95 (37 with MAD)	>20 and <65	25.9	50 %	17.9 ± 2.9	4.5 ± 2.6	1 year	Higher success with MAD
Tan 2002 [29]	RCT crossover	nCPAP	23	50.9 ± 10.1	31.9 ± 6.8	75 %	22.2 ± 9.6	8.0 ± 10.9	2 months	No difference in efficacy
Johnston 2002 [30]	RCT crossover	Placebo	20	55.1 ± 6.9	31.6 ± 5.9	75 %	31.9 ± 3.9	22.9 ± 22.8	4–6 weeks	MAD is more effective
Tegelberg 2003 [16]	RCT	MAD different protrusion amount	29 26	51.8 (CI = 49.0–54.6) 54.4 (CI = 52.4–56.4)	27.4 (CI = 26.4–28.4) 27.9 (CI = 26.6–29.3)	50 % 75 %	16.2 ± 2.9 18.9 ± 4.7	6.0 ± 3.7 6.3 ± 2.0	1 year	No difference in efficacy
Walker-Engstrom 2003 [17]	RCT	MAD different protrusion amount	37 40	50.4 54.3	30.5 ± 1.4	50 % 75 %	47.0 ± 5.1 50.4 ± 4.7	17.4 ± 5.7 15.6 ± 6.2	6 months	No difference in efficacy
Blanco 2005 [31]	RCT	Placebo	28 (8 with MAD)	55.6 ± 11.8	27.9 ± 4.3	75 %	33.8 ± 14.7	9.6 ± 12.1	3 months	No difference in efficacy
Hoekema 2007 [34]	RCT	CPAP	19 (9 with MAD)	47.6 ± 11.0	32.3 ± 6.6	89 % ± 23 %	43.2 ± 24.3	2.5 ± 6.7	81 days	No difference in efficacy
Petri 2008 [27]	RCT	Placebo and no treatment	27	50.0 ± 11.0	30.7 ± 5.2	74 %	39.1 ± 23.8	25.0 ± 27.5	1 month	MAD is more effective
Ghazal 2009 [33]	RCT	Different types of MAD	47 48	55.5 ± 10.6	25.9 ± 2.9	83 %	21.5 ± 13.5 21.5 ± 16.9	11.1 ± 11.8 6.7 ± 9.1	6 months	No difference in efficacy
Deane 2009 [32]	RCT crossover	TSD	22	49.4 ± 11.0	29.3 ± 5.6	75 %	27.0 ± 17.2	11.7 ± 8.9	4 weeks	No difference in efficacy
Campbell 2009 [20]	RCT	Subjective titration	12	49.8 ± 12.6	27.1 ± 3.9	70 %	26.5 ± 12.0	15.3 ± 13.5	3 weeks	No difference in efficacy
Aarab 2010 [15]	RCT crossover	MAD different protrusion amount	17	49.2 ± 8.5	27.7 ± 3.4	25 % 50 % 75 %	21.6 ± 11.1 21.6 ± 11.1 21.6 ± 11.1	10.7 ± 7.4 7.5 ± 6.0 5.8 ± 6.0	1 year	75 % is more effective but with more side effects

nCPAP non-continuous positive airway pressure, *CPAP* continuous positive airway pressure, *UPPP* uvulopalatopharingoplasty, *TSD* tongue stabilizing device

AHI at baseline], that is, the mean percentage of improving where 1 represents total healing.

Methodology of synthesis of the results of the individual studies

A fixed effect model was used if homogeneity was proved ($p > 0.10$); if homogeneity was rejected ($p < 0.10$), a random effects model was used to better aggregate the data [25].

Success rate and 95 % confidence interval (CI) of each treated group within the studies were computed; regarding the studies comparing the efficacy of different MADs at the same advancement amount, the success rate was computed for each group. In order to evaluate the effect of the advancement amount on success rate, a meta-regression analysis was performed. Calculations were carried out by means of Comprehensive Meta-Analysis software (Biostat Inc, Englewood, NJ).

