

ORIGINAL ARTICLE

Long-Term Oral Appliance Therapy Improves Daytime Function and Mood in Upper Airway Resistance Syndrome Patients

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Objectives: To evaluate the long-term effects of an oral appliance on clinical symptoms, respiratory sleep parameters, sleep quality, and sustained attention in patients with upper airway resistance syndrome (UARS) were compared with placebo.

Methods: This study was a randomized placebo-controlled clinical trial. Thirty UARS patients were randomized in two groups: placebo and mandibular advancement device (MAD) groups. UARS criteria were presence of sleepiness (Epworth Sleepiness Scale ≥ 10) and/or fatigue (Modified Fatigue Impact Scale ≥ 38) associated with an apnea/hypopnea index ≤ 5 and a respiratory disturbance index (RDI) > 5 events/hour of sleep, and/or flow limitation in more than 30% of total sleep time. All patients completed the Pittsburgh Sleep Quality Index (PSQI), the Functional Outcomes of Sleep Questionnaire, the Beck Anxiety and Depression Inventories, underwent full-night polysomnography, multiple sleep latency test, and Psychomotor Vigilance Test (PVT). Evaluations were performed before and after 1.5 years of treatment.

Results: RDI, number of respiratory effort-related arousal, percentage of total sleep time with flow limitation, and arousal index significantly decreased after 1.5 years of MAD treatment. PSQI total score improved, severity of depression symptoms decreased, and mean reaction time in the PVT, based on the first measurement taken at 8:00 am, significantly decreased ($p = .03$) at the end of the protocol.

Conclusions: The MAD was effective in decreasing respiratory events in UARS patients. For UARS, 1.5 years of oral appliance therapy also improved sleep quality and sustained attention, and decreased the severity of depression symptoms.

Clinical Trial: Efficacy of Oral Appliance for Upper Airway Resistance Syndrome: Randomized, Parallel, Placebo-Controlled Study, NCT02636621.

Keywords: Upper airway resistance syndrome, fatigue, excessive daytime sleepiness, mandibular advancement device, sleep disordered breathing, oral appliance therapy.

Statement of significance

Upper airway resistance syndrome (UARS) is suspected in individuals with excessive daytime sleepiness, fatigue, and sleep fragmentation due to increased respiratory effort. UARS can negatively affect daytime function and decrease quality of life. It is unclear what the best treatment for the condition is. One treatment has been the use of mandibular advancement device; however, to the best of our knowledge, there has been no randomized controlled double-blind clinical trial to evaluate its effectiveness. We therefore set out to do this. Future studies in this area could examine larger samples and consider other parameters of sleep microarchitecture such as cyclic alternating pattern and spectral analysis.

INTRODUCTION

Upper airway resistance syndrome (UARS) is characterized by episodes of increased respiratory efforts during sleep that can cause sleep disruption and is suspected in individuals with excessive daytime sleepiness, fatigue, and sleep fragmentation. The disorder was first described in adults with excessive daytime sleepiness and an increased number of arousals.¹ Excessive daytime sleepiness and fatigue are the main complaints of UARS patients and can negatively affect daytime function by decreasing patients' sustained attention. Sustained attention can be easily evaluated through the Psychomotor Vigilance Test (PVT), a reaction-timed task that measures the speed with which subjects respond to a visual stimulus.² Stoohs and colleagues in 2009 measured sustained attention using the PVT in UARS patients and found worse results in most PVT parameters than those found in obstructive sleep apnea (OSA) patients.³

Other symptoms, besides sleepiness and fatigue, have been described in UARS patients including bruxism, irritable bowel syndrome, insomnia, and depression.⁴⁻⁶ UARS patients have also been reported to present specific personality characteristics.⁷

In order to avoid the consequences of a daytime dysfunction, UARS should be properly identified and treated. Until now, treatment options for UARS have not been well defined. CPAP is the most common treatment, although there are few studies of its long-term efficacy.⁸ An oral appliance (OA) that increases

upper airway volume through anterior traction of the mandible and tongue has been suggested as a possible option, but most studies are case reports.⁹

The objective of the study was to evaluate the long-term effects of a mandibular advancement device (MAD) on clinical symptoms (excessive daytime sleepiness, fatigue, anxiety, and depression), respiratory sleep parameters, sleep quality, and sustained attention in patients with UARS compared with placebo.

