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SCIENTIFIC INVESTIGATIONS

Long term oral appliance therapy decreases stress symptoms in patients with upper airway resistance syndrome

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Study Objectives: To evaluate the long-term effects of a mandibular advancement device (MAD) on stress symptoms and cognitive function in patients with upper airway resistance syndrome (UARS) compared with placebo.

Methods: This study was a randomized placebo-controlled clinical trial. Thirty UARS patients were randomized into 2 groups: placebo and MAD groups. UARS criteria were the presence of sleepiness (Epworth Sleepiness Scale ≥ 10) and/or fatigue (Modified Fatigue Impact Scale ≥ 38) associated with an apnea-hypopnea index ≤ 5 events/h and a respiratory disturbance index > 5 events/h of sleep, and/or flow limitation in more than 30% of total sleep time. All patients completed the Rey Auditory-Verbal Learning Test, the Logical Memory test, the Stroop Color Test, the Trail Making Test, the Digit Symbol Substitution Test, and Inventory of Stress Symptoms. Cognition protocol was defined based on the most used neuropsychological tests in the literature. Evaluations were performed before and after 1.5 years of treatment.

Results: Mean adherence to placebo and to MAD was 6.6 ± 2.6 and 6.1 ± 2.4 h/night, respectively. Side effects reported by MAD group were minor and short-term. There was no statistically significant difference in Rey Auditory-Verbal Learning Test, Logical Memory test, Stroop Color Test, Trail Making Test, and Digit Symbol Substitution Test before and after 1.5 years of treatment in both groups. Inventory of Stress Symptoms score decreased at the alert phase and the resistance phase after 1.5 years of MAD treatment compared to the placebo.

Conclusions: Mandibular advancement devices were effective in decreasing stress symptoms in UARS patients after 1.5 years of treatment.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: Efficacy of Oral Appliance for Upper Airway Resistance Syndrome; URL: https://clinicaltrials.gov/ct2/show/record/NCT02636621; Identifier: NTC02636621.

Keywords: sleep, upper airway resistance syndrome, mandibular advancement device, stress, cognition

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Upper airway resistance syndrome is suspected in individuals with excessive daytime sleepiness, fatigue, and sleep fragmentation due to increased respiratory effort and can negatively impact daytime function and decrease quality of life. Cognitive impairment and stress effects in upper airway resistance syndrome patients has not been well established yet.

Study Impact: To the best of our knowledge, this is the first randomized double-blind clinical trial that investigated the long-term effect on stress symptoms and cognitive function of mandibular advancement device treatment in upper airway resistance syndrome patients. Early diagnosis is important since it allows us to adequately identify the disease and prevent worsening of daytime dysfunction, stress phases, and cognitive impairments.

INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder associated with significant clinical consequences. Cognitive impairment is one of the OSA consequences that have been recently studied. Most authors attribute the cognitive deficits to hypoxia episodes and sleep disruption.[1] Olaithe et al examined the findings from a systematic review and meta-analyses of the cognitive function effects of untreated OSA.[1] They found that OSA patients presented deficits in attention, memory, executive function, psychomotor function, and language abilities.[1] Fulda and Shulz had reported previously that driving simulation performance was reduced in OSA patients compared to controls.[2] They also concluded that OSA cognitive dysfunction is a complex issue since the neuropsychological functions comparison between OSA patients and control group was inconclusive.[2] As most study participants are moderate- to severe-OSA patients, less is known about cognitive impairment in mild sleep-related breathing disorder, such as mild OSA and 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 impact daytime function and decrease quality of life.[3] We previously compared some clinical consequences in OSA and UARS patients[4] and found that UARS patients had worse sleep quality, more

fatigue, and worse early morning sustained attention compared to mild OSA.[4] Gold et al demonstrated also that UARS patients present clinical complaints related to stress response.[5] As far as we know, cognitive impairment in UARS patients has not been well established yet.