Results

From the 674 articles initially retrieved, 13 studies were included for the qualitative analysis. Figure 1 reports the selection process and Table 1 describes the studies included. Among these, one trial compared the effectiveness of 25, 50, and 75 % of maximum mandibular protrusion [15] and two studies compared the efficacy of 50 and 75 % [16, 17]; nine studies performed only one advancement amount (50 [26], 70 [20], 74 [27], 75 [28–32], 83 [33], or 89 % [34]) in comparison with other therapies or no treatment. Two studies [28, 33] compared the two groups at the same protrusion amount wearing different devices: the analysis computed those groups separately.

Condition recordings and study treatments

Treatments were performed with different types of MAD. Some studies fully described the appliance and the way it produced mandibular protrusion [16, 17, 27, 29–31, 33, 34].

Few studies reported the assessment of the protrusion amount: with a steel ruler [16] or with a bite fork (George Gauge System [20, 27, 31, 34] or Projet bite forks [30]).

Ten papers described the type of PSG and the way it was performed [16, 17, 20, 26–29, 31, 33, 34]. Few authors reported the total sleep time of the registration night [28, 32].

Quality analysis and risk of bias in individual studies

The results of the EPHPP quality analysis are shown in Table 2. Selection bias was weak in two studies [28, 31] because the authors did not report the way the participants were enrolled in the study. Confounders (age, gender, BMI, neck circumference, smoke, alcohol consumption, and AHI at baseline) were not controlled in four studies [16, 26, 31, 34].

In only one study, both assessors and participants were blinded [27], in six studies assessors or participants were blinded [15–17, 26, 30, 32], and six studies did not use blinding for measurements [20, 28, 29, 31, 33, 34]. Regarding withdrawals, one study [26] gained a moderate score because the rate of patients that completed the follow-up was of only 60–79 %.

The risk of bias analysis resulted low or unclear for all studies (Table 3). The main shortcomings are that allocation concealment and sequence generation are not described in most of the studies.

Table 2 Quality evaluation in individual studies (EPHPP)

Article	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and drop-outs	Global ratings
Bloch 2000 [28]	Weak	Strong	Strong	Weak	Strong	Strong	Weak
Walker-Engstrom 2002 [26]	Moderate	Strong	Weak	Moderate	Strong	Moderate	Moderate
Tan 2002 [29]	Moderate	Strong	Strong	Weak	Strong	Strong	Moderate
Johnston 2002 [30]	Moderate	Strong	Strong	Moderate	Strong	Strong	Strong
Tegelberg 2003 [16]	Moderate	Strong	Weak	Moderate	Strong	Strong	Moderate
Walker-Engstrom 2003 [17]	Moderate	Strong	Strong	Moderate	Strong	Strong	Strong
Blanco 2005 [31]	Weak	Strong	Weak	Weak	Strong	Strong	Weak
Hoekema 2007 [34]	Moderate	Strong	Weak	Weak	Strong	Strong	Weak
Petri 2008 [27]	Moderate	Strong	Strong	Strong	Strong	Strong	Strong
Ghazal 2009 [33]	Moderate	Strong	Moderate	Weak	Strong	Strong	Moderate
Deane 2009 [32]	Moderate	Strong	Strong	Moderate	Strong	Strong	Strong
Campbell 2009 [20]	Moderate	Strong	Moderate	Weak	Strong	Strong	Moderate
Aarab 2010 [15]	Moderate	Strong	Strong	Moderate	Strong	Strong	Strong

Table 3 Risk of bias in individual studies (Cochrane Collaboration's tool)

