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Use of mandibular advancement devices for the treatment of primary snoring with or without Obstructive sleep apnea (OSA): A systematic review

Micheline M.D. De Meyer[1,2,5,7,9,10], Olivier M. Vanderveken[3,4], Sonia De Weerdt[5], Marks Luc A.M[6], Bernardita A. Cárcamo[7], Andrés M. Chavez[7], Felipe A. Matamoros[7], Wolfgang Jacquet[6,8,9,10]

[1] Oral Health in Special Needs, Sleep Breathing Disorders, Oral Health Sciences, Ghent University Hospital, Gent, Belgium

[2] Department of Dentistry, Radboud University Medical Center and Radboud Institute for Health Sciences, Nijmegen, The Netherlands

[3] Department of Ear, Nose, and Throat, Head and Neck Surgery, Antwerp University Hospital, Edegem, Belgium

[4] Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

[5] Department of Pneumology, UZ Brussels, Brussels, Belgium

[6] Special care in Dentistry, Oral Health Sciences, Ghent University Hospital, Gent, Belgium

[7] Faculty of Dentistry, University of Concepción, Concepción, Chile

[8] Department of Oral Health Sciences ORHE, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium

[9] Department of Educational Sciences EDWE-LOCI, Faculty of Psychology and Educational Sciences, Vrije Universiteit Brussel, Brussels, Belgium

[10] Department of Materials, Textiles and Chemical Engineering, Faculty of Engineering and Architecture, Ghent University, Belgium

Corresponding author

Email: Miche.DeMeyer@Ugent.be (M.M.D. De Meyer).

Tel: +3293324000

Fax: +3293323851

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Summary

The aim of this review was to systematically evaluate the available scientific evidence on the benefit of mandibular advancement devices (MADs) in the treatment of primary snoring (PS). From 905 initially identified articles, 18 were selected. Papers that provided indirect information regarding obstructive sleep apnea syndrome (OSAS) and/or sleep breathing disorders (SBD) were included. Information was obtained on monoblock and duoblock appliances from the selected studies. The devices were most commonly able to achieve 50%–70% of the maximum mandibular protrusion. The frequently used outcome measurements were the apnea-hypopnea index, Epworth sleepiness scale, and oxygen desaturation index, which all yielded positive post-treatment results. The most common side effects were temporomandibular joint pain and excessive salivation, which improved with time. Our findings indicated that the use of MADs, even with varying designs, improved outcomes in all the reported patient populations (PS, OSAS, and SBD). Despite the lack of studies on PS, the available evidence supports the use of MADs for treatment of PS. Snoring should be treated from a preventive and psychosocial perspective to avoid progression to more severe diseases that could have a significant medical and economic impact.

Keywords: primary snoring, mandibular advancement device, oral appliance, snoring

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Introduction

According to the American Academy of Sleep Medicine (AASM) 2014 revision of the International Classification of Sleep Disorders (ICSD-3), primary snoring (PS) is a sleep-related breathing disorder classified in the subcategory "isolated symptoms and normal variants" [1]. It affects approximately 40% of the population, wherein the majority are middle-aged males [2], and is characterized by audible vibrations of the upper airway when breathing during sleep. The corresponding apnea-hypopnea index (AHI) should be < 5 events per hour [3].

Snoring is a sleep-related breathing noise that occurs during the inspiratory, and sometimes expiratory, phase of the respiratory cycle. The sound source includes both nasal and pharyngeal segments of the upper airway with the sleep position affecting its intensity, severity, and duration [4]. Relative atony of the upper airway dilator muscles during sleep induces narrowing of the upper airway thereby increasing resistance. Consequently, the airflow becomes turbulent and the pharyngeal tissues vibrate as air passes through. Specifically, snoring is characterized by oscillations of the soft palate, pharyngeal walls, epiglottis, and tongue [5]. The soft palate is the most collapsible upper airway region [6]. Endoscopic evaluation of upper airway structures during snoring in drug-induced sleep has demonstrated soft palate vibration. This could be combined with noise generation via vibration of other structures, including the tonsils, tongue base, and epiglottis [5].

Snoring is considered a cardinal symptom of obstructive sleep apnea syndrome (OSAS). Moreover, primary snorers (in general, those considered to have an AHI < 5) have a high risk of developing OSAS, and PS could be an early stage. Anatomical upper airway abnormalities, including upper airway collapsibility, upper airway length and size, craniofacial structure alterations, and enlargement of the surrounding soft tissue structures (e.g., nose, tongue, and lateral pharyngeal walls) can play an important role in OSAS development [7], and these different phenotypes could be targeted in therapy. Four subtypes have been identified with a causal relation to OSAS [8,9]. A distinction between symptomatic and asymptomatic snorers has been observed [10].

Snoring has been associated with several medical consequences. Several studies have reported a correlation between the intensity of snoring and increased severity in OSAS expressed by the AHI [11-13]. Other studies provide strong evidence that snoring is associated with an increased risk of cardiovascular diseases, especially hypertension [14-15]. Lindberg et al. found that snoring without excessive daytime sleepiness (EDS) does not increase mortality. On the other hand, the combination of snoring and EDS appears to be associated with an increased mortality rate, although this association was age dependent [16]. Another aspect is the significant association between snoring and abdominal obesity, hyper triglyceride, and hypertension. Abdominal obesity and hyper triglyceride were observed more often in women, whereas hypertension was found to be more prevalent among males [17].

Snoring has social consequences and affects more than two-thirds of snorers' bedpartners [18], which results in them experiencing daytime sleepiness and disturbed sleep [19,20]. The persistence of noise, snoring, and abnormal breathing could prolong wakefulness during sleeping time [21]. Moreover, it could increase daytime stress, depression, and fatigue [18], with the latter affecting quality of life.

PS management can include lifestyle changes, weight loss, surgery, and oral appliance (OA) therapy [2]. OAs have been indicated as the best treatment option for PS [22]. Among the different OA types for treating sleep-disordered breathing, the most commonly used are mandibular advancement devices (MADs) [23,24]. The MADs used for snorers with an AHI < 5 have a similar design to those used in patients with OSAS (AHI ≥ 5) [19].

