Subjective efficacy of oral appliance design features in the management of obstructive sleep apnea: A systematic review

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Introduction: The purpose of this study was to review available evidence on the efficacy of various oral appliances on subjectively perceived symptoms of obstructive sleep apnea syndrome. **Methods:** A search of 4 databases was carried out. Articles were initially selected based on their titles or abstracts. Full articles were then retrieved and further scrutinized according to predetermined criteria. Reference lists of selected articles were searched for any missed publications. The finally selected articles were methodologically evaluated. **Results:** Of an initial 1475 references, 14 studies were randomized controlled trials, which formed the basis of this review. Mandibular advancement devices (MADs) were compared with either inactive appliances (6 studies) or MADs with different design features (8 studies). In comparison with inactive appliances, the majority of studies showed improved subjective outcomes with MADs, suggesting that mandibular advancement is a crucial design feature of oral appliance therapy for obstructive sleep apnea syndrome. **Conclusions:** There is no 1 MAD design that most effectively influences subjectively perceived treatment efficacy, but efficacy depends on many factors including materials and method used for fabrication, type of MAD (monoblock or Twin-block), and the degree of protrusion (sagittal and vertical). This review highlights the absence of universally agreed subjective assessment tools and health-related quality of life outcomes in the literature today. Future trials of MAD designs need to assess subjective efficacy with agreed standardized tools and health-related quality of life measures to guide clinical practicitioners about which design might be most effective in the treatment of obstructive sleep apnea syndrome with oral appliances. (Am J Orthod Dentofacial Orthop 2010;138:559-76)

Obstructive sleep apnea syndrome (OSAS) is the most common organic sleep disorder and is increasingly recognized as a serious public health issue.[1] Its prevalence worldwide is estimated at 3% to 7% in men and 2% to 5% in women.[2-4] Apart from having serious consequences for a patient's physiologic health, untreated OSAS causes particular morbidity in terms of the health-related quality of life (HRQL) a patient experiences.[5-7] The inability to sleep sufficiently at night causes excessive daytime somnolence, which impacts the ability to function at an optimum level, can lead to depression, contributes to traffic accidents, and disrupts social relationships.[7-9]

The latest Cochrane review on oral appliances (OAs) for OSAS highlighted that they are increasingly recognized as a suitable and effective treatment option.[10] Mandibular advancement devices (MADs) are the most commonly prescribed OAs in the treatment of OSAS. Although MADs are more effective than other types of OAs in treating OSAS,[11] it has been suggested that design features of the various appliances can have an impact on treatment efficacy.[12] The Cochrane review detailed some evidence that MADs improve subjective sleepiness compared with placebo appliances.[10] A review by Ahrens et al[13] evaluated the efficacy of various MAD designs on patients' objective polysomnographic outcomes; however, it is unclear how the different design features of the various MADs impact patients' subjective evaluations of treatment effect. Understanding whether a type or design of MAD is most effective in the subjective treatment of OSAS is imperative in informing patient-centered evidence-based practice. Therefore, in this review, we aimed to summarize the evidence on the efficacy of differently designed

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MADs on the subjective patient-centered outcome measures of OSAS.

MATERIAL AND METHODS

To identify studies relevant to OA treatment for OSAS, a computerized database search was carried out by using MEDLINE, EMBASE, Cinahl, and the Cochrane Library (Table I). No language limitations were set, and the search was limited to human studies. If articles contained the search thesaurus anywhere, they were selected to constitute a list of potentially eligible studies to be included in this review.

Titles and abstracts of study references on this list were reviewed by 2 independent researchers, who then determined whether they were relevant to the theme of this review: studies exclusively focusing on OA therapy for OSAS treatment (Fig). If the researchers disagreed about which articles were relevant, consensus was reached by discussion. To select articles that lent themselves to assessing the impact of appliance design on subjective treatment efficacy, 3 inclusion criteria were set. Only studies that investigated MAD vs other OA, MAD vs inactive OA, or the same MAD but with varying degrees of mandibular advancement or vertical bite opening were selected to remain on the list of potential studies for this review. The full texts of these studies were then obtained, and the reference lists were searched manually for additional relevant publications (reference linkage). All studies were methodologically appraised according to the American Association of Sleep Medicine's levels of evidence (Table II) to identify "effective" articles.[14]

Table I. Electronic search strategy

Obstructive sleep apnoea syndrome part	
1	Obstructive sleep apnea (MeSH word)
2	Obstructive sleep (apnoea or apnea)
3	Sleep (breathing disorder* or respiratory disorder*)
4	1 OR 2 OR 3
Oral appliance part	
5	Orthodontic appliances (MeSH word)
6	Oral (device* or appliance* or splint)
7	Dental (device* or appliance* or splint)
8	Orthodontic* (device* or appliance* or splint)
9	Mandib* advancement*
Final search syntax	
10	4 AND (5 or 6 or 7 or 8 or 9)

MeSH, thesaurus word.
*Truncation of a text word.

RESULTS

Initially, 1475 references (Fig) were retrieved from the primary database searches; among them, there were 470 duplicate references. An additional 467 references were excluded because they were not relevant for this review. Of the remaining 538 study references, a further 341 were excluded because they did not meet the criteria for inclusion (Fig). Full texts of the remaining 197 references were obtained, and an additional 3 articles were identified as potentially relevant by reference linkage. Among these 200 studies, 6 could be categorized as evidence level I, and 8 studies as level II of evidence. Fifty-nine studies reached evidence level III; 3 studies, level IV; and 124 studies, level V. Based on this classification of evidence, the 14 levels I and II randomized controlled trials were finally selected as the basis of this review. These studies were grouped according to the following outcome measures: (1) MAD vs inactive control OA, (2) studies comparing 1-piece MADs with 1-piece MADs, (3) studies comparing 2-piece MADs with 2-piece MADs, and (4) studies comparing 1-piece MADs with 2-piece MADs.