METHODS

Patient Selection

This study was a randomized, parallel, placebo-controlled clinical trial. It was approved by the Research and Ethics Committee (No. 304.697/13) of the Universidade Federal de São Paulo and was registered in Clinical Trials as NTC026366. All volunteers signed an informed consent form before data collection. They were recruited from the sleep disorders outpatient clinic at the Universidade Federal de São Paulo from 2014 to 2016. Individuals of both genders between the ages of 25 and 50 years with a body mass index (BMI) ≤ 30 kg/m² were included. UARS criteria were presence of sleepiness (Epworth Sleepiness Scale [ESS] ≥ 10) and/or fatigue (Modified Fatigue Impact Scale [MFIS] ≥ 38) associated with an apnea/hypopnea index (AHI) \leq

5 and a respiratory disturbance index (RDI) > 5 events/hour of sleep and/or more than 30% of total sleep time (TST) with flow limitation. Patients with a regular alcohol intake and/or use of psychoactive drugs; untreated clinical, neurological, and psychiatric diseases; sleep restriction (less than 6 hours of sleep); presence of severe dental conditions and/or temporomandibular dysfunction that preclude the use of dental appliance; or other sleep diseases (insomnia, circadian rhythm disorders, narcolepsy, periodic limb movement disorder, bruxism, restless leg syndrome, and parasomnias) were excluded (Figure 1).

Patients with a UARS diagnosis were randomized into two groups using block randomization of blocks of 10 patients: placebo and MAD groups. The MAD model used during sleep was the Brazilian Dental Appliance.¹⁰ It is a custom-made titrable bi-block MAD that is commercially available in Brazil. The device consists of two acrylic plates joined by two bilateral expanders in the region of the palate that fix the lower plate in the canine area. The retention is done through interproximal cleats. All MADs were set at 50% of patient's maximum mandibular protrusion and subsequently advanced progressively by 1 mm per week until 80% of maximum comfortable protrusion. It moves the mandible and the tongue positions forward to help maintain an open upper airway. The placebo consisted of an open arch dental protection plate made of acetate with no effect on upper airway patency. As the study was double blind, neither the researchers nor the patients knew which group each patient belonged to. The placebo had a palatal expansion that was not effectively activated, but during the dental visit, the dentist, who was not blind to patient's treatment condition, pretended to activate the expansion. We did not choose the same MAD design

as placebo, because it could affect the upper airway patency per se.^{11,12} Patients did not have contact with each other. Placebo and MAD adherence were evaluated subjectively through a sleep diary. We considered adherence to be good when a patient used the placebo or MAD for more than 70% of nights. A mean of six dental appointments were performed in order to properly adjust the MAD/placebo. Once every four months patients visited the dentist and/or the physician to be evaluated and to return the sleep diary, but telephone contact was performed every month in order to know if the patient was feeling comfortable and using the device properly. A mean of 12 medical and dentistry visits were performed.

All patients allocated in placebo group were assigned to effective treatment at the end of the protocol.

Evaluations

All patients completed the Pittsburgh Sleep Quality Index (PSQI), the Functional Outcomes of Sleep Questionnaire (FOSQ), the Beck Anxiety and Depression Inventories, underwent full-night polysomnography (PSG), the multiple sleep latency test (MSLT), and the PVT. Evaluations were performed before (baseline) and after 1.5 years of treatment. The full-night PSG was performed at the Sleep Institute of Sao Paulo, Brazil, using a digital PSG system (Embla®S7000, Embla Systems Inc., Broomfield, CO, USA). Sleep stages, arousals, and leg movements were scored according to standard criteria.¹³ Apneas were scored following the AASM recommended rule and hypopneas according to the AASM "alternative" rule.¹³ Respiratory effort-related arousal (RERA) was scored according to the AASM manual.¹³ Inspiratory flow limitation (IFL) was scored