Brown et al. reported two mechanisms of mandibular advancement improving airway collapsibility, specifically, anterior-posterior tongue motion and increased lateral airway dimensions [25]. The upper airway contains several muscle groups, including tongue muscles, palatal muscles, pharyngeal constrictor muscles, and muscles that control the hyoid bone. When a MAD is in the patient's oral cavity, tongue and palatal muscle movement play an important role in its outcome. The genioglossus, which is the extrinsic and primary protrusive tongue muscle, and its associated tendon, connect the tongue to the genial tubercle of the lingual aspect of the anterior mandible. This muscle and tendon protrude the tongue and prevent its posterior displacement into the pharynx. Upon positioning of the mandible during protrusion, the tongue is supposed to be pulled forward with the widening of the oropharynx in the anterior-posterior direction [26,27]. Moreover, the soft palate is connected with the tongue base via the anterior palatal pillar, which contains the palatoglossus muscle running through the soft palate and uvula, and inserted to the lateral tongue parts. The latter structure passively and actively pulls the soft palate inferiorly and anteriorly, which causes forward displacement of the velopharynx, stretches the soft palate, and stops it from collapsing [6,27]. This muscular activity and/or tongue stretching allows the use of MADs for PS treatment.

MADs are popular, easy to use, and furthermore, energy independent [23]. The comfort or discomfort of wearing a MAD is an important issue in obtaining a maintained treatment outcome [28,29]. Reported side effects and patients' experiences have been sparsely evaluated in relation to device design. We aimed to conduct a systematic review to evaluate the available scientific evidence on the use of MADs in PS treatment.

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Abbreviations			
AASM	**American Academy of Sleep Medicine**	**MDA**	**Mean disease alleviation**
AADSM	**American Academy of Dental Sleep Medicine**	**MPD**	**Mandibular protruding device**
AHI	**Apnea-hypopnea index**	**MRA**	**Mandibular reposition appliance**
BMI	**Body mass index**	**OA**	**Oral appliance**
BRA	**Bite raising device**	**OCA**	**Occlusal contact area**
CPAP	**Continuous positive airway pressure**	**ODI**	**Oxygen desaturation index**
EDS	**Excessive daytime sleepiness**	**OSA**	**Obstructive sleep apnea**
ESS	**Epworth sleeping scale**	**OSAS**	**Obstructive sleep apnea syndrome**
ETPP	**Effective target protrusive position**	**RDI**	**Respiratory disturbance index**
FOSQ	**Functional Outcome Sleep Questionnaire**	**RMCP**	**Remotely controlled mandibular positioner**
FSS	**Fatigue severity scale**	**SBD**	**Sleep breathing disorders**
ICSD	**International Classification of Sleep Disorders**	**SPE**	**Sleeping partner evaluation**
KSS	**Karolinska sleepiness scale**	**SR**	**Snoring rate**
KZY	**Karwetzky activator**	**SSI**	**Snoring Symptoms Inventory questionnaire**
LM	**Laryngomalacia**	**TMJ**	**Temporomandibular joint**
MAD	**Mandibular advancement device**	**TRD**	**Tongue retainer device**

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MAS	**Mandibular advancement splint**	**VAS**	**Visual analogue scale**
MBF	**Maximum bite force**		

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Materials and methods

In this systemic review, only studies on adults, snorers, appliances, and mandibular advancement were selected for further analysis. To identify relevant studies, we queried the PubMed, Web of Science, and Embase databases using the following search string (snore OR snoring OR snores OR snorer OR snorers) AND ("oral appliance" OR "mandibular advancement" OR "appliances" OR "appliance" OR "splint" OR "device" OR "devices" OR "repositioning") AND ("adult" OR "adults"). The search was limited to studies on humans published in the English language from April 2009.

The search identified 203, 99, and 603 articles from PubMed, Web of Science, and Embase, respectively. After the elimination of duplicates and erroneous hits based on publication type and language, 473 articles remained. Screening these records led to the exclusion of 434 articles unrelated to adults, snoring, and MAD. Initially, three evaluators (BC, AC, and FM) independently screened the article titles. When one reader doubted a paper, it was included for further abstract-based assessment in the subsequent phase. On the other hand, when all three evaluators agreed on a paper, it was directly included in the full article reading stage. Disagreements among the three evaluators were resolved by including two additional evaluators (MDM and WJ) to reach a consensus. Subsequently, 39 articles were identified for further screening.

The final inclusion was made by the three evaluators reading the full text to search for information on the direct and indirect use of MADs for PS treatment. Among the 39 articles, 21 did not meet the inclusion criteria; hence, 18 articles were included in the final analysis. Among the 21 excluded papers, nine did not report AHI- and snoring-related therapeutic effects; four only reported dental, skeletal, or craniofacial side effects; and eight were classified as guidelines (Figure 1).

Fig 1. Flowchart for article selection (N: number of studies).

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A quality of evidence evaluation was introduced based on the study by Grimes and Shultz—see column "quality of evidence" table. In addition, an assessment was made with respect to the directness of the evidence regarding snoring and population (AHI < 5 or not). Furthermore, a critical appreciation scale indicating whether the reported findings could contribute to the evidence of MAD snoring reduction efficacy was adopted [30].

Critical appreciation scale:

A: Good evidence

RCT patients with PS (AHI < 5) based on validated acoustical features and statistically sound comparison.

B: Fair evidence

RCT patient population with PS (AHI < 5) non-validated Visual Analogue Scale (VAS) self- and/or bedpartner reporting.

RCT patient population with PS (AHI < 5) non-validated acoustical features.

Non-RCT patient population with PS (AHI < 5) non-controlled design based on validated VAS self- and/or bedpartner reporting or validated acoustic measures.

RCT patient population without PS (AHI ≥ 5 not guaranteed) based on validated acoustical features and statistically sound comparison.

C: Weak evidence

RCT patient population without PS (AHI ≥ 5 not guaranteed) based on non-validated acoustical features and statistically sound comparison.

Non-RCT patient population with PS (AHI < 5) non-controlled design based on non-validated VAS self- and/or bedpartner reporting or non-validated acoustic measures.

D: No evidence

Claim without support.