To assess patients' subjective daytime sleepiness, all but 2 studies used the standardized and disease-specific Epworth sleepiness scale (ESS).[15,16] To pool the data, 2 studies had to be excluded because only median values were reported.[17,18] The ESS scores across the remaining 12 studies improved with the use of MADs and showed a mean reduction from 12.0 to 7.9. Gauthier et al[19] used a fatigue severity scale,[20] and Bloch et al[17] used the sleep disorder questionnaire[21] and a modified version of a sleep symptom questionnaire.[22]

Four trials assessed patients' HRQL by standardized tools.[18,19,23,24] These were either generic—the medical outcome survey short form (SF-36)—or sleep-specific—the functional outcomes of sleep questionnaire (FOSQ). One study used both assessment tools.[23]

Subjective treatment efficacy was assessed by nonstandardized (in-house) questionnaires or a visual analog scale (VAS) by 6 studies.[9,15-17,25,26] Treatment compliance, treatment satisfaction, appliance preference, side effects, snoring, and sleep quality were generally self-reported by questionnaire. Across all studies, symptoms were reported to be mild to moderate and temporary, with temporomandibular joint pain, muscular, dental and gingival discomfort, dry mouth, and excessive salivation as the most common. Treatment compliance was generally high (dropout rates, 0%-26%). Average usage of individual appliances could not be calculated because this was reported differently across the reviewed studies, with some reporting nightly usage per week and others hourly usage per night. The studies' durations ranged from 2 weeks to 12 months, and the sample sizes of the target study populations varied considerably from 16 to 93 subjects, but most studies specified a sample size between 20 and 30 (Tables III and VI).

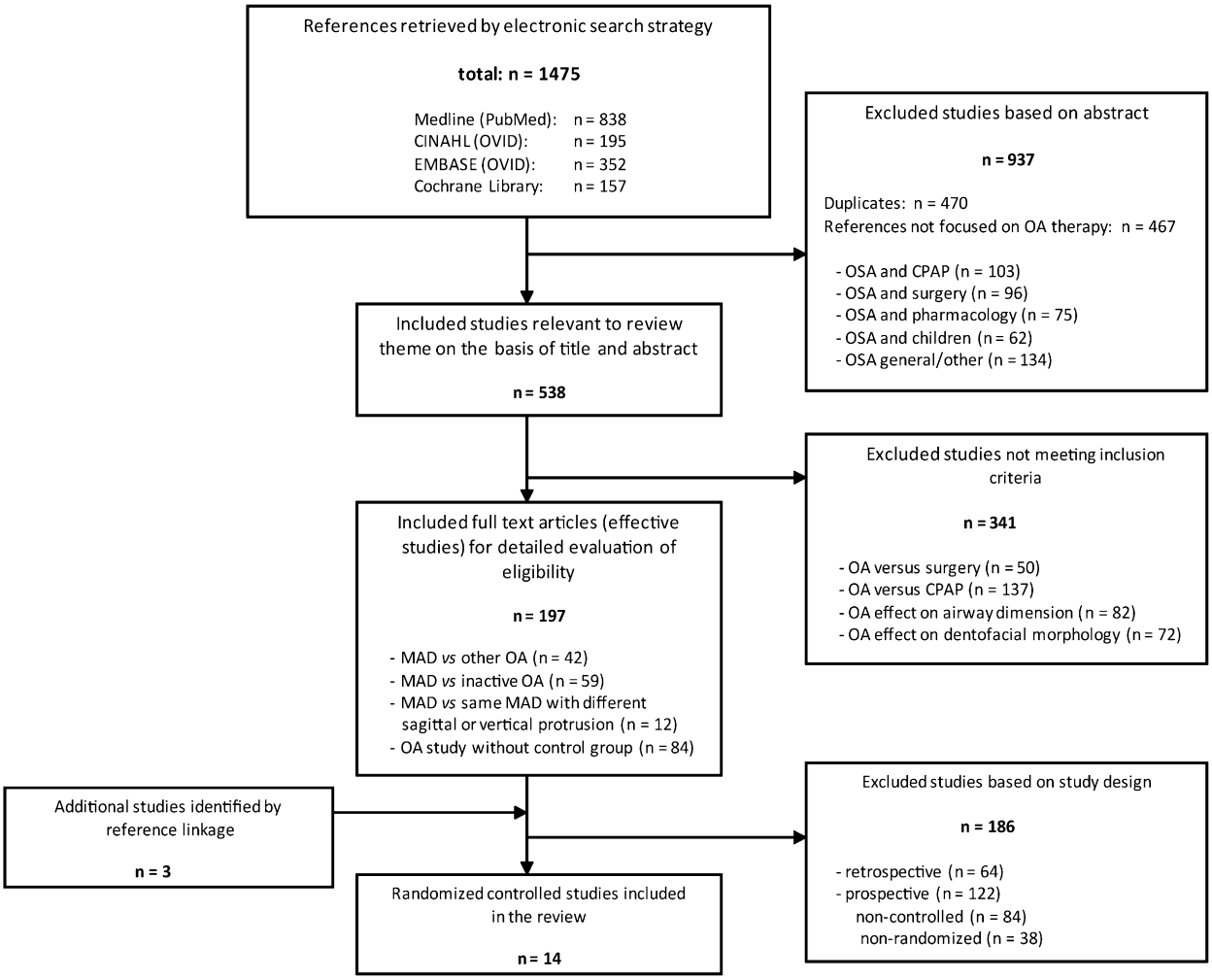

Fig. Flow diagram of study selection procedure. *OA*, Oral appliance; *OSAS*, obstructive sleep apnea syndrome; *CPAP*, continuous positive airway pressure.

Table II. American Association of Sleep Medicine classification of evidence

Evidence level	*Study design*
I	Randomized well-designed trials with low alpha and beta error*
II	Randomized trials with high alpha and beta error*
III	Nonrandomized concurrently controlled studies
IV	Nonrandomized historically controlled studies
V	Case series

Adapted from Sackett.[14]

*Alpha (type I error) refers to the probability that the null hypothesis is rejected when in fact it is true (generally acceptable at 5% or less, or $P < 0.05$). Beta (type II error) refers to the probability that the null hypothesis is mistakenly accepted when in fact it is false (generally trials accept a beta error of 0.20). The estimation of type II error is generally the result of a power analysis. The power analysis takes into account the variability and the effect size to determine whether the sample size is adequate to find a difference in means when it is present (power is generally acceptable at 80%-90%).