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Selective outcome reporting
Bloch 2000 [28]	Unclear	Unclear	High risk (no blinding)	Low risk (no drop-out)	Low risk
Walker-Engstrom 2002 [26]	Unclear	Unclear	Low risk (the assessor was blinded)	Low risk (ITT)	Low risk
Tan 2002 [29]	Unclear	Unclear	High risk (no blinding)	Unclear	Low risk
Johnston 2002 [30]	Unclear	Unclear	High risk (no blinding)	Low risk (10 % of patients dropped out)	Low risk
Tegelberg 2003 [16]	Low risk (closed envelops)	Unclear	Low risk (assessor was blinded)	Low risk (missing data balanced across groups)	Low risk
Walker-Engstrom 2003 [17]	Unclear	Low risk (closed envelope allocation)	Low risk (dentist and assessor were blinded)	Low risk (ITT)	Low risk
Blanco 2005 [31]	Unclear	Unclear	High risk (no blinding)	Low risk (missing data balanced across groups)	Low risk
Hoekema 2007 [34]	Unclear	Unclear	High risk (no blinding)	Low risk (no drop out)	Low risk
Petri 2008 [27]	Low risk (central generation)	Low risk (allocation computer generated)	Low risk (patients, dentist and assessor were blinded)	Low risk (missing data balanced across groups)	Low risk
Ghazal 2009 [33]	Low risk (computer generation)	Low risk (central randomization)	High risk (no blinding)	Low risk (missing data balanced across groups)	Low risk
Deane 2009 [32]	Unclear	Unclear	Low risk (the assessor was blinded)	Low risk (reasons unlikely to be related to true outcome)	Low risk
Campbell 2009 [20]	Unclear	Unclear	High risk (no blinding)	Low risk (reasons unlikely to be related to true outcome)	Low risk
Aarab 2010 [15]	Unclear	Unclear	Low risk (Assessors, participants and personnel blinded)	Low risk (15 % of patients dropped out)	Low risk

The GRADE scores are shown in Table 4. The reason for lowering the quality of the evidence to the moderate score was the indirectness.

Results of individual studies

Table 1 reports the results of individual studies. Aarab et al. [15] compared the advancements of 0, 25, 50, and 75 % of the maximum protrusion with a cross over study design showing that the advancements of 50 and 75 % were effective in reducing AHI. Other two cross over studies [16, 17] compared different protrusion amounts (50 and 75 %) using the same MAD. Three studies compared different types of MAD at the same protrusion amount [20, 28, 33]. Three authors compared MADs with non-advanced appliances [27, 30, 31]. Two studies [29, 34] compared the efficacy of the MAD versus CPAP in reducing AHI. In one study [26], MAD was compared with uvulopalatopharyngoplasty.

Synthesis of results

One study [34] reported the AHI values as median and interquartile ranges: in order to compute the success rate, the mean values were obtained contacting the authors. Heterogeneity of the groups was 8.7 % therefore a fixed effect model was used. Figure 2 reports the success rates and confidence intervals of each group included in the quantitative analysis. The meta-regression analysis showed that the mandibular advancement amount does not significantly influence the success rate ($Q = 0.018$, $p = 0.892$) as reported in Fig. 3.

Risk of bias across studies

Concerning the publication bias, Funnel plot of healing improvement (success rate) against its standard error is reported in Fig. 4; results of Egger's test (intercept 0.467, $p = 0.623$) demonstrate no significant deviation of the intercept from the symmetry, and consequently, studies with greater size are distributed near the mean and studies of less size are spread.

Discussion

The aim of the present systematic review with meta-regression analysis was to investigate the effectiveness of different mandibular advancement amounts to treat OSA patients with the MAD. The literature does not provide common guidelines: a large number of studies reported the efficacy of different devices without explaining the rationale to choose the advancement amount.

Thirteen RCTs were included for the qualitative analysis and resulted to be of a medium-high quality on average. The meta-regression analysis was conducted to evaluate the effect of different amounts of mandibular advancement on success rate defined as the improvement of AHI after treatment weighted on the AHI value at baseline. The results show that the advancement amounts do not influence the success rate: in fact, the regression line in the bubble plot remains almost flat, without upward or downward trends (Fig. 3). The mean value of the success rate among the analyzed studies is 62.3 % (Fig. 2), and they include advancements from 25 to 89 % of the maximum mandibular capacity. All the studies included except one [15] investigated the efficacy of a protrusion amount of 50 % or higher. The mandibular advancement of 50 % is widely used as the minimum effective advancement to start the MAD therapy, but this parameter has not been adequately determined on the basis of comparisons with lower mandibular advancements. In fact, the literature provides only two studies that investigated the efficacy of mandibular advancements lower than 50 % [15, 35]. What emerges from the present analysis is that the success rate of the study with the advancement of 25 % is not the lowest registered. As shown in Fig. 2, success rates lower than 50 % derive from investigations with mandibular advancements from 74 to 83 % [20, 27, 30, 33]. On the other hand, among the studies that registered a success rate higher than 70 %, there is also one investigation that performed an advancement of 50 % [26]. It is also important to underline that in most of the analyzed studies the success rate has wide confidence intervals (Fig. 2) suggesting a high inter-individual variability in response to the MAD therapy supporting the findings of a recent systematic-review