The objective of the study was to evaluate the long-term effects of a mandibular advancement device (MAD) on stress symptoms and cognitive function 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 Sao Paulo and was registered in Clinical Trials as NTC02636621. 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 sexes, between the ages of 25 and 50 years of age, and with a body mass index ≤ 30 kg/m^2 were included. UARS criteria were presence of sleepiness (Epworth Sleepiness Scale ≥ 10)[6,7] and/or fatigue (Modified Fatigue Impact Scale ≥ 38)[8] associated with an apnea-hypopnea index ≤ 5 events/h and a respiratory disturbance index > 5 events/h of sleep and/or more than 30% of total sleep time 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 which preclude the use of dental appliance; or other sleep diseases (insomnia, circadian rhythm disorders, narcolepsy, periodic limb movement disorder, bruxism, restless legs syndrome, parasomnias) were excluded.

Patients with a UARS diagnosis were randomized into 2 groups: placebo and MAD groups. The MAD model used during sleep was the Brazilian Dental Appliance.[9] It is a custom-made titratable biblock MAD that is commercially available in Brazil. The device has been described previously.[3] It moves the mandible and the tongue positions forward to help maintain an open upper airway. All MADs were set at 50% of the patient's maximum mandibular protrusion and subsequently advanced progressively by 1 mm per week until 80% of the maximum comfortable protrusion. 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. Placebo and MAD adherence were evaluated via self-reported sleep diaries. We considered adherence to be good when a patient used the placebo or MAD for more than 70% of nights.

Evaluations

All patients completed the Rey Auditory-Verbal Learning Test (RAVLT),[10] the Logical Memory test,[11] the Stroop Color Test,[12] the Trail Making Test,[13] the Digit Symbol Substitution Test,[14] and Inventory of Stress Symptoms of Lipp (ISSL).[15,16] Cognition protocol was defined based on the most used neuropsychological tests in the literature. Evaluations were performed before (baseline) and after 1.5 years of treatment. The full-night polysomnography (PSG) was performed at the Sleep Institute of Sao Paulo, Brazil, using a digital PSG system (Embla®S7000, Embla Systems Inc., Broomfield, CO). Sleep stages, arousals, and leg movements were scored according to standard criteria.[17] Apneas were scored following the American Academy of Sleep Medicine recommended rule and hypopneas according to the American Academy of Sleep Medicine "alternative" rule.[17] Respiratory effort–related arousal was scored according to the American Academy of Sleep Medicine manual.[17] Inspiratory flow limitation was scored 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 4 consecutive breaths with "flattened shape" were required to score inspiratory flow limitation events.[18] Those events should not have met the criteria for hypopnea. The percent of total sleep time during which there was inspiratory flow limitation was calculated. All the sleep studies were scored by the same person. The scorer was blind regarding the treatment arm. Each patient performed 2 PSGs, 1 at baseline and another with placebo or MAD after 1.5 years of treatment. In addition, snoring intensity was evaluated by the patient with a 10-cm visual analog scale. Each participant, based on descriptions from a bed partner, was asked to estimate the severity of their snoring using a 10-cm visual analog scale from 0 (no snoring) to 10 (very severe snoring, bed partner leaves the room) at baseline and after 1.5 years of treatment.

The ISSL was based on a quadratic model of physical (somatic) and psychological symptoms of stress. The instrument consists of 37 items, divided into 3 blocks, each block or frame referring to the respective stress phase (alert, resistance, almost exhaustion, and exhaustion).

In the first block (corresponding to the alert phase), 15 items that correspond to the signs of stress are presented, 12 referring to physical symptoms and 3 referring to psychological symptoms experienced by the person in the last 24 hours.

The second block (corresponding to the phase of resistance and near exhaustion) consists of 10 physical and 5 psychological symptoms. The items related to each symptom that are checked must be related to symptoms from the week before the test. And the third picture (corresponding to the exhaustion phase), composed of 12 physical and 11 psychological symptoms, refers to symptoms present the month before the test.

The phases are calculated according to the raw scores of each part, revealing the presence or absence of stress, as well as the stress phase, and the predominance of physical or psychological symptoms of stress. The results are obtained based on the sum of the raw scores (symptoms marked in each block of questions). Signs of stress will be considered with the following scores: chart 1 (alert phase) > 6, chart 2 (resistance and near-exhaustion phase) > 3, and chart 3 (exhaustion) > 8 points.[19–21]

A neuropsychologist blind to the patient's condition performed the cognition protocol during the morning at baseline and after 1.5 years of treatment.

Table 1—Cognition variables: baseline data and 1.5 years after placebo or MAD.