Six studies compared a MAD with inactive control appliances (designed not to advance the mandible) (Table III).[9,24,27-29] Although all studies reported improvement in ESS scores for both appliance groups, 4 found the improvement to be significant for the MAD ($P < 0.001$-$P < 0.05$).[23,24,27,28] Two studies comparing MADs with inactive control appliances assessed HRQL with the same tool but showed different results: whereas MAD treatment had a significant effect on the vitality domain of the generic SF-36 ($P < 0.001$) in 1 study,[24] Blanco et al[23] found no significant difference in mean SF-36 scores for MAD or the inactive appliance group. However, they reported significantly improved scores ($P < 0.05$) for the MAD group in the sleep-specific FOSQ assessment.[23] Nine patients (60%) preferred the MAD because it was perceived to be more effective, and easier

Table III. Studies comparing MADs with inactive oral appliances: patient-centered and subjective outcomes

Author	Patients (n)		Oral appliance (OA)	Advancement		Assessment tool used		Result		Statistical significance	Subjective treatment satisfaction
	Baseline	Complete		Sagittal	Vertical			Pretreatment	Posttreatment		
Blanco et al[23]	24	15	A: MAD (1-piece soft elastic silicone positioner)	75% of maximum protrusion	5 mm	ESS	MAD	14.7 ± 5.1	5.1 ± 1.9	P <0.05	Not reported
							Inactive OA	16.3 ± 2.5	13.6 ± 6.7	NS	
			B: inactive OA	–	–	SF-36					
						Physical functioning	MAD	70.7 (16.4)	74.1 (18.4)	NS	
							Inactive OA	71.5 (20.7)	78.8 (19.1)	NS	
						Role physiological	MAD	83.4 (30.2)	87.5 (30.6)	NS	
							Inactive OA	81.2 (34.7)	87.5 (35.6)	NS	
						Role emotional	MAD	81.0 (37.7)	77.7 (46.6)	NS	
							Inactive OA	80.0 (29.9)	87.5 (12.5)	NS	
						Social functioning	MAD:	78.3 (13.6)	78.2 (12.4)	NS	
							Inactive OA	81.3 (18.8)	79.4 (26.9)	NS	
						Mental health	MAD	60.1 (19.3)	59.4 (19.2)	NS	
							Inactive OA	52.0 (15.7)	56.0 (18.0)	NS	
						Energy	MAD	49.3 (18.8)	50.7 (8.4)	NS	
							Inactive OA	55.2 (12.2)	56.2 (19.2)	NS	
						Bodily pain	MAD	70.3 (38.7)	67.0 (21.3)	NS	
							Inactive OA	65.3 (37.4)	65.5 (19.2)	NS	
						General health perception	MAD	60.7 (22.0)	61.0 (20.7)	NS	
							Inactive OA	57.4 (6.8)	58.4 (10.5)	NS	
						FOSQ	MAD	78.1 (22.6)	99.3 (14.4)	P <0.05	
							Inactive OA	83.7 (20.8)	82.3 (13.9)	NS	
						General sleep questionnaire: snoring levels	MAD	15.4 ±1.9	10.1 ± 3.2	P <0.05	
							Inactive OA	14.4 ± 3.0	14.6 ± 1.7	NS	
Gotsopoulos et al[27]	73	73	A: MAD (custom-made 2-piece)	Mean 80% ± 9% (range, 50%-95%) of maximum protrusion mean 7 ± 2 mm (range, 3-13 mm)	3-4 mm	ESS	MAD	11 ± 5	7 ± 1	MAD vs inactive:	MAD produced normal ESS in 60 (82%) patients compared with 45 (62%) on inactive treatment (P <0.01)
							Inactive OA		9 ± 1	P <0.001	

Table III. Continued

Author	Patients (n)		Oral appliance (OA)	Advancement		Assessment tool used		Result		Statistical significance	Subjective treatment satisfaction
	Baseline	Complete		Sagittal	Vertical			Pretreatment	Posttreatment		
			B: inactive OA	–	–	Symptom questionnaire:					
						Snoring frequency	MAD	Not reported	207 ± 20	MAD vs inactive:	Treatment with MAD
							Inactive OA	Not reported	366 ± 21	P <0.001	was significantly
						Snoring loudness	MAD	Not reported	48 ± 1	MAD vs inactive:	more satisfactory
							Inactive OA	Not reported	51 ± 1	P <0.001	(P <0.001)
						Improved sleep quality	MAD	Not reported	Not reported	MAD vs inactive:	
							Inactive OA	Not reported	Not reported	P <0.001	
Hans et al[29]	24	18	A: MAD (commercial thermoplastic 1-piece SnoreGuard)	6-8 mm	8 mm	ESS	MAD	12.0 ± 3.9	8.2 ± 4.0	P <0.033	Not reported
			B: inactive OA	–	1 mm		Inactive OA	13.0 ± 4.5	12.5 ± 5.7	NS MAD vs inactive: NS	
Johnston et al[9]	21	20	A: MAD (customized 1-piece)	75% of maximum protrusion mean, 5.7 mm (range, 4-9 mm)	4 mm inter-incisal	ESS	MAD	13.90 ± 6.39	11.6 ± 6.7	MAD vs inactive:	MAD produced posttreatment
							Inactive OA		12.6 ± 6.3	NS	ESS of ≤10/h in 45% of patients; however, 60% of those showed ESS of ≤10/h
			B: inactive OA	–	1.5 mm	Sleep questionnaire	MAD	Not reported	2.58 ± 1.26	MAD vs inactive:	at baseline
							Inactive OA	Not reported	3.16 ± 1.38	NS	
Mehta et al[28]	28	24	A: MAD (custom-made 2-piece)	Mean, 78% (range, 63%-89%) maximum protrusion mean, 7.5 ± 1.8 mm (range, 5-11.5 mm)	Not reported	ESS	MAD	10.1 ± 1.1	3.9 ± 0.6	Posttreatment vs pretreatment: P <0.01	Majority of patients reported substantial improvements in snoring (n =17, 70%) and sleep quality (n = 22, 91%)
							Inactive OA		Not reported		