Table 4 Quality assessment and summary of findings across studies (GRADE)

Quality assessment						Summary of findings		
Number of studies (Design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Number of patients	Mean Success rate [95 % CI]	Quality
Effectiveness of different advancements in reducing AHI								
Outcome: Success rate								
Thirteen (RCTs)	Unclear/Low RoB for most of the studies	No inconsistency	Serious indirectness for most of the studies	No serious imprecision	No serious publication bias	484	0.623 [0.562–0.678]	Moderate

RoB risk of bias

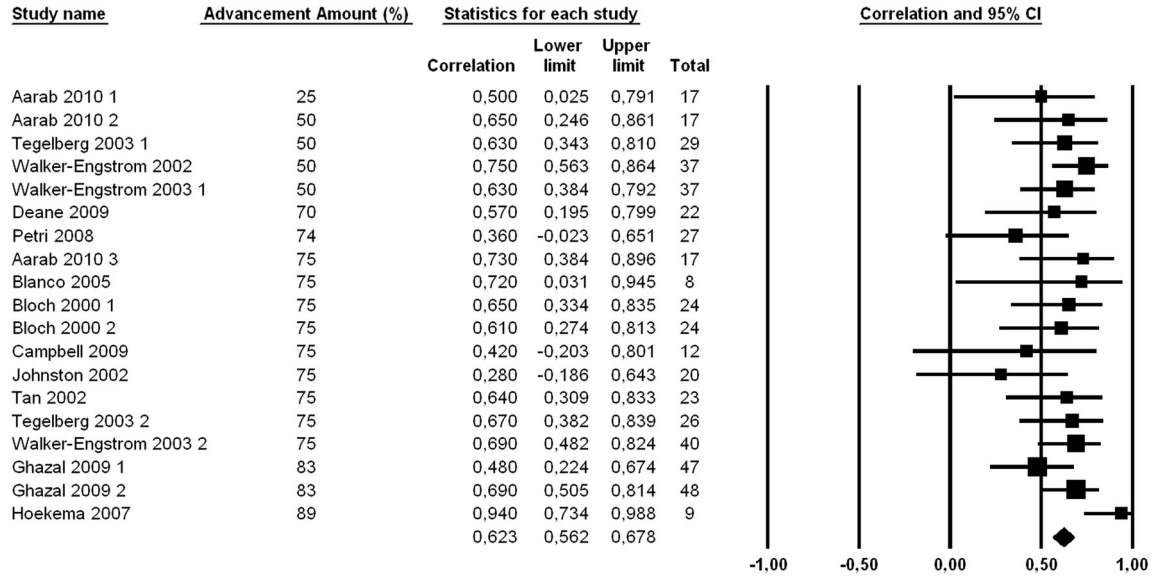

Fig. 2 Forest plot of success rates in the included groups (correlation = success rate)

[36]. The present results seem to be in contrast with the current opinion that the more the mandible is stretched forward the more the AHI improves [37].

The outcomes of the present meta-regression suggest that the amount of mandibular protrusion could not be the unique factor that influences the effectiveness of a MAD therapy, but also other elements could contribute to determine the reaction of a single patient to the treatment and a careful control of predictive parameters would be crucial to personalize the treatment.

To date, the data provided regarding possible predictive parameters of the efficacy of MAD treatment are quite few and inconclusive [38]. To the question of tailoring the treatment according to the single patient's characteristics, the video sleep endoscopy may represent a useful answer since during the investigation it could be possible to identify the effective protrusion amount controlling the progressive improvement of the airway patency [8, 11, 12].