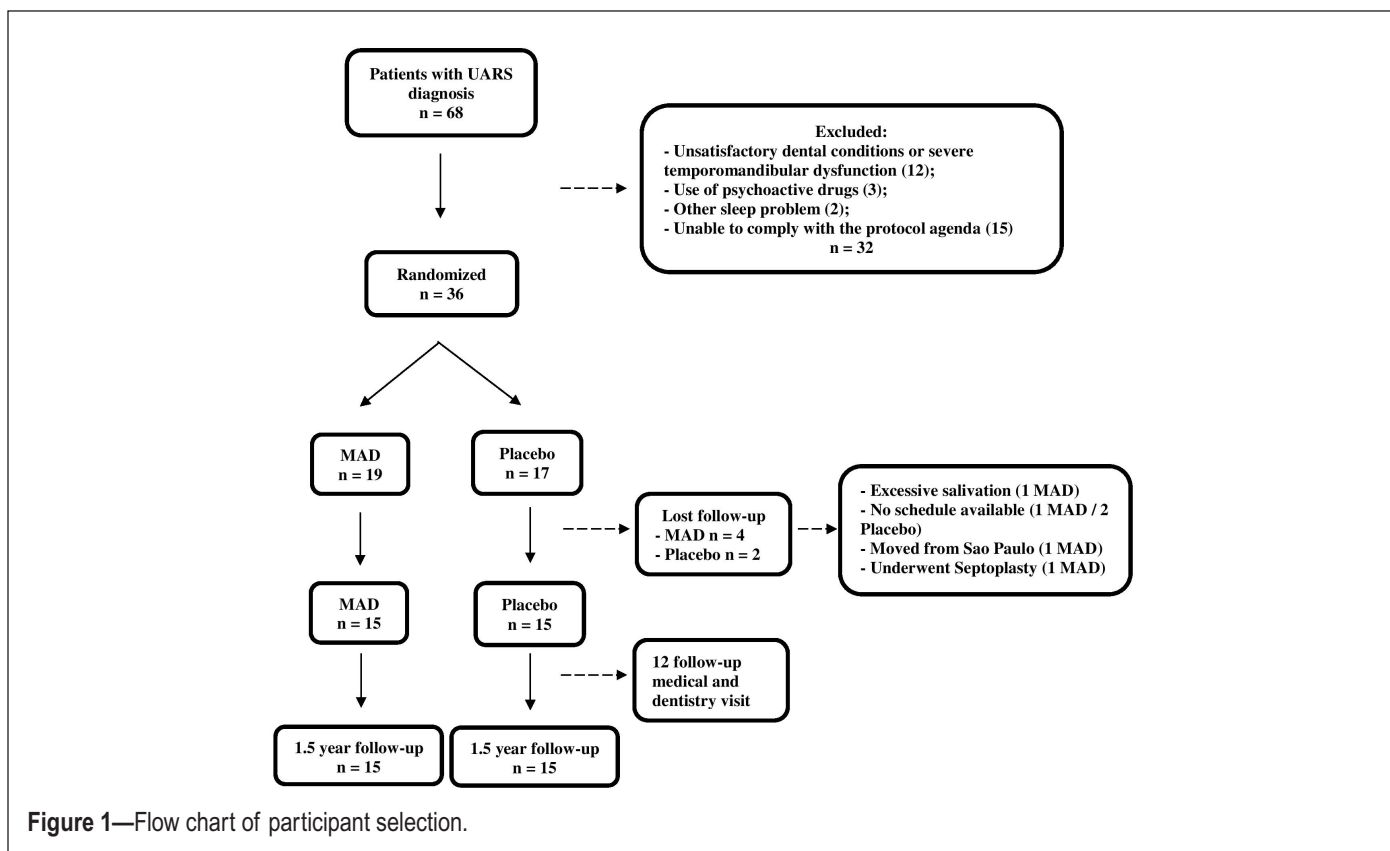


Figure 1—Flow chart of participant selection.

manually and visually identified as a “flattened shape” of the inspiratory airflow contour at nasal cannula pressure using the Embla system (square root of the flow signal), with no filters applied. At least four consecutive breaths with “flattened shape” were required to score IFL events.¹⁴ Those events should not meet the criteria for hypopnea. The percent of TST, during which there was IFL, was calculated.

The volunteers from both groups remained in the sleep laboratory the day after completing the PSG and performed the MSLT.¹³ During the MSLT intervals, patients completed the questionnaires (ESS,^{15,16} MFIS,¹⁷ PSQI,¹⁸ FOSQ,¹⁹ and the Beck Anxiety and Depression Inventories^{20,21}) and performed PVT.

PVT consisted of a sustained attention test carried out using a portable monitor (model PVT-192, CWE, Inc., Ardmore, PA, USA) that evaluates the state of alertness, psychomotor performance, sustained attention, and vigilance over a 10-minute period. The task consists of responding to a small, bright red-light stimulus (LED digital counter) by pressing a button as soon as it appears. The stimuli are consecutive and random and occur over the range of 2 to 10 seconds per minute. The participants were instructed to press a button as soon as each stimulus appeared, but not too soon, as this yielded a false start warning on the display.² All patients performed PVT five times during the day, every 2 hours (20 minutes before each nap of the MSLT).

A neuropsychologist blind to the patient’s condition performed the Beck Anxiety and Depression Inventories on a different day from the MSLT.

Statistical Analysis

Statistical analysis was performed using the SPSS statistics software (version 21.0 for Windows). For characterization of the groups, we performed a descriptive analysis mean \pm standard deviation and effect size considering $\alpha \leq 0.05$. Descriptive variables were analyzed through the Univariate General Linear Model (GLM). The Generalized Estimation Equation (GEE) test was used in order to analyze the group and time effects and group \times time interaction. The choice of distribution considered was based on parsimony between the exploratory analysis of histograms and a balance of the good fit Akaike information criterion (AIC) and Bayesian information criterion (BIC). The

variables of the questionnaires, PSG, and PVT repeated-measures were analyzed by Gamma distribution. The covariates used were delta BMI after 1.5 years and schooling years. Information was collected on schooling years and it was used as a covariate because it may affect a cognitive task performance such as those measured by PVT. Bonferroni correction was used to adjust for multiple comparisons.