E: Good evidence to the contrary

Results

The evidence levels for treatment effect with respect to snoring according to the introduced scale are: **Good evidence**: Terryn et al., 2015 [41]; **Fair evidence**: Gauthier et al., 2009 [33]; Jayan et al., 2009 [31]; Maguire et al., 2010 [20]; Marklund et al., 2015 [45]; Marty et al., 2015 [38]; Wiman Eriksson et al., 2015 [32]; **Weak evidence:** Bhamrah et al., 2014 [35]; Dieltjens et al., 2013 [44]; Dieltjens et al., 2015 [43]; Johal et al., 2011 [34]; Norrhem et al., 2016 [37]; Van Leeuwen et al., 2015 [40]; **No evidence:** Church et al., 2009 [2]; Flanagan, 2009 [26]; Flanagan, 2010 [39]; Jaiswal et al., 2015 [36]; **No evidence**: Church et al., 2009 [2]; Flanagan, 2009 [26]; Flanagan, 2010 [39]; Jaiswal et al., 2015 [36]. Claim non-efficiency of the intervention without supportive data (Ueda et al., 2012 [42]) – see Table 2.

None of the 18 included papers had a "snoring" definition that corresponded to the conceptual notion of "primary snoring" (non-apneic snoring). Only one study by Jayan et

al. [31] reported measuring the therapeutic effect on patients with primary or non-apneic snoring. However, the baseline AHI in that study was high (AHI ≥ 5) and did not conform to the regularly used AHI < 5 criterion for PS definition, and the evidence with respect to the effect on snoring was considered to be only fair [3].

Among the included articles, 4 articles (Table 1) reported direct information on the use of MADs for PS treatment [2,26,31,32]. While the evidence was weak for two of them, the other two provided fair evidence [2,17]. Specifically, those providing fair evidence studied patients with OSAS and PS [31,32]. They provided individualized results for each included patient group while the other papers described only patients with PS without solid evidence with respect to aspects of snoring [2,26]. The remaining 14 articles provided indirect information on the use of MADs in patients with a diagnosis other than PS. Among these 14 articles, 8 reported on patients with OSAS [33–40] while the remaining 6 articles reported on a mixed spectrum of patients with SBD without distinguishing the different OSAS categories [20, 41-45].

Moreover, 15 of the 18 included studies employed a prospective design [2,10,19–24,26–43,45] with a study duration ranging from a couple of hours [28] to 10 years [32], with four studies having a follow-up period of 3 months [2,20,34,43]. Two of the three remaining studies were case reports [26,39]; among them, only one specified the 3-month follow-up period. The remaining study [44] employed a retrospective design and included patients who had started OA treatment within 3 to 6 years prior.

Some of the studies used monoblock [2,20,26,32,39] or duoblock MADs without any further specifications [36–38,44]. Two studies compared the use of monoblock and duoblock MADs [30,32]. Different MAD designs were employed; specifically, the Karwetzky appliance [31], the Klearway and Silencer MADs [45], the Herbst appliance [34], the RespiDent Butterfly MAD [43], the Bite raising device (BRA) [20], and an adjustable mandibular positioning appliance [40]. Two studies did not specify the employed MAD type [35,41].

The most common adverse effects were temporomandibular joint (TJM) pain (9/10 studies) [2,31,35–38,43-45]; excessive salivation (7/10 studies) [2,24–26,31–33,45]; sensitivity in muscles or teeth (7/10 studies) [2,35,38,39,43–45]; and dry mouth or throat (5/10 studies) [2,20,35,38,44]. Notably, five studies reported progressive diminution of these side effects during treatment [2,20,31,36,43].

Eight out of 18 papers (44%) reported on the subjective comfort characteristics of the used appliances [2,20,26,31,33,37,39,43]. No well-defined consensus emerged from the included papers with respect to the definition and criteria of design and comfort of the MAD.

Regarding the therapy outcomes, 15 out of 18 articles (83%) reported the mean age of their population groups [20,26,31–34,36–45]. Only one study reported a relatively young population with a mean age of 26.2 years, with the remaining studies studying a middle-aged patient population aged 44-75 years [42].

Twelve of the 18 selected articles reported the mean body mass index (BMI) [20,31,33,34,37,39,41,43,44]. Among them, 10 studies had an overweight population with the average BMI ranging from 25 kg/m² to 29.9 kg/m^2 [20,31,33,34,37,40,41,43–45]. The remaining two studies had an obese population (BMI > 30 kg/m^2) [32,39]. Moreover, 8 of the 12 studies (66%) mentioned the effect of BMI on snoring. However, none of the papers considered BMI or age as moderating variables of the effect of MAD on snoring.

One paper reported that MAD therapy was ineffective for snoring [44]; five reported that it reduced snoring [31,32,37,29,41] with one reporting an intermittent snoring cessation [31] without using objective measures, including snore-sound intensity, severity, and frequency, or their derivations.

Three studies used specific subjective measurements, including the Snoring Symptoms Inventory questionnaire (SSI) [20], as well as a snoring intensity scale with a VAS ranging from 0 to 10 [43,44]. Both the mandibular advancement splint (MAS) and the BRA resulted in a statistically significant reduction in mean SSI of 5.5 and 3.1, respectively. The snoring intensity scale, using a VAS, was used for bed partners, [43,44] where 0 indicated no snoring and 10 indicated snoring that causes the bed partner to leave the room or to sleep separately. In one study, 37% of patients reached a positive therapy outcome with a decrease of 3 points on the VAS [43].

One study reported an association of MAD treatment discontinuation with the type of MAD and type D personality [44]. Type D personality (D abbreviated from “distressed”) is a concept used in medical psychology defined as the joint tendency toward negative affectivity (e.g., worry, irritability, and gloom) and social inhibition (e.g., reticence and a lack of self-assurance) [46,47]. Monoblock MAD types had a higher discontinuation rate. Moreover, patients with type D personality had a lower self-reported adherence to MAD treatment. MAD therapy was discontinued on grounds of an insufficient effect on self-perceived snoring.

Only 12 of the 18 articles reported the applied degree of mandibular protrusion [2,20,31–33,36–38,40,42,43,44]. The reported protrusion ranged from 50% to 80% of the maximum protrusion, with 50% [2,20,33] and 70% [31,36,37] being the most commonly applied. The protrusion of the mandible until the patient’s comfort limit was adopted as a criterion [44], while in another study participants were asked to simulate the snoring sound while advancing the appliance until the patient could no longer simulate snoring [40].

None of the studies evaluated the action of MADs at an anatomical level. Only three studies recognized the importance of muscle activation for opening the upper airway; however, there was no study on how the MAD activated a single muscle or a muscle group [26,31,39].