Cognition Variables	Placebo		MAD		Effect Size Baseline × 1.5 Years	Expected Values (Normal)[£]
	Baseline Mean ± SD	1.5 Years Mean ± SD	Baseline Mean ± SD	1.5 Years Mean ± SD		
Learning and memory						
RAVLT1 (no. of words)	4.8 ± 19.8	5.4 ± 20	5.3 ± 21.9	6.3 ± 26.7	0.1	6.1[§]
RAVLT2 no. of words)	6.8 ± 26.8	8.2 ± 32.7	7.4 ± 28.9	8.5 ± 33.8	0.1	8.9[§]
RAVLT3 (no. of words)	8.3 ± 32.7	10.2 ± 42.5	9.2 ± 35.4	10.2 ± 39.4	0.1	10.6[§]
RAVLT4 (no. of words)	10.2 ± 46.7	11.1 ± 51.8	10 ± 44.5	10.8 ± 48.2	0.1	12.0[§]
RAVLT5 (no. of words)	10.4 ± 46.2	11.2 ± 49.9	11.1 ± 48.1	11.7 ± 50.8	0.1	13.0[§]
RAVLTB (no. of words)	3.8 ± 13.8	5.2 ± 18.3	5 ± 17.7	6.4 ± 22.4	0.2	5.1[§]
RAVLT6 (no. of words)	8.8 ± 51.5	9.2 ± 53.6	8 ± 46	9.5 ± 54.7	0.1	11.5[§]
RAVLT7 (no. of words)	5.7 ± 38.5	9 ± 45.1	7.4 ± 37.6	9.3 ± 48.1	0.1	10.7[§]
RAVLT total (no. of words)	40.4 ± 241.8	42.7 ± 277	43.4 ± 254.3	47.7 ± 280.8	0.1	50.7[§]
Memory: immediate and long term						
Logical Memory test: immediate (no. of words)	13.9 ± 99.5	19.8 ± 142.2	16.9 ± 112.9	21.8 ± 148.4	0.1	25[§]
Logical Memory test: long term (no. of words)	12.5 ± 57.2	14.9 ± 72.8	14.1 ± 66.1	17.8 ± 84	0.1	22[§]
Attention and executive function						
Trail making test A (s)	38.7 ± 198.9	29.8 ± 153.5	34.1 ± 114.1	39.1 ± 126.8	0.7	30.81[§]
Trail making test B (s)	85.8 ± 409.2	84.9 ± 388	81.8 ± 411.4	84.2 ± 418.1	0.1	64.42[§]
STROOP 1 (s)	22 ± 259.5	22.5 ± 296.5	22.3 ± 256.8	20 ± 228.8	0.1	17.05[§]
STROOP 2 (s)	34.7 ± 104.5	22.5 ± 62.2	32.9 ± 92.8	26.2 ± 73.9	0.2	25.99[§]
Digits	13.2 ± 50.3	12.4 ± 50.3	14.7 ± 57.2	15.1 ± 59.4	0.1	11[§]
DSST (total)	60.2 ± 283.9	66 ± 317.1	61.3 ± 281.2	66.4 ± 306.5	0.1	39 to 45[§]
Stress–Lipp						
ISSL 24 h (alert)	4.9 ± 44.4	6 ± 51.5	5.7 ± 57.8	4.8 ± 42.6*	0.3	6
ISSL 1 month (resistance)	7.6 ± 65.5	9.1 ± 76.2	10.5 ± 84.1	7.1 ± 56.7*	0.3	3[§]
ISSL 3 months (exhaustion)	10.8 ± 95.7	12.1 ± 102.7	9.7 ± 77.4	8.5 ± 68.7	0.2	8

Generalized estimated equation (GEE), schooling years as covariate. Cohen's *d* effect size (baseline × 1.5 years). *$P \leq 0.05$ group and time interaction (group: placebo and MAD × time: baseline and after 1.5 years of treatment). [£]Expected values at baseline and based on data mean age (43.7 years) and schooling years (13.4 years). [§]$P \leq 0.05$ baseline mean value × expected value based in data and mean ages. DSST = Digit Symbol Substitution Test, ISSL = Inventory of Stress Symptoms, MAD = mandibular advancement device, RAVLT = Rey Auditory-Verbal Learning Test. SD = standard deviation.