RESULTS

Thirty UARS patients were included in the study: 21 women and 9 men; mean age was 43.7 ± 7.7 years; mean BMI was 26.6 ± 4.1 kg/m²; and mean schooling years was 13.37 ± 4.3 years. Since the placebo group had a statistically significant higher BMI than the MAD group at baseline evaluation, delta BMI (1.5-year treatment BMI—baseline BMI) was used as covariant in the analysis of the PSG data and questionnaires (Table 1).

Mean follow-up was 18 months. Mean treatment adherence was 6.3 ± 1.8 hours/night and 77% of nights. Mean adherence to placebo was 6.6 ± 2.6 hours/night and mean adherence to MAD was 6.1 ± 2.4 hours/night ($p = .5$). Minor and short-term side effects reported by MAD group were excessive salivation ($n = 1$), tooth and jaw discomfort ($n = 4$), and temporary bite changes ($n = 1$). One patient left the study because of side effects. Placebo group side effects were tooth discomfort ($n = 2$) and claustrophobia ($n = 1$). Sleep latency significantly increased in the placebo group after 1.5 years and decreased in the MAD group ($p = .03$). Arousal index, RDI, number of RERA, and percentage of TST with flow limitation significantly decreased after 1.5 years of OA treatment ($p = .04$, $p = .04$, $p = .02$, and $p = .001$, respectively) compared with placebo (Table 2).

No significant differences were found in the ESS and MFIS ($p = .3$ and $p = .08$, respectively) after treatment. Component 4 (sleep efficiency) and total score of PSQI significantly improved after 1.5 years of MAD treatment ($p = .02$ and $p = .03$, respectively). The domain “level of activity” and the total FOSQ score significantly increased after 1.5 years independently of group ($p < .01$ and $p = .03$, respectively). The Beck Anxiety Inventory score did not change between groups ($p = .1$); however, the Beck Depression Inventory score decreased in the MAD group after 1.5 years compared with the placebo group ($p < .01$) (Table 3).

Table 1—Descriptive data.

Descriptive variables	MAD ($n = 15$)	Placebo ($n = 15$)	p	Effect size (d)
Gender (male/female)	3/12	6/9	.1	—
Age (y)	43.1 ± 9	44.5 ± 6.1	.6	0.2
BMI (kg/m ²)	25.4 ± 1	28.1 ± 1.1	.05*	0.5
Schooling years	13.8 ± 6.5	12.8 ± 6.7	.6	0.2
Epworth Sleepiness Scale	13.2 ± 7.8	11 ± 12	.3	0.7
Fatigue (MFIS)	51 ± 24.5	51.8 ± 46.9	.7	0.1

MAD = mandibular advancement device; BMI = body mass index; MFIS = Modified Fatigue Impact Scale; GLM = general linear model.

Data represented by mean \pm standard deviation.

Effect size: Cohen’s d .

* $p \leq .05$.

Mean reaction time in the PVT, based on the first measurement taken at 8:00 am, significantly decreased after 1.5 years of MAD treatment compared with placebo ($p = .03$) (Figure 2), although false starts, lapses, and total errors did not change after treatment (Table 4).

DISCUSSION

Our study demonstrated that MAD was effective and safe in UARS patients. To the best of our knowledge, this is the first randomized double-blind clinical trial that has investigated the long-term effect of MAD therapy in UARS patients. Until now,

only case reports on MAD in UARS have been published.^{9,22-25} Most case reports only evaluated subjective daytime sleepiness and polysomnographic parameters, whereas our study addressed a broader range of symptoms and features of the syndrome (fatigue, subjective, and objective excessive daytime sleepiness, sleep quality, sustained attention, and severity of anxiety and depression symptoms). Considering that there is still no consensus on the diagnostic criteria and whether UARS represents a distinct syndrome from OSA, this is a relevant study on the subject.

PSG criteria for mild sleep-related breathing disorder (SRBD) include RDI, AHI, and RERA. We considered RDI, AHI, and

Table 2—Polysomnographic variables.