Regarding efficacy, 12 articles used the Epworth sleepiness scale (ESS) scores as the primary outcome—with all of them reporting that MAD usage reduced the ESS scores [2,20,31,33,34,36–39,41,43,45]. The majority of the studies used the AHI to measure the efficacy of MAD treatment with nine studies reporting a decrease in AHI [31,34,36–38,41,43–45]; however, none of them studied patients with PS (AHI < 5). Five studies used

the oxygen desaturation index (ODI) as an outcome. One study [31] looked at patients with PS and reported an ODI reduction, which is consistent with four other articles [37,38,43,44]. Three studies reported improved snoring with respect to cessation, reduction, intensity, severity, or frequency in patients with PS [26,31,32]. Other studies [35,37–39,41-43] reported similar outcomes for different patient populations. Moreover, other studies employed efficiency measures for evaluating MAD treatment, including the snoring rate (SR) [45], respiratory disturbance index (RDI) [33], and sleeping partner evaluation (SPE) [2], and all reported satisfactory outcomes.

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Table 1. Overview of the selected studies

	POPULATION												
	PS	OSAS	SBD	TYPE OF MAD/MAS	AHI	MEAN AGE (Y)	MEAN BMI	OUTCOMES	SIDE EFFECTS	PROT-RUSION	QUALITY OF EVIDENCE	Direct or Indirect evidence	PS - MAD	Remarks
Bhamrah et al., 2014 [35]		93		Hard cured acrylic or vacuum formed appliance.				Among the patients, 44% stopped snoring, 47% showed reduced snoring, 69% showed resolution of OSAS symptoms, 15% still experienced sleep apnea, 77% showed improved sleep quality, 2% reported worsened sleep quality, and 86% bed partners reported improved sleep quality.	Among the patients, 37%, 32%, and 33% presented with aching teeth, aching jaws, and dry throat, respectively.		II One center non-randomizatio n two treatments -	indirect PS apneic - direct MAD	C Efficiency for both MAD treatments, no validated scale	Self-reporting one treatment satisfaction question with respect to snoring
Church et al., 2009 [2]	60			Monoblock.				1. SPE: Success rate of 48%. 2. ESS: From 9 to 7.5.	Muscle discomfort: 21% TMJ discomfort: 31% Abnormal bite: 32% Dry mouth: 44% Excessive salivation: 45%	50% of the max.	V Multi center (3) non-randomized observa-tionnel	indirect PS apneic patients - direct MAD	D Unclear positive treatment effect, might be snoring, no validated scale	Self-reporting no specific snoring reporting
Dieltjens et al., 2013 [44]			82	Monoblock and Duoblock.	17	50	27.9	Based on 50% AHI reduction from baseline: Monoblock, 46% responders; Duoblock, 59% responders. Monoblock had a higher discontinuation rate odds ratio 9.12 (insufficient effect on snoring, snoring VAS, or daytime sleepiness ESS). Both appliances decreased the AHI (from 17.7 to 10.02). Both appliances decreased the ODI (from 6.8 to 4.0). Persistent snoring was mentioned as the reason for	TMJ or teeth pain: 47% Excessive salivation: 38% Dry mouth: 33% Sensitive teeth: 29%	Monoblock: 65% of the max. Duoblock: until the comfort limit.	V One center non-randomized observationa l	indirect PS apneic patients - direct MAD	C VAS improveme nt, no validated scale	Self-reporting

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discontinuation.

Dieltjens et al., 2015 [43]		51	Custom-made oral appliance. (RespiDent Butterfly, Dormoco)	14.9	49.3	26.3	The AHI improved from 14.9 to 8.3 with 51% and 41% of the patients showing treatment response and success, respectively. 41% treatment success. ESS: 10.1 to 6.8. 37% decreased 3 or more points in snoring VAS. ODI: From 4.9 to 2.1.	Unpleasant teeth sensation: 70% Teeth pain: 60% Hypersalivation: 53% Jaw pain: 53%		V One center non-randomized observational	indirect PS apneic patients - direct MAD	C VAS improvement no validated scale	Self-reporting
Flanagan D, 2009 [26]	1		Monoblock.		75		Reduced snoring. Better sleep for the partner.			V One center non-randomized observational	indirect PS apneic patients - direct MAD	D Claim without snoring assessment no evidence	
Flanagan D., 2010 [39]		4	Monoblock.		49.5	31.45	ESS scores reduced from 11.7 to 3.5. Reduction of snoring and sleepiness symptoms in all the patients.			V One center non-randomized observational	indirect PS apneic patients - direct MAD	D Claim without snoring assessment no evidence	
Gauthier et al., 2009 [33]		16	Klearway and Silencer.		47.9	28.7	Success in RDI reduction: 50% for Klearway and 63% for Silencer. Both MADs significantly reduced the ESS, FOSQ, and FSS scores. There were improved partner relationships for 75% of the participants.		Klearway 2/3 of the max. Silencer 1/2 of the max.	I One center randomized experimental	indirect PS apneic patients - direct MAD	B Fair evidence measurement on snoring with patient self-assessment	One question self-reporting and partner
Jaiswal et al., 2015 [36]		30	Duoblock medical dental sleep appliance (MDSA).	26.2			AHI improved from 26.2 to 13.7 while the ESS score improved from 14.2 to 6.1.	TMJ discomfort. Excessive salivation.	≤ 70% of the max.	V One center cross-sectional observational	indirect PS apneic patients - direct MAD	D Claim without reporting on snoring, on PS no evidence	Self-reporting