Table III. Continued

Author	Patients (n)		Oral appliance (OA)	Advancement		Assessment tool used		Result		Statistical significance	Subjective treatment satisfaction
	Baseline	Complete		Sagittal	Vertical			Pretreatment	Posttreatment		
			B: inactive OA	–	–	Questionnaire: Snoring, sleep quality	MAD	Not reported	Not reported	Not reported	
							Inactive OA	Not reported	Not reported	Not reported	
Petri et al[24]	93	81	A: MAD (custom-made 1-piece acrylic)	Mean protrusion, 74% (range, 64%-85%)	5 mm in front	ESS				Posttreatment vs pretreatment:	Not reported
							MAD	11.7 ± 4.3	8.4 ± 4.3	$P < 0.001$	
							Inactive OA	10.8 ± 4.6	9.6 ± 4.2	$P = 0.05$	
							No intervention	10.7 ± 4.6	10 ± 4.8	NS	
							MAD		8.4 ± 4.3	Difference in means between groups: 0.044†	
							Inactive OA		9.6 ± 4.3		
							No intervention		10.0 ± 4.8		
			B: inactive OA	–	Not reported	SF-36:				Posttreatment vs pretreatment:	
						MCS*	MAD	47.2 ± 8.5	51.1 ± 8.0	$P = 0.039$	
							Inactive OA	48.8 ± 10.0	49.8 ± 8.5	NS	
							No intervention	50.2 ± 8.9	51.2 ± 7.8	NS	
			C: no intervention	–	–	PCS*	MAD	45.5 ± 9.5	46.5 ± 8.0	NS	
							Inactive OA	48.1 ± 9.2	47.5 ± 11.2	NS	
							No intervention	46.6 ± 9.6	47.3 ± 8.7	NS	
						General health*	MAD	60.7 ± 21.9	66.7 ± 20.8	$P = 0.011$	
							Inactive OA	66.6 ± 22.1	66.0 ± 22.1	NS	
							No intervention	62.7 ± 19.8	67.0 ± 19.5	NS	
						Mental health*	MAD	71.0 ± 14.7	76.4 ± 13.8	$P = 0.016$	
							Inactive OA	78.4 ± 19.5	80.4 ± 12.9	NS	
							No intervention	79.6 ± 15.2	79.0 ± 15.4	NS	
						Vitality*	MAD	41.5 ± 23.4	59.4 ± 24.7	$P < 0.001$	
							Inactive OA	47.8 ± 26.7	47.0 ± 26.4	NS	
							No intervention	48.1 ± 24.3	51.3 ± 23.4	NS	
							MAD		59.4 ± 24.7	Difference in means between groups: 0.001†	
							Inactive OA		47.0 ± 26.4		
							No intervention		51.3 ± 23.4		

NS, Not significant; *SF-36*, medical outcome survey short form; *FOSQ*, functional outcomes of sleep questionnaire; *ESS*, Epworth sleepiness scale.
*Mental component summary (*MCS*) and physical component summary (*PCS*) and 3 domains, general health, mental health and vitality in SF-36; †Only vitality domain and ESS score differed significantly between intervention groups, with means in MAD group significantly different from means in inactive OA and no intervention groups (means of latter 2 groups did not differ significantly).

to clean and handle. Six patients (40%) preferred the control appliance. Nonstandardized in-house questionnaires used to assess subjective treatment efficacy found significant improvements in patients' sleep quality and snoring (P <0.001) when using the MAD.[27,28] The majority of patients perceived the MAD to be more effective in treating symptoms of OSAS and preferred it to the inactive appliance.[27-29] One study (a crossover trial) did not report patient preference for either appliance.[9] Side effects with the MAD were more common than with the inactive OA but were mostly mild and did not preclude continued use of the MAD (Table VII) .[9,27-29]

Three studies compared 1-piece MADs with 1-piece MADs (Table IV).[15,25,26] Of those, 2 studies compared 50% (group 50) to 75% (group 75) of maximum mandibular protrusion in identical 1-piece MADs.[15,25] The third study compared a custom-made MAD with a commercial MAD.[26] By using the same nonstandardized in-house questionnaire, both studies found daytime sleepiness improved in both protrusion groups with a greater improvement in group 75 (n = 42, 54%) than in group 50 (n = 33, 5%).[25] Sleepiness assessed by the ESS was significantly (P <0.001) improved by both MADs, but with no difference between the groups in 1 study,[25] but another showed no improvement for either MAD.[26] Problems with apneas improved and snoring improved significantly with both MADs (P <0.01), but with significantly greater improvement for the custom-made MAD (P <0.05)[26] and the MAD with the greater degree (75%) of protrusion (59 [77%] vs 48 patients [62%]).[25] Interestingly, in the study by Tegelberg et al,[15] this was reversed: more patients reported improvement in apneas and snoring while using the MAD with the smaller degree (50%) of protrusion (48 [87%] vs 43 patients [79%] in group 75). The difference was, however, not significant. Few side effects were reported for any type of MAD, and nearly all patients (n = 69; 90%) were satisfied with their treatment.[25] Vanderveken et al[26] found that more patients were unable to continue (compliance failure) with the thermoplastic MAD than with the custom-made MAD (n = 11 [31%] vs n = 2 [6%]), and more patients (n = 32; 92%) reported using the custom-made MAD more frequently than the thermoplastic MAD (n = 22; 64%). Nineteen (82%) patients preferred the custom-made MAD (Table VII).[26]

All 3 studies comparing 2-piece MADs with 2-piece MADs (Table V) reported improvements in ESS scores for both types of MADs but with no significant difference between them.[18,19,30] Gauthier et al[19] and Lawton et al[18] also found no difference between MADs in improved HRQL scores (FOSQ and SF-36, respectively). The VAS or in-house questionnaire assessing frequency and symptoms of sleepiness showed no difference between the 2 MAD groups in 1 study,[19] but scores were significantly improved (P <0.05) in favor of the Herbst MAD in another study.[18] Snoring was not statistically different between the 2 MADs in that study. Although no side effects were reported for either MAD, patients preferred the Klearway MAD (n = 9; 56%) to the Silencer MAD (n = 6; 38%) because of its significantly more comfortable fit (P <0.05).[19] In a study with common side effects for both MADs (Herbst MAD, temporomandibular joint problems and abnormal bite; Twin-block MAD, dry mouth), 9 (56%) of 16 patients preferred the Herbst MAD (Table VII).[18] Pitsis et al[30] investigated the effect of different vertical openings (4 and 14 mm) in 2 otherwise identical 2-piece MADs. Sleep quality and improvement in snoring did not differ between the MADs, nor did severity, frequency, and duration of side effects or compliance. Significantly more patients preferred the MAD with the smaller (4 mm) vertical opening (P = 0.007).