PSG variables	MAD (n = 15)		Placebo (n = 15)		p group × time	Effect size (d)
	Baseline Mean ± SD	1.5-year mean ± SD	Baseline mean ± SD	1.5-year mean ± SD		
Sleep latency	11.6 ± 30.3	8.8 ± 10.6	12.7 ± 22.6	36.3 ± 69.6	.03*	13.75
REM sleep latency	93.7 ± 141.9	115.8 ± 198.2	124.2 ± 182.9	98.9 ± 150.1	.1	8.45
Total sleep time (min) ^a	365.9 ± 76.2	403.1 ± 87.2	372.3 ± 135	414.1 ± 88.5	.8	5.5
Sleep efficiency (%)	84.1 ± 11.7	82.5 ± 17	83.8 ± 26.9	82.1 ± 20.6	.5	0.2
N1 (%)	9.4 ± 6.1	10.3 ± 6	10.3 ± 8.5	14.2 ± 15.1	.5	1.95
N2 (%)	51.7 ± 22.2	45.7 ± 19.3	45.7 ± 17.9	44.4 ± 23.5	.3	0.65
N3(%)	18.9 ± 13.6	21.3 ± 14.6	28.6 ± 15.3	22.7 ± 27.1	.2	0.7
REM (%)	20.5 ± 20.6	22.2 ± 16.9	15.2 ± 18.5	17.3 ± 22.9	1	2.45
WASO	56.6 ± 50.2	71.5 ± 74.6	60.5 ± 116.8	47.7 ± 65.5	.5	11.9
Arousal index	13.7 ± 7.1	10.2 ± 5.9	16.3 ± 9.3	17.2 ± 19.9	.04*	3.5
RDI	9.8 ± 11.6	5.4 ± 11.5	10.7 ± 12.4	14.6 ± 30.8	.04*	4.6
AHI	1.8 ± 3.8	4.2 ± 13.6	2.5 ± 3.4	6.7 ± 17.2	.8	1.25
RERA	38.7 ± 58.6	11.8 ± 22.5	69.6 ± 124.5	65.6 ± 131.8	.02*	26.9
IFL (%TST)	37.3 ± 35.3	25.3 ± 39.4	19.4 ± 35.3	23.8 ± 19	.01*	0.75
Mean oxygen saturation	96.4 ± 3.2	95.9 ± 3.7	95.6 ± 3.8	94.9 ± 3.8	.8	0.5
Minimum oxygen saturation	89.9 ± 9.3	89 ± 9.4	89.1 ± 6	87.7 ± 9.3	.8	0.65
REM desaturation index	3.8 ± 10.6	8.7 ± 21.5	9.8 ± 17.3	10 ± 19.3	.1	0.65
NREM desaturation index	0.8 ± 1.3	3.6 ± 14.1	1.1 ± 1.2	8.9 ± 18.7	.4	2.65
Oxygen saturation < 90% (%TST)	1.1 ± 0.1	0.3 ± 0.8	0.1 ± 0.3	0.4 ± 0.9	.7	0.05
MSLT sleep latency (min)	6.5 ± 12.1	5.8 ± 9	7.7 ± 16.5	4.1 ± 8.6	.1	0.85

MAD = mandibular advancement device; PSG = polysomnography; REM = rapid eye movement; WASO = wake-time after sleep onset; RDI = respiratory disturbance index; AHI = apnea/hypopnea index; RERA = respiratory effort related arousal; IFL = inspiratory flow limitation; TST = total sleep time; MSLT = multiple sleep latency test.

Data represented by mean ± standard deviation.

Generalized Estimation Equation (GEE) (time, group, interaction time × group), covariates: δ -BMI (1.5-year treatment-baseline).

Effect size: Cohen's *d*.

* $p \leq .05$ interaction group (placebo and UARS) and time (baseline and after 1.5-year treatment).

^a $p \leq .05$ between time independently of group.

Table 3—Questionnaires.

Questionnaires	MAD (n = 15)		Placebo (n = 15)		p group × time	Effect size (d)
	Baseline mean ± SD	1.5-year mean ± SD	Baseline mean ± SD	1.5-year mean ± SD		
Epworth Sleepiness Scale	13.2 ± 7.8	12.1 ± 8.9	11 ± 12	7.2 ± 8.0	.3	2.45
Fatigue (MFIS)	51 ± 24.5	35.3 ± 35.6	51.8 ± 46.9	48 ± 34.9	.08	6.35
PSQI component 1	2.3 ± 1.7	2 ± 2	2 ± 2	2.2 ± 2.2	.4	0.1
PSQI component 2	2 ± 1.3	1.8 ± 1.1	1.8 ± 1.7	1.5 ± 1.4	.7	0.15
PSQI component 3	1.7 ± 1.4	1.9 ± 1.9	1.7 ± 1.5	1.6 ± 2	.4	0.15
PSQI component 4	1.8 ± 1.1	1.1 ± 0.7	1.7 ± 0.9	2.2 ± 3	.02*	0.55
PSQI component 5	2.1 ± 1.3	1.8 ± 1.6	1.8 ± 1.5	1.7 ± 1.4	.5	0.05
PSQI component 6	2.1 ± 1.4	1.6 ± 1.5	1.7 ± 1.7	1.8 ± 1.7	.1	0.1
PSQI component 7	1.8 ± 1.3	1.8 ± 1.6	1.7 ± 1.9	1.7 ± 2.7	.9	0.05
PSQI total	12.9 ± 8.4	9.5 ± 8.1	9.7 ± 10.5	10.3 ± 12	.03*	0.4
FOSQ general productivity	2.8 ± 2	3.2 ± 2	2.5 ± 2.6	3.1 ± 1.1	.6	0.05
FOSQ social outcome	3 ± 3.3	3.4 ± 3	2.5 ± 3.2	3.3 ± 2.6	.5	0.05
FOSQ activity level ^a	2.5 ± 2	3 ± 1.7	2.4 ± 1.6	3.3 ± 1.4	.2	0.15
FOSQ vigilance	2.6 ± 2.2	2.9 ± 1.9	2.8 ± 2.2	3.4 ± 1.4	.6	0.25
FOSQ intimate relationships and sexual activity	2.8 ± 3.8	3.3 ± 3.2	1.9 ± 2.5	2.5 ± 2.7	.7	0.4
FOSQ total ^a	13.3 ± 11.5	15.8 ± 10.2	12.1 ± 10.5	15.5 ± 7.7	.6	0.15
Beck Anxiety Inventory	16.9 ± 24.8	10.7 ± 17	22.5 ± 33.4	20.3 ± 26.6	.1	4.8
Beck Depression Inventory	21.6 ± 18.6	10.8 ± 10.9	16.2 ± 21.5	14.4 ± 18.3	<.01*	1.8