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Jayan et al., 2009 [31]	8	30		1. Karwetzky activator (KZY) for non-apneic snorers. 2. MAS. 3. TRD. 4. Herbst appliance.	OSAS: 51.4	OSAS: 52.3	OSAS: 29.5	PS: 62.5% showed reduction/cessation in the snoring intensity and frequency while 37.5% showed no response. OSAS: AHI improved from 51.4 to 32.7 and the ESS score improved from 12.50 to 7.20	TMJ pain and headache during the first week: 18%	≤ 70% of the max.	V One center cross-sectional observational	direct on PS apneic patients - direct MAD	B Fair evidence but small group	8 cases non apneic snoring - based on partner information 5 are reported to have a gross reduction/cessation of snoring intensity and frequency no details
Johal et al., 2011 [34]		75		Herbst appliance.	MAS: 16 Conservative: 15	MAS: 49.3 Conservative: 51.4	MAS: 25.9 Conservative: 26.2	MAS reduced the ESS score from 10 to 6 and AHI from 16 to 4.6 Conservative reduced the ESS score from 12 to 11 and AHI from 15 to 5.4			V One center cross-sectional observational	indirect PS apneic patients - direct MAD	C Weak evidence	Snoring used as selection criterion, reference to paper reporting improvement in 16 out of 18 cases.
Maguire et al., 2010 [20]			38	MAS (Monoblock) vs. BRA. (Control bite raising device)	8.8	44.6	28.8	SSI: Reduction 5.5 (MAS) and 3.1 (BRA). ESS: Reduction 1.0 (MAS) and 0.3 (BRA)	MAS had more side effects than BRA, which could be attributed to its greater bulk and active mandibular protrusion. Dry mouth was the most common long-term side effect (56%).	50% of the max.	I One center Randomized cross- over CT experimental	indirect PS apneic patients - direct MAD	B Fair evidence, no validated scale	Self-reporting

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Marklund et al., 2015 [45]		91	Duoblock. Placebo device.	Duo bloc k 15.6 Plac ebo 15.3	Duoblock 49.8 Placebo 54.1	Duo bloc k 27.6 Plac ebo 27.9	Duoblock improved AHI from 15.6 to 6.7, ESS from 11 to 6, and the SR from daily to weekly. Placebo improved AHI from 15.3 to 16.7, ESS from 11 to 9, and SR from daily to weekly.	Jaw pain, tooth pain, hypersalivation, and bite changes were the most frequent and more common in Duoblock than in Placebo.	6.8 mm.	I Two center randomized, parallel placebo-controlled cohort study, single blind experimental	indirect PS apneic patients - direct MAD	B Fair evidence no validated scale	Self-reporting no PS definition only: snore rate
Marty et al., 2015 [38]	35		Duoblock.	34.1	49.6		AHI: 34.1 to 12.8 ODI: 26.6 to 12.6 ESS: 10.7 to 4.5. Snoring VAS (1–10) (VAS unspecified): 7.4 to 2.5	Excessive salivation, dry mouth, muscle, tooth, and joint sensitivity.	60%–80% of the max.	III Four centers analytical cohort study/ non RCT experimental	indirect PS apneic patients - direct MAD	B Fair evidence no validated scale	Self-reporting what is the difference with non RCT and analytical cohort
Norrhem et al., 2016 [37]	10		Duoblock (Narval) with and without elastic bands.	19.7	58	26.8	AHI without band: 19.7 to 3.1. AHI with band: 19.7 to 5.1. ESS without band: 10 to 6. ESS with band: 10 to 5. KSS without band: 13 to 7 KSS with band: 13 to 8. ODI without band: 22.3 to 5.7. ODI with band: 22.3 to 9.0. Both designs improved snoring.	Change in occlusion, jaw pain, sensitive teeth, excessive salivation.	8.0 mm.	I One center RCT experimental	indirect PS apneic patients - direct MAD	C Weak evidence; no validated scale no control group	snoring time % no description of determination
Terryn et al., 2015 [41]		30	No specification.	13.2	48.2	26.1	There was a decrease in snoring intensity and severity. AHI decreased from 13.2 to 9.7 and there was a significant decrease in the ESS score.			V One center prospective comparative study surgery, CPAP, MAD; Analytical	indirect PS apneic patients	A Fair evidence	Self-reporting snoring Intensity, Severity, Score. and measured

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									cross-sectional observational			acoustic intensity parameter.
Ueda et al., 2012 [42]		10	Monoblock and Duoblock.		26.2		Compared with 1-piece, the OCA and MBF were larger in 2-piece at 5 minutes after removal. Tooth pain disappeared faster with the 2-piece. The 2-piece allows lateral movement with less influence in occlusal function and tooth pain. Both improved snoring.	Start: 2/3 of the max both. End 1 piece: 6.2 mm. End 2 piece: 6.4 mm.	IV Analytical case-controls observational	no description; no observation of snoring	E Evidence to the contrary	This evidence is speculative with respect to drop out.
Van Leeuwen et al., 2015 [40]		9	Adjustable mandibular positioning gauge.	12.2	45.2	28.04	Airway volume: 13.5 cc to 19.7 cc.	Patients were asked to simulate a snoring sound. The gadget was advanced until the snoring sound could not be simulated.	IV Analytical case-controls observational	no measurement PS or apneic snoring	C Weak evidence	gauge - mand. advancement and volume UA titration can be steered based on snore possibility
Wiman et al., 2015 [32]	15	30	Monoblock. (Microdent®, Forshaga, Sweden)		Snorers: 50 OSAS: 56	Snorers: 28 OSAS: 30	Snorers ODI: 93% < 5 OSAS and snorers: reduced snoring, apnea, and daytime tiredness. (ad-hoc questionnaire).	Patients were asked to simulate a snoring sound. The gadget was advanced until the snoring sound could not be simulated.	III Analytical cohort study observational	indirect PS apneic patients - direct MAD	B Fair evidence no validated scale with comparison	Self-reporting

Responder = reduction of 50% AHI compared to baseline; AHI: Apnea-hypopnea index; BMI: Body mass index; BRA: Bite raising device; ESS: Epworth sleeping scale; FOSQ: Functional outcome sleep questionnaire; FSS: Fatigue severity scale; MAD: Mandibular advancement device; KSS: Karolinska sleepiness scale; KZY: Karwetzky activator; MAS: Mandibular advancement splint; MBF: Maximum bite force; MDSA: Medical dental sleep appliance; OCA: Occlusal contact area; ODI: Oxygen desaturation index; OSAS: Obstructive sleep apnea syndrome; PS: Primary snoring; RDI: Respiratory disturbance index; SBD: Sleep breathing disorders; SPE: Sleeping partner evaluation; SR: Snoring rate; SSI: Snoring Symptoms Inventory questionnaire; TMJ: Temporomandibular joint; TRD: Tongue retainer device; VAS: Visual analogue scale.