Statistical analysis

Statistical analysis was performed using the SPSS statistics software (version 21.0 for Windows; IBM, Armonk, NY). For the characterization of the groups, we performed a descriptive analysis mean ± standard deviation and effect size considering $\alpha \leq 0.05$. Descriptive variables were analyzed through the univariate general linear model. Baseline scores of cognitive tests were compared to expected values of the normal general population through One-Sample *t* Test. The generalized estimation equation test was used in order to analyze the group and time effects and group × 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 and Bayesian information criterion). The variables of the questionnaires were analyzed by gamma distribution. The covariates used were change in body mass index (BMI) after 1.5 years and schooling years. Bonferroni correction was used to adjust for multiple comparisons.

RESULTS

The study included 30 patients with UARS: 21 women and 9 men; mean age was 43.7 ± 7.7 years, mean BMI was 26.6 ± 4.1kg/m^2, 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, change in BMI (1.5-year treatment BMI – baseline BMI) was used as covariant in the analysis of the PSG data and questionnaires (**Table 1**).

No statistically significant differences were found in the Epworth Sleepiness Scale and Modified Fatigue Impact Scale ($P = .3$ and $P = .08$, respectively) after treatment as previously published.[3] Self-reported snoring significantly decreased after

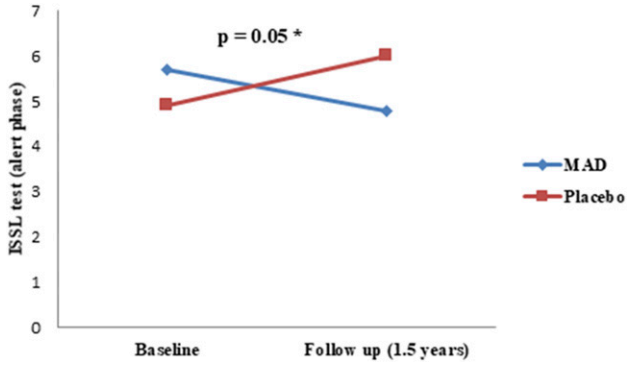
1.5 years of MAD treatment (mean value of 8.8 ± 2.4 at baseline and 4.6 ± 3.9 after treatment) compared to placebo (mean value of 9.0 ± 3.9 at baseline and 7.4 ± 4.8 after treatment) ($P = .05$). When we compared UARS baseline cognitive test scores with the expected normal values of general population, we noticed statistically significant differences in most scores (RAVLT: $P < .001$ in all domains; immediate and late Logical Memory test: $P < .001$; the Stroop Color Test 1 and 2: $P < .001$ and $P = .003$; Trail Making Test A and B: $P = .002$ and .001; the Digit Symbol Substitution Test: $P < .001$; ISSL alert phase: $P = .3$; ISSL resistance phase: $P < .001$, and ISSL exhaustion phase: $P = .2$). UARS patients had statistically significant worse results than expected normal data in most cognitive tests at baseline in our protocol (**Table 1**).

The mean follow-up was 18 months. Mean treatment self-reported adherence was 6.3 ± 1.8 h/night and 77% of nights. Mean adherence to placebo was 6.6 ± 2.6 h/night and mean adherence to MAD was 6.1 ± 2.4 h/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). Polysomnography findings were described previously.[3] In summary, arousal index, respiratory disturbance index, number of respiratory effort–related arousals, and percentage of total sleep time with flow limitation significantly decreased after 1.5 years of oral appliance treatment ($P = .04$, $P = .04$, $P = .02$, $P = .001$, respectively) compared to placebo. Sleep latency significantly increased in the placebo group after 1.5 years and decreased in the MAD group ($P = .03$). No statistically significant difference was found regarding the other PSG parameters.

No significant differences were found in RAVLT, Logical Memory test (I and II), Stroop Color Test (I and II), Trail Making Test (A and B), and Digit Symbol Substitution Test ($P = .8$, $P = .5$ and .7, $P = .6$ and .1, $P = .2$ and .8, and $P = .4$, respectively) after treatment (**Table 1**).