It could be interesting to better investigate the possibility of performing lower advancements in order to limit the side effects: the MAD forces the mandible in a forward and downward position that elongates the fibers of jaw elevator muscles and temporomandibular joint ligament causing a strain in those muscles and in the retrodiscal tissues, that could induce the onset of tenderness or pain in the temporomandibular structures [39, 40]. As a consequence, a cautious approach with a lower mandibular advancement could control these events, considering also that the American Academy of Sleep Medicine guidelines recognize the development of temporomandibular disorders as the main reason for interrupting the therapy with the MAD [41].

It is also important to consider that a significant intra-individual night to night variability in AHI was demonstrated: in a sample of 193 patients, Ahmadi and coworkers [42] registered a difference of AHI > 5 between two consecutive PSGs in 21 % of the subjects; White and colleagues registered a difference of AHI > 10 between the two consecutive PSGs in the 35 % of their sample ($n = 26$) [43]. To this regard, Aarab and coworkers suggested to be cautious in diagnosing OSA on the basis of a single PSG registration [44]. Consequently, further methodologically sound clinical studies considering the intra-individual AHI variability are needed.

The limitations of the present review are linked to the small sample size of the studies. In addition, not all the included

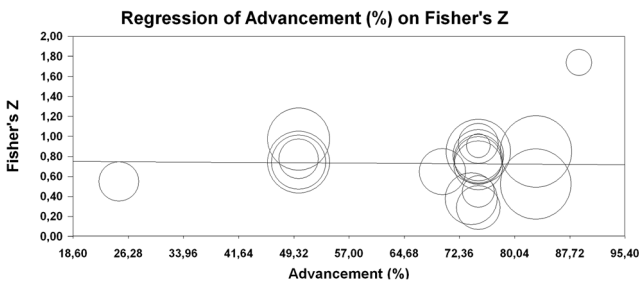

Fig. 3 Bubble plot of the relationship between success rate (reported as Fisher's Z) and mandibular advancement (the size of the bubbles is proportional to the weight of the studies in the meta-regression)

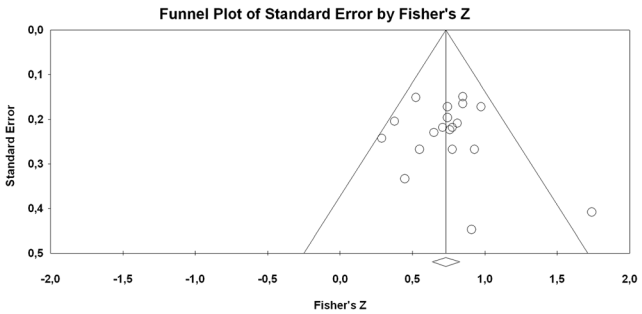

Fig. 4 Funnel plot of the effect size of studies included against its Standard Error

studies controlled the confounding variables such as BMI, neck circumference, and AHI at baseline, which could be causally related to the outcome of interest.

The risk of bias of all the studies resulted low or unclear (Table 3), and the EPHPP quality analysis showed that although only RCTs were included, their quality resulted strong in five studies, moderate in five, and weak in the other three. The insufficient control of the possible confounders and the lack of blinding negatively influenced the scores attributed to the studies. Regarding the body of evidence quality assessment (GRADE), the moderate score is due to the indirectness: most of the studies aimed at comparing different therapies or different devices at the same protrusion amount, but not the efficacy of different mandibular advancements.

The present study revealed some weakness of the current evidence; therefore, there is a need for further studies aimed at detecting possible confounders able to influence the response to the therapy and at comparing the efficacy of different mandibular protrusion amounts also lower than 50 %, in order to verify the results of this meta-regression.

Since some authors suggest to use adjustable MADs that allow to perform a progressive advancement and to manage the possible symptoms during the titration [8, 14, 15, 17, 45] and in light of the present results, it would be recommended to careful titrate the advancement of the MAD starting with minimum protrusions in order to better individualize the therapy and to induce an adaptation of the masticatory system.

Conclusions

There is small body of moderate quality evidence to suggest that increasing the mandibular advancement does not produce significant improvements in the success rate since there is a high inter-individual variability in response to the MAD therapy.

It would be cautious to begin the therapy addressing the minimum effective mandibular advancement.

Compliance with ethical standards The manuscript does not contain clinical studies or patient data.

Conflict of interest The authors declare that they have no competing interest.

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