Quality of Evidence	Articles
A Good	Terryn et al., 2015 [41]
B Fair	Gauthier et al., 2009 [33] Jayan et al., 2009 [31] Maguire et al., 2010 [20] Marklund et al., 2015 [45] Marty et al., 2015 [38] Wiman Eriksson et al., 2015 [32]
C Weak	Bhamrah et al., 2014 [35] Dieltjens et al., 2013 [43] Dieltjens et al., 2015 [44] Johal et al., 2011 [34] Norrhem et al., 2016 [37] Van Leeuwen et al., 2015 [40]
D No evidence	Church et al., 2009 [2] Flanagan D., 2009 [26] Flanagan D., 2010 [39] Jaiswal et al., 2015 [36] Ueda et al., 2012 [42]
E Good evidence against the intervention	

Table 2. Evidence levels for treatment effect with respect to snoring

Discussion

In 2015, the AASM published clinical practice guidelines and recommended OA treatment of OSA and snoring in patients with PS, as well as patients with OSA intolerant to Continuous positive airway pressure (CPAP) therapy or those who prefer alternative therapy [48]. In this study, we defined primary snorers as "adult patients without obstructive sleep apnea" and described different OA types. All the included studies aimed to maintain a patent airway during sleep through mandibular advancement and stabilization, with the latter having been well defined in an American Academy of dental sleep medicine (AADSM) paper in 2014 [1, 49].

Unfortunately, there is currently no universal terminology for describing OAs used for OSA treatment and moreover, the various terms used are potentially confusing. Currently, the commonly used terms include: MAD, mandibular advancement device; MAS,

mandibular advancement splint; and MRA, mandibular repositioning appliance [1]. In this review, we focused on OAs with a titratable function; specifically, mandibular advancement or protrusion.

The AASM strongly recommends OA therapy for PS since its possible benefits outweigh its risks. However, they stated that there is insufficient evidence on whether OA treatment of PS improves other health-related outcomes. In this article, the term OA is used to refer to all these different treatment types.

Despite the important pioneering role of the AASM in developing guidelines for therapeutic modalities for OSAS and isolated snoring, important gaps remain. There is currently no validated and consistently used consensus definition for various OSAS subcategories. Various study designs have been employed with varying study durations, follow-up periods, OA terminologies, and OA modes of action, as well as with or without mandibular movement possibilities. The comparability of previous findings is limited due to differences in treatment duration and protrusion degree. Moreover, there have been varying methods for indicating or defining treatment success, including snoring assessments, AHI (OSAS severity), ODI, ESS (daytime somnolence), and the effect on cardiovascular function.

Treatment outcomes

None of the selected studies provided information regarding the duration and frequency necessary for effective MAD treatment. Moreover, they did not report the association between the patient's snoring and the partner's wellbeing or other clinical parameters.

In the selected studies, various outcome measures for assessing treatment efficacy were not included. Studies on patients with OSAS or other SBD used similar scales for outcome evaluation. Eight (44%) studies evaluated snoring using questionnaires involving a VAS [32,35,37–39,43,43,45]; moreover, AHI was employed in nine (50%) studies [31,34,36–38,41,43–45], RDI in one study [33], ESS in 11 (61%) studies [20,31,33,34,36–39,41,43,45], and ODI in four (22%) studies. There were significant improvements indicated by these indices, which is consistent with the AASM recommendations for quality of evidence.

There is no consensus on outcome measurements for evaluating MAD therapy in patients with PS. Some studies employed the SPE [2,26], with only one study using the ESS [2]. One study considered quantitative changes such as snoring intensity [32], or used the ODI [32].

All the selected studies reported a positive outcome of MAD treatment regardless of the outcome criteria or the SBD clinical category, including PS. This is consistent with a study that evaluated the SPE, snoring frequency, and ESS scores in patients with PS using MAD [50].

In a comparison between the use of a MAS with a BRA, with the former having 0% of the maximum protrusion and the latter lacking mandibular advancement in patients with PS (AHI $\leq$ 15)[20], they observed a qualitative snoring increase with the MAS, which was measured using the SSI and ESS. On the other hand, the BRA reduced the SSI scores to a lesser extent, with no significant changes in the ESS scores. This indicates the importance

of mandibular advancement in reducing snoring, as also shown by Walker-Engström et al. [51]. However, the SSI is a questionnaire self-reported by the patient; therefore, it is not an accurate reflection of the bedpartner's score, and is at most indirectly influenced by the bedpartner's perspective. Therefore, caution is necessary when using SSI outcomes obtained from the snorer's responses.

PS appears to be more of a social than a medical problem [4]. The bedpartner often suffers from poor sleep quality [49] and daytime fatigue [52]. Moreover, PS could cause relationship problems. A study focusing on bedpartners found that 40% of all affected bedpartners slept in separate bedrooms at least once a week—with 26% of them using aids, including sleeping pills, earplugs, or both [52]. Moreover, 35% of the participants reported snoring-induced relationship problems. In addition, 75% of patients treated with MAD reported improved relationships with their bedpartners [33]. Bedpartners often have the most influence on the snorer's decision to seek medical attention and in evaluating treatment progress [53]. In the majority of the studies in this review, the bedpartner was responsible for completing the VAS, surveys, or different questionnaires for evaluating the improvement or deterioration of snoring [54]. Moreover, many studies have considered the bedpartners' evaluation as the most relevant outcome [26,35]. A vast majority (86%) of bedpartners reported improved quality of sleep during MAD treatment [35].

Both age and BMI are considered as important parameters; however, they were not systematically addressed as intervening factors in MAD efficacy for PS. Increased age and BMI have been reported to predispose PS development and its progression to OSAS [55,56]. In a retrospective, longitudinal case study of untreated adult males who had PS and various degrees of OSA, patients with PS and mild and moderate obstructive sleep apnea presented with a consistent increase in the AHI over time, which was largely dependent on weight gain and, to a lesser extent, age progression [55].

OSAS is closely related to snoring, and thus, studies on OSAS can provide some information on PS. A retrospective study reported a direct relationship of age with OSAS prevalence and that the OSAS prevalence was 13% in participants aged 30–70 years [56]. This confirms the influence of age but also the influence of BMI on the AHI, OSAS severity, and snoring (apneic and non-apneic) [57]. These findings are consistent with a positive correlation of OSAS severity with BMI; in other words, patients with OSAS had higher BMI values than patients with PS [32]. Moreover, there is a direct correlation of severity and duration of apnea and hypopnea with age and BMI [56,4]. Among the four selected studies on patients with PS, only one reported in relation to BMI.