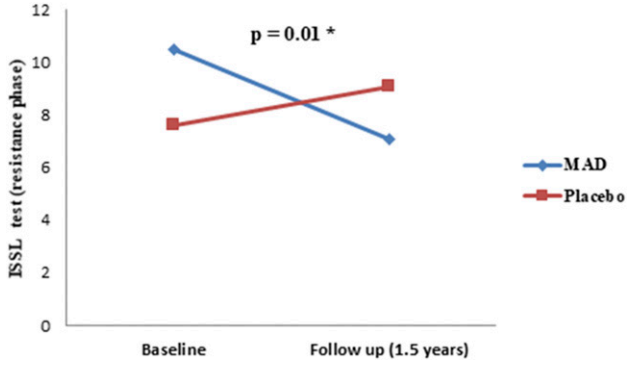
The Inventory of Stress Symptoms of Lipp scores in alert and resistance phases decreased in the MAD group after 1.5 years of treatment compared with the placebo group ($P = .05$ and $P = .01$, respectively) (**Table 1**, **Figure 1**, and **Figure 2**). No significant difference was found in the ISSL score in the exhaustion phase (**Table 1**).

Figure 1—Inventory of Stress Symptoms of Lipp (ISSL) test scores in the alert phase.



ISSL test scores (means) in the alert phase in placebo and MAD groups at baseline and after 1.5 years. MAD = mandibular advancement device. *$P \leq .05$.

Figure 2—Inventory of Stress Symptoms of Lipp (ISSL) test scores in the resistance phase.



ISSL test scores (means) in the resistance phase in placebo and MAD groups at baseline and after 1.5 years. MAD = mandibular advancement device. *$P \leq .05$.

DISCUSSION

To the best of our knowledge, this is the first randomized double-blind clinical trial that investigated the long-term effects of MAD treatment in cognitive function and stress symptoms in UARS patients. Cognition protocol was defined based on the most used neuropsychological tests in the literature. We chose the tests that had already been applied in patients with sleep-related breathing disorder[22,23] and were validated to the Portuguese language. This study aimed to evaluate changes in attention, immediate and long-term memory, flexibility of thought, and processing speed in UARS individuals.

In our study, UARS patients presented cognitive impairment and increased stress levels at baseline compared to the expected scores of the general population. We found changes in attention, alert function, learning, short and long-term memory, and executive functions at baseline in UARS individuals; however, there was no significant improvement in test performance after 1.5 years of treatment with MAD. Nevertheless, there was a statistically significant decrease in stress symptoms after 1.5 years of MAD treatment.

Fatigue may impair cognitive function, even though the effect of fatigue on cognitive function is not well established. The absence of significant improvement in cognitive function observed in our study may be related to the residual fatigue presented after treatment. We demonstrated in a previous paper that our UARS patients had a decrease in the fatigue scores after 1.5 years of MAD treatment to normal values with a high effect size (Cohen's $d = 6.35$) but without statistically significant difference compared to placebo ($P = .08$).[3] The lack of statistical significance may be related to the small sample size. Cockshell et al published a systematic review and suggested that objective cognitive test abnormalities are associated with memory and concentration problems reported by individuals with chronic fatigue.[24]

Another important aspect is the discrepancy that has been demonstrated between objective cognitive complaints and self-reported complaints. Most studies have not found a relationship between self-reported cognitive problems in people with fatigue and their performance in objective cognitive tests. Wearden et al could not demonstrate a correlation between participants' cognitive complaints and objective cognitive scores.[25] In a study with athletes, the authors observed that neither physical nor cognitive performance was affected by mental fatigue in objective cognitive tests, whereas self-reported evaluations revealed significant differences in individuals with chronic fatigue.[26] We did not evaluate cognitive complaints self-reported in this study, which may have demonstrated significant improvement, even though the objective cognitive tests had no statistically significant results.

Some authors have compared cognitive functions in patients with OSA and primary snoring. OSA patients have worse RAVLT 1, Stroop Color Test, and Digit Symbol Substitution Test scores than primary snoring groups.[22] However, as far as we know, there are no studies on neurocognitive evaluation of UARS patients, neither at baseline nor after treatment.