MAD = mandibular advancement device; MFIS = Modified Fatigue Impact Scale; PSQI = Pittsburgh Sleep Quality Index; FOSQ = Functional Outcomes of Sleep Questionnaire.

Data represented by mean ± standard deviation.

Generalized Estimation Equation (GEE) (time, group, interaction time × group), covariates: delta BMI (1.5-year treatment-baseline).

Effect size: Cohen's *d*.

**p* ≤ .05 interaction group (placebo and UARS) and time (baseline and after 1.5-year treatment).

^a*p* ≤ .05 between time independently of group.

RERA as UARS PSG criteria, but also included IFL. It consists of a respiratory parameter that has been associated with some adverse physiological consequences (such as systemic hypertension^{26,27} and impaired immune response),²⁸ however, the cut-off point defining the sleep disturbance is not yet well defined. Palombini et al. evaluated the distribution of IFL in a representative sample of the general population and found that normal individuals can present up to 30% of the TST with IFL.²⁹ Based on this study, we used more than 30% criterion for flow limitation to characterize UARS patients, although it still lacks validation.

The UARS treatment modality most studied is CPAP.^{1,30,31} CPAP significantly decreased transient arousals, increased non-rapid eye movement (NREM) stage 3 and sleep latency in MSLT in UARS patients,¹ and CPAP therapy also improved excessive daytime sleepiness, fatigue,^{1,30} and snoring.³¹ Nevertheless, as some patients may not improve daytime sleepiness or fatigue after CPAP, adherence sometimes is compromised.³¹ Even though CPAP may be an effective treatment for UARS, compliance seems to be low in this group of patients.

Untreated UARS affects patients' quality of life. In a longitudinal study in which a significant part of patients did not use the recommended nasal CPAP treatment due to refusal by the Medicare to cover its prescriptions, the authors observed the natural evolution of UARS patients after 4.5 years of diagnosis.⁸ Daytime fatigue, insomnia, and depressive mood increased by 12–20 times and, as a consequence, the prescription of hypnotic and antidepressant increased.

MADs are made with the goal of moving the mandible and tongue forward to decrease the oropharyngeal obstruction. For UARS patients, it could increase the upper airway dimension and decrease the episodes of the upper airway resistance characteristic of the syndrome.

The MAD is an effective well-known therapy modality for OSA, but there are few studies on UARS patients.^{9,20–23} According to the 2015 AASM update to clinical practice guidelines for the treatment of OSA and snoring with MAD therapy, the MAD is a recommended OSA treatment modality for adults who are intolerant to CPAP or prefer alternate therapy.³² An