The MAD effect through muscle activity is mainly attributable to the genioglossus muscle [18] (Edwards) and the palatoglossal muscle [6]. Only three (17%) selected studies mentioned the importance of muscle activation in opening the upper airway. There is a need for further studies on the relationship between muscle activation and efficiency to possibly provide the basis for predicting individual treatment outcomes and customizing personalized therapy. This review reveals that there has been scarce research on PS, which makes it difficult to quantitatively evaluate the effect of MADs in these patients.

Study design, study duration, and follow-up period

No standard recommendations for choosing the study design, study duration, and follow-up period for evaluating the treatment of patients with SBD remain. Only one retrospective study was included [44]. The majority—15 out of 18 (83%)—of the included studies employed a prospective study design with varying study durations ranging from a couple of hours to ten years. Approximately 31% of the studies, including one case report, reported an evaluation or follow-up period of 3 months. A 3-month follow-up period appears to be the minimum required time for OA adaption. There are currently no reports on the minimum adherence per night and the minimal adherence time necessary for an efficient therapy.

A review of efficacy and effectiveness (2015) comparing MAD and CPAP in treatment of OSAS concluded that results were comparable, but only limited data was available [58]. When considering the seven papers with fair to good snoring evidence, the follow-up ranges from one month up to ten years [20,31-33,38,41,45]. Four of these studies can be considered to aim at an evaluation of effectiveness [32,33,41,45].

The study by Terryn et al. depicts a detailed image that includes the bedpartner and patient after a six-month period for three treatment modalities: surgery, MAD, and CPAP [41]. The effectiveness is studied based on AHI, ESS, and compliance, combined with success as mean disease alleviation (MDA) [41], snoring intensity, and severity. Despite this effort, the relevance of the study with respect to PS with or without apnea (AHI < 5) remains limited since median AHI ranged from 8.7 (surgery), over 9.8 (MAD), and up to 40.3 (CPAP). Furthermore, the study itself remains explorative in nature and approach, due to the statistically limited number of patients and its analysis design. Groups have been compared at baseline, thus, drop out due to lack of treatment effect cannot be excluded. Overall, all therapies show treatment effect after 6 months for included patients ranging from 67% (surgery, MAD) up to 76% (CPAP). The 10-year follow-up study of the effectiveness of an MPD is retrospective and explorative in nature [45]. An adherence to MPD treatment of 58% was reported. When limiting the analysis to respondents, 10-year adherence becomes 70.3%, with patients shifting to CPAP (14.1%), and no treatment (15.6%). The study included a wide variety of patients ranging from ODI ≥ 20 to snoring patients with ODI < 5. The AHI was not used as a criterion and not reported; therefore, the study is informative for our patient population without being conclusive since the comparison with CPAP was ad-hoc. All responding patients that adhered to the MPD (n=38) reported loud and disturbing snoring at baseline, whereas 29.9% still reported loud snoring at the 10-year follow-up (n=11). The study with a follow-up of four months was set up to compare with placebo and used a rather nonrestrictive threshold of AHI < 30 [45] while the study over three months is a comparative study with a limited number of patients (n=16) comparing two MADs [33].

MAD design and movement facilities, mandibular advancement degree, and side effects

The AASM and AADSM guidelines indicate that OAs are devices mainly used for mandibular protrusion and stabilization to maintain a patent airway during sleep [1,49]. Moreover, there are OAs known as tongue retaining devices (TRDs) that hold the tongue forward and should be distinguished from other OAs. There remains insufficient evidence

on the efficacy of TRDs for treating OSA in adult patients. Therefore, we did not include studies on the use of TRDs for PS treatment.

There is currently no consensus on the optimal MAD design. The possible design choices include customized and non-customized monoblock and duoblock designs with facilities for implementing lateral movements and increasing protrusion, specifically, titrability. The AASM solely recommends the use of titratable custom-made devices since they appear to have better therapeutic outcomes in decreasing the AHI and ODI [48]. However, the AASM guidelines do not provide instructions on the specific modality choices for different clinical SBD categories.

In 2001, a study demonstrated that using adjustable MADs for protrusion reduced the obstructive events to AHI < 5 in 56.8% of the patients compared to 47.0% in patients on fixed appliances [59]. Consistent with these findings, another study reported that patients treated with a titratable duoblock MAD and a non-adjustable monoblock MAD showed a 50% and 46% reduction in the AHI, respectively [44]. However, these previous studies failed to highlight or compare specifications that can influence therapy outcomes, including the material choice (soft or hard acrylic), dental retention, volume, safety, and the protrusion system on the lateral or frontal MAD side for mandibular stabilization.

Consistent with our observations, MADs allow different movement types, including advancement and occasional supplementary lateral mandibular movements, in particular, "freedom of movement," to mitigate the side effects of MAD therapy [60].

Moreover, there is no consensus regarding the mandibular advancement degree: four studies used a titration level of 50% of the maximum protrusion [2,20,31,36]. One study opted for a titration level equal to 65% of the maximum protrusion [45]. Yet another study used two-thirds of the maximal protrusion and obtained a positive effect on the RDI, ESS, Functional Outcome Sleep Questionnaire, and the fatigue severity scale [33]. Two studies concluded that a higher protrusion (75%) was more effective for AHI reduction than a lower protrusion (50%) [51,61].

The lack of MAD treatment response could be attributed to the limitations imposed by an insufficient or excessive protrusion (latter: > 75% or maximum protrusion). One study stipulated that a rebound of the stretching capacity of the upper airway muscles can be observed when there is an extensive mandibular protrusion which can be a possible explanation for treatment failure [61].

When phenotyping OSAS patients, the impairment of the upper airway is one of the cardinal aspects causing OSAS. Osman et al. stated that the position of the abnormal dorsal collapse of the epiglottis, among several other pharyngeal structures, must be taken into consideration [62]. The collapse of the epiglottis in dorsal position in patients with adult laryngomalacia (LM) has been shown to cause CPAP and MAD treatment failures. However, this aspect is not investigated on admission [63] and, therefore, can be underdiagnosed. Congenital-related LM in adults can be sub-classified into three primary variants [63]:

1. Type 1: antero-medial prolapse or collapse of the bodies of the arytenoid cartilages over the laryngeal inlet.
2. Type 2: significantly reduced antero-posterior airway dimension by abnormally short aryepiglottic folds.
3. Type 3: an abnormal degree of posterior deflection of the epiglottis during inspiratory aerodynamics, which results in pronounced laryngeal lumen narrowing.