Two studies compared 1-piece MADs with 2-piece MADs (Table VI).[16,17] Bloch et al[17] found that, although both MAD groups showed significantly improved ESS scores compared with the no-treatment group (P <0.05), no difference was found between the 2 MADs. All aspects of daytime performance improved in both MAD groups compared with the no-treatment group. Although side effects were reported equally for both MADs, 15 patients (63%) indicated a preference for the monobloc because it was perceived to be superior in relieving the symptoms of OSAS, and it is a simpler and more robust device. Eight (33%) patients had no preference. Rose et al[16] compared a 2-piece soft polyethylene Silencor MAD with an acrylic 1-piece Karwetzky MAD. Both MADs had a mandibular protrusion of 75%, but different vertical openings (5 and 11-12 mm, respectively). Both MADs improved daytime sleepiness, quality of sleep, and snoring, but no statistical details were given in the article. No difference was found in patients' subjective relief of symptoms between the 2 MADs. Side effects were more commonly reported with the Karwetzky MAD, and 2 patients withdrew because of them. However, more patients preferred it to the Silencor MAD (Table VII).

DISCUSSION

Over the last 10 years, increasing numbers of studies have investigated the efficacy of MADs as a treatment option for OSAS (Fig). The included studies (effective articles) in this review were all randomized controlled

Table IV. Studies comparing 1-piece MADs with 1-piece MADs: patient-centered and subjective outcomes

Author	*Patients (n)*		*Oral appliance (OA)*	*Advancement*	
	Baseline	*Complete*		*Sagittal*	*Vertical*
Tegelberg et al[15]	74	55	A: MAD (1 piece)	50% of maximum protrusion mean, 4.5 ± 0.93 mm	Not reported
			B: MAD (1 piece)	75% of maximum protrusion mean, 6.4 ± 1.16 mm	Not reported
Vanderveken et al[26]	38	35	A: MAD (custom-made monobloc)	65% ± 10% of maximum protrusion	Not reported
			B: MAD (thermoplastic Somnoguard Plus monobloc)	50% ± 20% of maximum protrusion	Not reported
Walker-Engström et al[25]	86	77	A: MAD (1 piece)	A: 50% of maximum protrusion mean, 5 mm (4.8-5.3)	2 mm
			B: MAD (1 piece)	B: 75% of maximum protrusion mean, 7.2 mm (6.7-7.6)	2 mm

NS, Not significant; *VAS,* visual analog scale of patient self-evaluation of MAD efficacy; *ESS*, Epworth sleepiness scale.

trials, and most used a crossover study design, which allows for within-subject comparisons. Few studies were long-term follow-ups. The reviewed studies varied greatly in duration from as little as 2 weeks to a maximum of 12 months; however, OSAS is a chronic and often life-long condition. Thus, there is a need for long-term studies to assess patient compliance, reasons for discontinuation, subjectively perceived efficacy, and preference in a time frame that reflects the nature of this condition.

The studies included in this systematic review used several tools to assess the subjective treatment efficacy of MADs. Most studies used the standardized and disease-specific ESS and showed statistically significant improvements in subjective daytime sleepiness with MAD treatment. Therefore, MADs can be deemed effective in improving subjective daytime sleepiness in patients with OSAS.

There was little consistency with other subjective tools to assess patients' perceptions of the efficacy of treatment and the impact on HRQL. Johal[31] reported that few articles include quality-of-life outcome measures when investigating OA efficacy in OSAS treatment. This review supported these findings, since the methods of subjective treatment efficacy assessments varied in nearly every investigation, and only 4 studies[18,19,23,24] used standardized HRQL assessment methods, 2 of which were sleep-specific.[19,23] The study by Blanco et al[23] was the only trial that used both a sleep-specific and a generic tool (FOSQ and SF-36). The results showed that only the FOSQ was significantly improved by MAD treatment. Although the SF-36 has been shown to be a reliable and valid instrument for measuring HRQL, it has been suggested that the impact of OSAS and the benefit of treatment on

Table IV. Continued

Assessment tool used		*Result*		*Statistical significance*	*Subjective treatment satisfaction*
		Pretreatment	*Posttreatment*		
Questionnaire: Daytime sleepiness, apneas, and snoring	MAD A MAD B	Not reported Not reported	Not reported Not reported	Not reported Not reported	Daytime sleepiness decrease MAD A: 45 (82%) MAD B: 46 (84%) Decrease in apneas and snoring MAD A: 48 (87%) MAD B: 43 (79%)
VAS snoring	MAD A	8 ± 2	2 ± 3	P <0.01	Satisfactory reduction in snoring MAD A: 23 (80%) MAD B: 18 (51%)
	MAD B	8 ± 2	4 ± 3	P <0.01	
ESS	MAD A	7 ± 5	5 ± 4	NS	
	MAD B	7 ± 5	6 ± 4	NS	
ESS	MAD A	11.7 ± 3.1	8.6 ± 2.8	P <0.001	
	MAD B	11.5 ± 3.1	7.5 ± 2.6	P <0.001	
Questionnaire: Daytime sleepiness, apneas and snoring				MAD A vs MAD B: NS	Satisfaction with MAD A: 69 (90%) patients at 6-mo follow-up were satisfied or very satisfied; 7 (9%) neither satisfied nor dissatisfied Large decrease in daytime sleepiness: MAD A: 33 (43%) MAD B: 42 (54%) Decrease in apneas and snoring: MAD A: 48 (62%) MAD B: 59 (77%)

HRQL might be more likely to be shown with disease-specific measures.[32,33]

The results of studies comparing MADs with inactive appliances show that MADs are significantly better at improving the subjective daytime sleepiness (ESS score). This suggests that mandibular advancement is a key design feature in the efficacy of MADs to reduce subjective daytime sleepiness. Two studies reported no difference between MADs and inactive control appliances in improving ESS scores.[9,29] This finding suggests that studies comparing an active treatment to an inactive (sometimes called placebo appliance) treatment can demonstrate a significant placebo effect, and results of such studies must be interpreted with this in mind.[34] Although inactive appliances are designed to keep changes to the sagittal and vertical opening to a minimum, they inevitably introduce slight changes because of the thickness of the material.