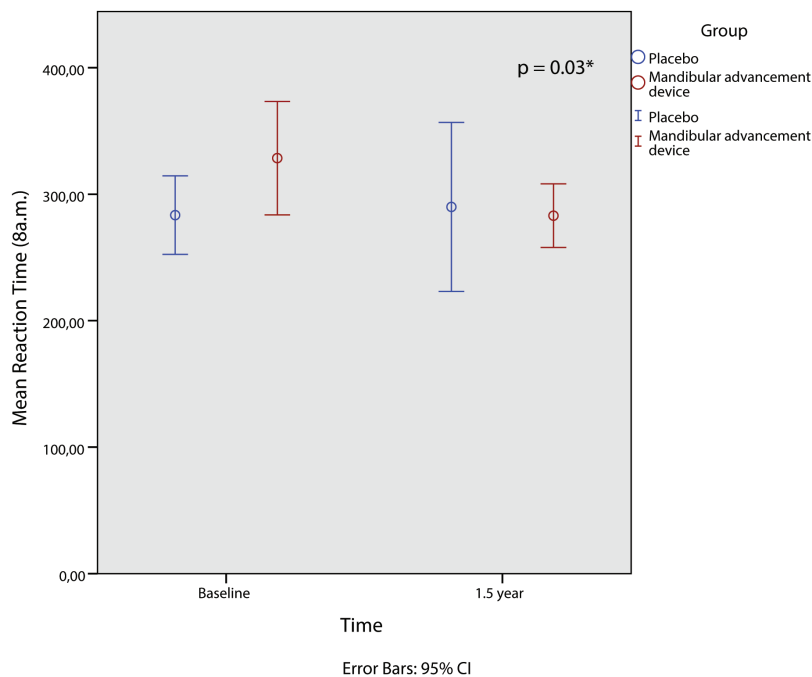


Figure 2—PVT mean reaction time (first measurement at 8:00 am).

AASM systematic review showed that a custom-made, titratable MAD reduced the AHI, arousal index, oxygen desaturation index, subjective excessive daytime sleepiness, and improved quality of life in OSA patients. MADs also tend to be used more than CPAP for snoring and OSA and in many studies were preferred to CPAP when the treatments were compared.³³ In our study, the MAD was well tolerated by UARS patients, with good compliance, and was effective in reducing respiratory events during sleep.

We did not find a statistically significant difference when comparing placebo with MAD on subjective and objective excessive daytime sleepiness and fatigue. Nevertheless, the fatigue score of the MAD group after 1.5 years decreased to normal values (MFIS < 38), which may have had some clinical meaning. The *p*-value was .08, with a large effect size of 6.35. We acknowledge that perhaps future studies should include higher number of UARS patients and of sleep centers involved. Some case reports found a significant difference when comparing UARS symptoms before and after MAD. In one study, MAD improved subjective daytime sleepiness after 2 weeks of use.^{9,22} A case-control study demonstrated an improvement in asthma symptoms in a UARS patient after MAD treatment, besides normalizing esophageal pressure (an indirect measure of thoracic pressure) and decreasing arousal index.²⁴ The possibility of decreasing the mental and somatic symptoms of UARS patients may help us to improve others clinical features of the syndrome.

Gold et al.³⁴ suggested that complaints of fatigue and excessive daytime sleepiness may be related to stress response and somatic arousals, which varies between subjects. Gold et al. found that fatigue and excessive daytime sleepiness in UARS patients were positively correlated with subjective somatic arousal and that nasal CPAP treatment decreased fatigue,

sleepiness, and somatic arousal. To investigate the role of stress response in UARS, sleepiness and fatigue in future studies might add relevant information about UARS pathophysiology and might help us to improve treatment outcomes.

In our study, we demonstrated that 1.5-year treatment with a mandibular advancement appliance improved subjective sleep quality and objective sustained attention. Poor sleep quality and sustained attention are the main causes of many driving and work accidents. Improving the quality of sleep and objective-sustained attention can positively affect daytime function and quality of life.

Clinical complaints most cited in UARS patients are excessive daytime sleepiness and fatigue; however, other symptoms such as mood changes have also been described. Some authors have already published studies that suggest that UARS patients usually have increased mood complaints rather than excessive daytime sleepiness and fatigue.⁷ We demonstrated a significant decrease in the severity of depression symptoms after 1.5 years of OA use. Other symptoms/signs described besides excessive daytime sleepiness and fatigue were stress (somatic arousal),³⁵ insomnia, headaches, irritable bowel syndrome, and α - δ sleep.⁴

Mandibular advancement appliance decreased polysomnographic variables such as RDI, RERA, arousal index, and IFL of UARS patients. Other authors have noticed polysomnographic differences in their case reports, such as a decrease in the arousal index,^{9,22,23} a less negative mean esophageal pressure (Pes),^{22,23} an improvement in sleep efficiency,⁹ and a lower oxygen saturation.⁹ Although some authors found a significant increase in mean sleep latency in the MSLT^{23,24} and absence of sleep during the Maintenance of Wakefulness Test (MWT)²³ in their case reports, we did not find a significant difference in objective daytime sleepiness according to the MSLT. The consequences of UARS may be better

Table 4—Psychomotor Vigilance Test (PVT) variables.