LM has also been described as acquired airway obstruction in adults induced by excessive, hypotensive, hyperactive, or floppy status of the supraglottic tissue [64,65]. Since LM could cause MAD treatment failure, anatomical observations using 2D and 3D imaging and/or awake/drug-induced nasolaryngoscopy, are imperative for locating the epiglottis when in normal dental occlusion as well as in maximal protrusion.

Only one study reported the different movements allowed by MADs. Specifically, they showed that duoblock MADs allow greater lateral movement than monoblock MADs [42]. This two-piece appliance has significantly less influence on tooth pain, occlusal function, and orofacial discomfort. Rhythmic masticatory muscle activity occurs during sleep. This natural nocturnal activity increases salivation, which lubricates the mouth [66]. The various movements allowed by these duoblock MADs provide space for the orofacial muscles to perform their physiological functions. Additionally, this phenomenon decreases side effects responsible for treatment discontinuation and reduced patient adherence. A blind randomized controlled study reported that specific mandibular exercises enable MAD usage in patients with temporomandibular disorder [67]. They found that these exercises effectively reduced pain compared to placebo therapy; moreover, they increased MAD compliance and significantly improved the quality of life and sleep in patients [67]. Only one study reported an association of the MAD type with a type D personality with respect to therapy compliance [44]. Compared to patients without type D personality, those with type D personality had a higher discontinuation rate and lower adherence to MAD therapy. There was no significant difference in the discontinuation reason. Patients with PS probably do not seek diagnosis and therapy due to a lack of medical need. Bedpartners and cohabitants are the main sources of incentive to undergo polysomnography due to the chronic social nuisance during “dyadic sleep” [68,69,70]. Treatment adherence could be lower due to a lack of self-motivation to continue MAD therapy. From a clinical perspective, the prevalence of PS is 20% among individuals undergoing multichannel polysomnography for snoring without additional complaints suggestive of SBD [71,72,73]. Therefore, it is likely that PS remains underdiagnosed.

There were no studies with dynamic mandibular repositioning devices in our selection. Remmers et al. (2015) only focused on the predicted treatment outcome with an MRA by using the MATRx system, which is classified as a remotely controlled mandibular positioner (RCMP) device. The aim is to predict an effective target protrusive position (ETPP) based on the AHI, the incidence of arousals associated with mandibular movement and dynamically adjust the protrusion. The effect on snoring was not investigated [74].

Regarding improved treatment compliance, there are some indications that the management of side effects is essential for maximizing treatment adherence and the clinical effectiveness of OAs for patients with OSA [60]. In this review, nine of the 18 studies reported side

effects of MAD treatment [2,20,31,35–38,43–45]. However, almost 50% of these studies reported that the side effects progressively disappeared spontaneously or with temporary assistance using medication, physiotherapy, or exercises. This was further confirmed by the recommendations for managing these side effects [60].

PS definition and Patients with PS

We aimed to evaluate the use of MAD in patients with PS. Therefore, it was necessary to clarify the characteristics of patients with PS. There is currently no universal definition of PS [3]. Moreover, a systematic review conducted in 2019 with respect to the definition of PS revealed that the included studies did not use an explicit or common PS definition. One study reported that the patients had no apnea or hypopnea events [2]. Given the lack of a study exclusively on patients with PS, we also considered studies on patients with OSAS and SBD with snoring symptoms. This procured indirect information for our specific research question.

Conclusions

Despite the limited information on MAD treatment of PS, currently available evidence indicates that MADs should be considered as a potential first-line treatment option for patients with PS. Moreover, there is evidence suggesting that treating PS can have social, medical, and economic benefits. There is a need for further research to evaluate efficacy, long-term effectiveness, and prediction at an individual level. To provide a basis for such individualization and increase and evaluate effectiveness, minimum standards for evaluation and monitoring should be developed based on a sound definition of PS. The effectiveness of MAD in PS is understudied in the literature, although positive signals are emitted.

Practical points and research agenda: advancement

Practical points

- The different terminologies for oral devices and their modes of action with or without mandibular movement possibilities makes it difficult for the practitioner to apply the findings reported in literature.
- Different methods have been used to indicate or define treatment success, including snoring assessments, AHI (OSAS severity), ODI, ESS (daytime somnolence), and the effect on cardiovascular function. Therefore, the practitioner has to be extra careful interpreting results while making decisions.

Research agenda

- Structured evaluation of efficacy assessment of mandibular advancement associated with the breathing mechanism of inspiration and expiration for PS. Investigation of the underlying causes, phenotyping, for example, the collapse of the epiglottis and its influence on obstructed breathing and influencing factors such as BMI and age.

- There is insufficient evidence indicating that OA treatment of PS improves other health-related outcomes other than snoring.
- Investigation of the necessary duration, advancement degree, frequency, and compliance for MAD treatment of PS and its effectiveness.
- Assessment of the association of the relationship [31], between the patient's snoring and the partner's wellbeing or other clinical parameters with the evaluation of outcome measures of MAD therapy in patients with PS.
- The information with respect to MAD design and individual morphology is limited. There is a need for more quantitative and qualitative studies that examine side effects and comfort related to MAD design and individual morphology of the patients.

Conflicts of interest: The authors have declared that no conflict of interest exists.

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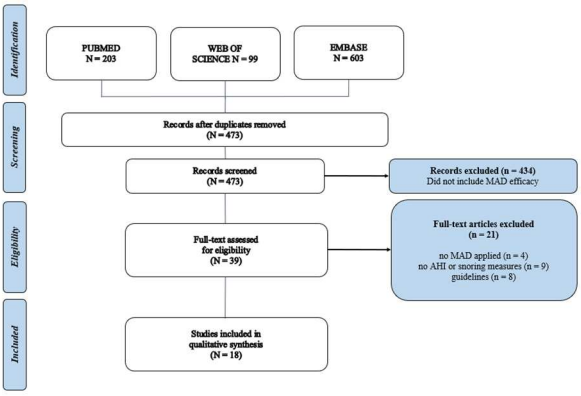

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