The evidence about whether various degrees of mandibular protrusion influence subjective treatment efficacy is conflicting. The 2 studies investigating this found opposing results: greater improvement of daytime sleepiness and symptom relief with greater mandibular protrusion in 1 study,[25] and similar daytime sleepiness improvement in both protrusion groups, but greater symptom relief with less mandibular protrusion.[15] Therefore, it is important for the clinician to acknowledge that the optimum amount of advancement might not necessarily be the maximum achievable degree of protrusion for all OSAS patients. Subjective outcomes showed no difference between the amounts of vertical opening and therefore do not seem to have an impact on treatment efficacy.[30] However, because

Table V. Studies comparing 2-piece MADs with 2-piece MADs: patient-centered and subjective outcomes

	Patients (n)			*Advancement*	
Author	*Baseline*	*Complete*	*Oral appliance (OA)*	*Sagittal*	*Vertical*
Gauthier et al[19]	23	16	A: MAD (commercial two-piece Silencer)	50% of max protrusion average 10.5 mm	9-12 mm
			B: MAD (commercial two-piece Klearway)	66% of max protrusion average 12.5 mm	9-12 mm
Lawton et al[18]	16	16	A: MAD (twinbloc)	Not reported	Not reported
			B: MAD (Herbst)	Not reported	Not reported
Pitsis et al[30]	24	23	A: MAD (two-piece)	87 ± 4% of max protrusion mean 7.3 ± 0.5 mm	4 mm
			B: MAD (two-piece)	87 ± 4% of max protrusion mean 7.3 ± 0.5 mm	14 mm

NS, Not significant; *VAS*, visual analog scale of patient self-evaluation of MAD efficacy; *SF-36*, medical outcome survey short form; *FOSQ,* functional outcomes of sleep questionnaire; *ESS*, Epworth sleepiness scale; *FSS*, fatigue severity scale.
*Median (range) values reported.

patient preference was indicated for the MAD with the smaller opening, it can be suggested to keep MAD's vertical opening small.

The various MAD design features generally did not significantly influence symptom severity, frequency, or duration in the reviewed studies. Almost every study detailed the side effects that patients reported after wearing MADs. These were mainly temporary and mild to moderate. Although side effects were more commonly reported with MADs, patients generally preferred them to inactive control appliances and continued to use the MAD despite experiencing these side effects. The main reasons reported for choosing 1 MAD over another were greater comfort, ease of use, perception of better symptom relief, and robustness of the device. Therefore, a range of MAD design features could influence patient preference and, ultimately, treatment efficacy, since patients might chose to discontinue using the appliance.

Hoffstein[35] suggested that subjective treatment efficacy depends on the type of appliance used and the degree of protrusion. Our review could confirm this finding only partially: although mandibular protrusion has been found to be a crucial design feature of MADs in the subjective improvement of daytime sleepiness and HRQL, no definite conclusion can be drawn regarding the type of MAD. It is as yet unclear which type of MAD will bring about the desired subjective treatment effect for patients with OSAS, and further research directly comparing different appliances and different designs is needed to shed light on this issue. The most effective MAD appears to be the one that is most acceptable to the patient and meets the criteria for treatment success at the same time. This highlights the role of a trained dental practitioner in the treatment of OSAS, because MADs need to be chosen on an individual basis and regularly supervised to achieve the desired efficacy.

CONCLUSIONS

This systematic review identified 14 high-quality trials comparing MADs of various designs with inactive control appliances or control MADs with different design features as treatment options for OSAS. Although the ESS is a widely used tool to assess subjective daytime sleepiness, other areas of subjectively perceived treatment efficacy show great variability in how they are assessed. There is a particular paucity of

Table V. Continued

Assessment tool used		Result		Statistical significance	Subjective treatment satisfaction
		Pretreatment	Postreatment		
ESS	MAD A	13.9 ± 1.3	9.9 ± 1.3	$P \leq 0.01$	Subjects and sleep partners reported that both MADs significantly reduced snoring frequency, choking, cessation of breathing, number of arousals, daytime sleepiness, frequency of morning headaches, daytime aggressive or irritable reactions and decreased libido ($P < 0.05$ to 0.001).
	MAD B	13.9 ± 1.3	9.3 ± 1.2	$P \leq 0.001$	
				MAD vs MAD: NS	
FOSQ	MAD A	13.8 ± 0.7	16.8 ± 0.6	$P \leq 0.001$	
	MAD B		17.2 ± 0.5	$P \leq 0.001$	
				MAD vs MAD: NS	
VAS	MAD A	Not reported	6.5 ± 0.5	MAD vs MAD: NS	
	MAD B	Not reported	7.4 ± 0.4		
FSS	MAD A	45.4 ± 2.7	39.0 ± 2.6	NS	Cessation of breathing and perception of choking showed greater reduction with Silencer than Klearway ($P < 0.05$).
	MAD B		39.4 ± 3.6	NS	
ESS	MAD A	10 (2-18)*	8.5 (3-17)*	MAD A vs MAD B: NS	Not reported
	MAD B	10 (2-18)*	8.0 (4-18)*		
SF-36				All categories ns	
VAS: daytime sleepiness	MAD A	3 (1-4)*	2.5 (1-4)*	MAD A vs MAD B: $P = 0.04$	MAD B less sleepy than MAD A
	MAD B	3 (1-4)*	2.0 (1-4)*		
VAS: snoring	MAD A	4.0 (3.0-4.0)*	4.0 (2.0-4.0)*	MAD A vs MAD B: NS	
	MAD B	4.0 (3.0-4.0)*	3.5 (1.0-4.0)*		
ESS	MAD A	18 ± 1	12 ± 1	$P < 0.001$	Not reported
	MAD B	18 ± 1	12 ± 1	$P < 0.001$	

quality-of-life assessments in the field. In comparison with inactive control appliances, MADs generally were successful in improving subjective daytime sleepiness; this suggests that mandibular advancement is crucial in establishing efficacy. However, attention must be paid to a possible placebo effect when interpreting the results of such studies. No definite conclusions can be drawn regarding which type or design of MAD has a beneficial influence on subjective treatment efficacy, and more research is needed to investigate how different design features might affect this outcome. There is no "one for all" MAD—the choice of which MAD is best in improving subjectively perceived OSAS symptoms depends on a variety of factors ranging from materials used for fabrication and method of fabrication, and design features to individually determined sagittal and vertical protrusion.