PVT	MAD (<i>n</i> = 15)		Placebo (<i>n</i> = 15)		<i>p</i> group × time	Effect size (<i>d</i>)
	Baseline Mean ± SD	1.5 year Mean ± SD	Baseline Mean ± SD	1.5 year Mean ± SD		
Time	Mean RT					
1	330.7 ± 155	283 ± 92.6	280 ± 97.9	289.9 ± 231.1	.03*	3.45
2	288.5 ± 118.5	287.1 ± 104	269.5 ± 109.5	278.7 ± 185.5	.6	4.2
3	288.8 ± 115.5	276.2 ± 95.6	269.7 ± 109.9	279.8 ± 218.6	.2	1.8
4	284.7 ± 104.3	271.8 ± 87.7	277.8 ± 162.6	278.3 ± 202	.4	3.25
5	289.5 ± 121.4	267.9 ± 96.3	267.7 ± 146.6	278.3 ± 212.5	.1	5.2
Time	False start					
1	2.4 ± 5.6	6.7 ± 26	4.4 ± 7.9	3.9 ± 6.1	.1	1.4
2	3.0 ± 4.6	7.2 ± 25.6	6.0 ± 14.4	6.3 ± 10.7	.2	0.45
3	4.5 ± 9.7	8.6 ± 28.9	4.9 ± 15	7.7 ± 15.7	.9	0.45
4	5.1 ± 10.4	11.7 ± 38.3	6.7 ± 23.3	7.7 ± 20.1	.1	2
5	3.5 ± 5.8	16.1 ± 46.8	9 ± 27	9.7 ± 21.6	.1	3.2
Time	Lapses					
1	4.8 ± 6.4	3.2 ± 4.2	3.0 ± 3.7	2.9 ± 7.2	.3	0.15
2	2.6 ± 5.0	2.7 ± 4.1	2.2 ± 3.2	2.6 ± 6.7	.8	0.05
3	3.1 ± 5	2.5 ± 3.6	2.9 ± 4.1	2.6 ± 7.7	.8	0.05
4	2.8 ± 4.6	2.5 ± 3.9	3.1 ± 4.9	2.5 ± 7.3	.9	0.00
5	3.0 ± 4.8	2.5 ± 3.4	2.3 ± 4.7	2.0 ± 6.6	.8	0.25
Time	Total errors					
1	2.3 ± 5.3	2.4 ± 4.3	4.6 ± 8.1	3.9 ± 6.4	.3	0.75
2	3.1 ± 4.6	3.3 ± 4.7	6.1 ± 15.1	6.9 ± 12.4	.8	1.8
3	4.1 ± 9.1	4.2 ± 8.3	5.1 ± 15.3	8.1 ± 16.6	.4	1.95
4	4.9 ± 11.2	6.5 ± 17.6	7.2 ± 25.8	8.1 ± 21.9	.2	0.8
5	3.2 ± 6.4	10.1 ± 28.5	9.7 ± 30.6	10.4 ± 25.5	.2	0.15

MAD = mandibular advancement device.

Data represented by mean ± standard deviation.

Generalized Estimation Equation (GEE) (time, group, interaction time × group), covariates: gender, age, and schooling years.

Effect size: Cohen's *d*.

**p* ≤ .05 interaction group (placebo and UARS) and time (baseline and after 1.5-year treatment).

demonstrated by PSG parameters not routinely evaluated, such as cyclic alternating pattern (CAP), spectral analysis, and autonomic arousal. δ -Band activity in a spectral analysis of UARS electroencephalographic data was increased before and after Pes reversal regardless of the presence or absence of standard arousal,³⁶ and a CAP analysis of UARS PSG demonstrated abnormal NREM sleep with abnormally increased CAP rate, arousals, A2 index, and A3 index.³⁷ We did not include these analyses in our study since it is not part of clinical routine, but these parameters may be useful to better evaluate the impact of UARS on sleep quality. Nonetheless, we found a decrease in sleep fragmentation, indicated by the arousal index (AASM manual),¹¹ and in the

severity of respiratory events after MAD treatment according to the current PSG respiratory parameters.

This study has some limitations. Some patients did not participate in the study due to inability to comply with the protocol agenda. The protocol was extensive and volunteers needed to stay longer than 20 hours at the sleep lab to perform PSG, MSLT, and PVT and to complete the questionnaires, and this evaluation was performed twice. Patients also had a high number of follow-up visits to dentist to fit the MAD (or placebo) and to physicians. These factors limited the number of volunteers in the study. As mentioned before, future studies with higher number of individuals and a multicenter design are warranted. In addition, treatment adherence was evaluated subjectively.

However, one study compared objective measures with self-reported compliance during MAD therapy for SRBD and found a high agreement between measures, with a mean subjective overestimation of 30 minutes.³⁸

Although minor side effects have been noted, and easily dealt, we did not perform image studies during follow-up; therefore, we could not ensure absence of dental or occlusal changes. Finally, we did not measure intrathoracic pressure, the gold standard measure of increased respiratory effort; however, good agreement has been reported for nasal cannula flow limitation, a less invasive and widely used sensor.³⁹

CONCLUSION

MAD treatment for 1.5 years improved sleep quality and sustained attention and decreased the severity of depression symptoms. It also reduced sleep fragmentation and decreased the severity of respiratory events in UARS patients according to polysomnographic parameters. MAD therapy was well tolerated by UARS patients who presented good compliance with the treatment, with a low incidence of side effects. Treatment with MAD can therefore be considered a good option for UARS patients.

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DISCLOSURE STATEMENT

None declared.