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Table VI. Studies comparing 1-piece MADs with 2-piece MADs: patient-centered and subjective outcomes

Author	*Patients (n)*		*Oral appliance (OA)*	*Advancement*	
	Baseline	*Complete*		*Sagittal*	*Vertical*
Bloch et al[17]	24	24	A: MAD (monobloc)	75% of maximum protrusion mean, 10 ± 0.4 mm	5-10 mm
			B: MAD (Herbst)	75% of maximum protrusion mean, 10 ± 0.4 mm	4-6 mm range of opening, >15 mm
			C: no treatment	–	–
Rose et al[16]	26	16	A: MAD (2-piece soft polyethylene Silencor)	75% maximum protrusion	5 mm
			B: MAD (acrylic 1-piece Karwetzky)	75% maximum protrusion	10-12 mm

NS, Not significant; *VAS,* visual analog scale of patient self-evaluation of MAD efficacy; *ESS*, Epworth sleepiness scale.
*Median (range) values reported.

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Table VI. Continued

Assessment tool used		Result		Statistical significance	Subjective treatment satisfaction
		Pretreatment	Posttreatment		
ESS	MAD A	9.0*	(6.5-10)*	MAD A vs no treatment: P <0.001	Not reported
	MAD B	9.0*	(6.5-11)*	MAD B vs no treatment: P <0.001	
	No treatment	13.5*	(9.5-16)*	MAD B vs MAD A: NS	
Sleep symptoms questionnaire:					
Interference with daily tasks	MAD A	1.5*	(1.0-2.0)*	MAD A vs no treatment: P <0.001	
	MAD B	2.0*	(1.0-3.0)*	MAD B vs no treatment: P <0.03	
	No treatment	3.5*	(2.5-4.0)*	MAD B vs MAD A: P <0.05	
Perform ability	MAD A	2.0*	(1.0-2.0)*	MAD A vs no treatment: P <0.001	
	MAD B	2.0*	(2.0-3.5)*	MAD B vs no treatment: P <0.03	
	No treatment	3.0*	(2.0-4.0)*	MAD B vs MAD A: P <0.05	
Energy level	MAD A	2.0*	(2.0-3.0)*	MAD A vs no treatment: P <0.001	
	MAD B	2.0*	(2.0-3.0)*	MAD B vs no treatment: P <0.03	
	No treatment	3.0*	(2.5-4.0)*	MAD A vs MAD B: NS	
Snoring frequency	MAD A	2.0*	(1.0-3.0)*	MAD A vs no treatment: P <0.001	
	MAD B	2.0*	(1.0-3.5)*	MAD B vs no treatment: P <0.001	
	No treatment	4.0*	(4.0-4.0)*	MAD A vs MAD B: NS	
Snoring loudness	MAD A	1.5*	(1.0-2.0)*	MAD A vs no treatment: P <0.001	
	MAD B	2.0*	(1.0-2.5)*	MAD B vs no treatment: P <0.001	
	No treatment	3.5*	3.5 (3.0-4.0)*	MAD A vs MAD B: P <0.05	
VAS: daytime sleepiness, Snoring	MAD A	7.2 (1.7)	5.4 (1.0)	Both MADs reduced daytime sleepiness and snoring significantly while Enhancing sleep quality (no details given); no differences were found in this respect between the 2 MADs	Not reported
	MAD B	7.0 (1.5)	4.1 (0.7)		
	MAD A	9.1 (0.8)	3.2 (1.4)		
	MAD B	8.8 (1.0)	3.4 (2.7)		
Sleep quality	MAD A	6.4 (1.8)	4.1 (1.4)		
	MAD B	6.2 (1.2)	4.5 (2.1)		

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Table VII. Patient usage of oral appliances, compliance, and side effects

Author	Patients (n)		Oral appliance (OA)	Advancement		Compliance	Reported usage	Assessment	Side effects	Preference	Reasons
	Baseline	Complete		Sagittal	Vertical						
Blanco et al[23]	24	15	A: MAD (1-piece soft elastic silicone positioner)	75% of maximum protrusion	5 mm	Every night for 6 h throughout trial	MAD 7.7 ± 0.5 h nonadvancement OA 6.5 ± 1.4 h	Questionnaire by patient and partner	MAD: 2 patients showed excessive salivation, nausea	MAD: 9 (60%) patients inactive OA: 6 (40%) patients	Preference for MAD: more effective, easier to clean and handle
			B: inactive OA	–	–						
Bloch et al[17]	24	24	A: MAD (monobloc)	75% of maximum protrusion mean, 10 ± 0.4 mm	5-10 mm	Not reported	4-7 nights/wk	Questionnaire	MAD A and MAD B: TMJ pain (7), muscle discomfort (4), dental discomfort (3) MAD B: mild mucosal muscle erosions (1)	15 (63%) patients preferred monobloc; 8 (33%) patients had no preference, 1 (4%) patient preferred Herbst OA	Preference for monobloc: relieving symptoms better, simpler device and more robust, lack of side effects
			B: MAD (Herbst)	75% of maximum protrusion mean, 10 ± 0.4 mm	4-6 mm gap range of opening, >15 mm						Preference for Herbst: greater effectiveness in relieving symptoms
			C: no treatment	–	–						
Gauthier et al[19]	23	16	A: MAD (commercial 2-piece Silencer)	50% of maximum protrusion average, 10.5 mm	9-12 mm	Not reported	Mean, 7.0 ± 0.2 h/night on 5.7 nights/wk	Questionnaire	Not reported	6 (38%) preferred Silencer	Preference for Klearway: significantly more comfortable to wear ($P < 0.05$)
			B: MAD (commercial 2-piece Klearway)	66% of maximum protrusion average, 12.5 mm	9-12 mm					9 (56%) preferred Klearway; 1 (6%) had no preference	

Table VII. Continued

Author	Patients (n)		Oral appliance (OA)	Advancement		Compliance	Reported usage	Assessment	Side effects	Preference	Reasons
	Baseline	Complete		Sagittal	Vertical						
Gotsopoulos et al[27]	73	73	A: MAD (custom-made 2-piece)	Mean, 80 ± 9% (range, 50%-95%) of maximum protrusion mean, 7 ± 2 mm (range, 3-13 mm)	3-4 mm	Not reported	6.7 ± 0.1 h/night for both OA	Diary/ questionnaire	MAS vs inactive OA: jaw discomfort (P <0.0001), tooth tenderness (P <0.0001), excess salivation (P <0.05)	72 patients (99%) wanted to continue with MAD treatment, 36 (49%) wanted to continue with inactive OA	Not reported
			B: inactive OA	–	–						
Hans et al[29]	24	18	A: MAD (commercial thermoplastic 1-piece SnoreGuard)	6-8 mm	8 mm	Noncompliance with MAD: 2 patients	Not reported	Not reported	Not reported	Not reported	MAD noncompliance: poor tolerance of device
			B: inactive OA	–	1 mm	Noncompliance with control: 4 patients					Control noncompliance: ineffectivness in treating symptoms
Johnston et al[9]	21	20	A: MAD (customized 1-piece)	75% of maximum protrusion mean, 5.7 mm (range, 4-9 mm)	4 mm inter-incisal	Not reported	68% wore MAD every or almost every night; 79% wore MAD 4 or more hours per night	Questionnaire	Excessive salivation (68%), temporary occlusal changes in the morning (44%), temporary TMJ discomfort on waking (42%)	Not reported	Not reported
			B: inactive OA	–	1.5 mm						
Lawton et al[18]	16	16	A: MAD (Twin-block)	Not reported	Not reported	Not reported	Not reported	Questionnaire	MAD A: muscular discomfort (50%); TMJ (38%); abnormal bite (38%); dry mouth (75%) excessive salivation (44%)	5 (31%) patients preferred Twin-block	Not reported

Table VII. Continued

Author	Patients (n)		Oral appliance (OA)	Advancement		Compliance	Reported usage	Assessment	Side effects	Preference	Reasons
	Baseline	Complete		Sagittal	Vertical						
			B: MAD (Herbst)	Not reported	Not reported				MAD B: muscular discomfort (56%), TMJ (69%), abnormal bite (69%), dry mouth (63%) excessive salivation (31%)	9 (56%) patients preferred Herbst 2 (13%) patients had no preference	
Mehta et al[28]	28	24	A: MAD (custom-made 2-piece)	Mean, 78% (63%-89%) maximum protrusion mean, 7.5 ± 1.8 mm (range, 5-11.5 mm)	Not reported	Not reported	87.5% of patients wear OA every night	Questionnaire	Excessive salivation (50%), gum irritation (20%), mouth dryness (46%), jaw discomfort (12.5%), tooth grinding (12.5%)	23 (96%) patients wanted to continue with MAD	MAD was perceived to better improve symptoms
			B: inactive OA	–	–						
Petri et al[24]	93	81	A: MAD (custom-made 1-piece acrylic)	Nean protrusion, 74% (range, 64%-85%)	5 mm in front	Not reported	Not reported	Not reported	MAD: 2 patients did not tolerate, 1 patient's teeth loosened, 1 suffered TMJ pain	Not reported	Not reported
			B: inactive OA	–	–						
			C: no intervention	–	–						

Table VII. Continued

Author	Patients (n)		Oral appliance (OA)	Advancement		Compliance	Reported usage	Assessment	Side effects	Preference	Reasons
	Baseline	Complete		Sagittal	Vertical						
Pitsis et al[30]	24	23	A: MAD (2 piece)	A: 87% ± 4% of maximum protrusion mean, 7.3 ± 0.5 mm	4 mm	Not reported	Nightly use MAD A: 91% MAD B: 78%	Questionnaire		22 (96%) patients would continue with either MAD, but a higher proportion preferred to use MAD A (78 vs 22%, $P = 0.007$)	Not reported
			B: MAD (2 piece)	B: 87% ± 4% of maximum protrusion mean, 7.3 ± 0.5 mm	14 mm				MAD B: more patients reported jaw discomfort; no difference in severity, frequency, or duration of side effects between groups		
Rose et al[16]	26	16	A: MAD (2-piece soft polyethylene Silencor)	75% maximum protrusion	5 mm	Every night for at least 6 h for at least 3 weeks before assessment	Not reported	Self-reported by patients and partners	MAD A: higher salivation, pain in gingivae and teeth	5 (31%) patients preferred MAD A	Preference for MAD A: smaller, soft material
			B: MAD (acrylic 1-piece Karwetzky)	75% maximum protrusion	10-12 mm				MAD B: increased salivation, TMJ pain, pain in masseter muscle; 2 withdrew because of side effects	11 (69%) patients preferred MAD B	Preference for MAD B: more stable, less need for repair

Table VII. Continued

Author	Patients (n)		Oral appliance (OA)	Advancement		Compliance	Reported usage	Assessment	Side effects	Preference	Reasons
	Baseline	Complete		Sagittal	Vertical						
Tegelberg et al[15]	74	55	A: MAD (1 piece)	50% of maximum protrusion mean, 4.5 ± 0.93 mm	Not reported		On average, 6.7 nights/wk (median, 7.0; range, 5-7); compliance for MAD A: 76% MAD B: 72% (at 1 year follow-up)	questionnaire	Few patients (<5%) reported symptoms from stomatognathic system; 2 patients reported TMJ pain in either group; headaches were significantly reduced at follow-up in both groups	Not reported; no cross-over study	Not reported
			B: MAD (1 piece)	75% of maximum protrusion mean, 6.4 ± 1.16 mm	Not reported						
Vanderveken et al[26]	38	35	A: MAD (custom-made monobloc)	65% ± 10% of maximum protrusion	Not reported		MAD A: 6.4 h/night/wk	Questionnaire	No serious side effects reported for either MAD group	29 (82%) patients who completed both treatments preferred the custom-made device; 3 (9%) had no preference	Preference for MAD A: better retention, more comfortable
			B: MAD (thermoplastic monobloc)	50% ± 20% of maximum protrusion	Not reported		MAD B: 6.3 h/night/wk compliance failure: MAD A2 (6%) MAD B 11 (31%)				
Walker-Engström et al[25]	86	77	A: MAD (1 piece)	50% of maximum protrusion mean, 5 mm (4.8-5.3)	2 mm		on average 6.4 nights/wk (median 7.0; range, 3-7)	Questionnaire	MAD B: 5 (4%) patients reported TMJ pain; headaches were significantly reduced posttreatment	Not reported; no cross-over study	Not reported
			B: MAD (1 piece)	75% of maximum protrusion mean, 7.2 mm (6.7-7.6)	2 mm		Overall compliance of 92% after 6 mo treatment				

TMJ, Temporomandibular joint.