UARS individuals presented increased stress levels at baseline. We used the ISSL test to evaluate the stress level and its phases. This scale evaluates the presence of physical and psychological symptoms of stress as well as the phase or stage of stress that the patient is in. The phases are alert, resistance, and exhaustion. The alert phase is considered the positive phase of stress, when the human being gets energized and gets ready for action. It is characterized by adrenaline production, which causes the feeling of more motivation and energy. The second stress phase, called resistance, is established when the alert phase is maintained for prolonged periods or when stressful events occur. The individual automatically tries to deal with stressors in order to maintain internal homeostasis. If the stressors persist in frequency or intensity, there is a drop in the individual's resistance, and a change to the exhaustion phase. This third phase is the most negatively stressful one. It is pathological, with biological, physical, and mental impairments. At this stage, serious diseases can occur in the most vulnerable organs, such as strokes, ulcers, psoriasis, depression, and others.[16,27]

The most important finding of our study is that stress level in alert and resistance phases decreased in the MAD group after 1.5 years of treatment and increased in the placebo group according to the ISSL test. Therefore, there was an increase in physical and psychological symptoms of stress in the last 24 hours and in the last month in the placebo group and a decrease in these symptoms in the MAD group after 1.5 years of treatment. There was no progression to the exhaustion phase and there was no significant deterioration in UARS patients' quality of life. They still had the energy to perform their daily activities. In accord with our results, Gold et al demonstrated that UARS patients presented increased levels of stress, indicated by an increased component of somatic arousal, and the increased somatic arousal was correlated with poor sleep quality, increased sleepiness and fatigue, decreased perceived physical and mental health, and decreased perceived cognitive function (but not objective cognitive function).[5]

In summary, UARS individuals presented objective cognitive impairment that did not significantly improve after 1.5 years of treatment with MAD. UARS was also associated with increased stress complaints at baseline that decreased in the alert and resistance phases after 1.5 years of MAD treatment. It is important that UARS is diagnosed early to prevent the progression to pathological stress phases and to avoid the worsening cognitive impairment.

CONCLUSIONS

A mandibular advancement device was effective in decreasing stress symptoms in UARS patients after 1.5 years of treatment. There was no significant improvement in neuropsychological test results. It is important to understand the consequences of UARS in order to select treatment and prevent long-term consequences.

ABBREVIATIONS

BMI, body mass index
ISSL, Inventory of Stress Symptoms of Lipp
MAD, mandibular advancement device
OSA, obstructive sleep apnea
PSG, polysomnography
RAVLT, Rey Auditory-Verbal Learning Test
UARS, upper airway resistance syndrome

REFERENCES

1. Olaithe M, Bucks RS, Hillman DR, Eastwood PR. Cognitive deficits in obstructive sleep apnea: Insights from a meta-review and comparison with deficits observed in COPD, insomnia, and sleep deprivation. *Sleep Med Rev*. 2018;38:39–49.
2. Fulda S, Schulz H. Cognitive dysfunction in sleep disorders. *Sleep Med Rev*. 2001;5(6):423–445.
3. Godoy LBM, Palombini L, Poyares D, et al. Long-term oral appliance therapy improves daytime function and mood in upper airway resistance syndrome patients. *Sleep*. 2017;40(12):zsx175.
4. de Godoy LB, Luz GP, Palombini LO, et al. Upper Airway resistance syndrome patients have worse sleep quality compared to mild obstructive sleep apnea. *PLoS One*. 2016;11(5):e0156244.
5. Broderick JE, Gold MS, Amin MM, Gold AR. The association of somatic arousal with the symptoms of upper airway resistance syndrome. *Sleep Med*. 2014;15(4):436–443.
6. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540–545.
7. Bertolazi AN, Fagondes SC, Hoff LS, Pedro VD, Menna Barreto SS, Johns MW. Portuguese-language version of the Epworth sleepiness scale: validation for use in Brazil. *J Bras Pneumol*. 2009;35(9):877–883.
8. Pavan K, Schmidt K, Marangoni B, Mendes MF, Tilbery CP, Lianza S. [Multiple sclerosis: cross-cultural adaptation and validation of the modified fatigue impact scale] Esclerose múltipla: adaptação transcultural e validação da escala modificada de impacto de fadiga. *Arq Neuropsiquiatr*. 2007;65(3A):669–673.
9. Dal-Fabbro C, Bittencourt LRA. [Clinical and polysomnographic assessment of the BRD appliance in the treatment of obstructive sleep apnea syndrome] Avaliação clínica e polissonográfica do aparelho BRD no tratamento da síndrome da apneia obstrutiva do sono. *Dental Press J Orthod*. 2010;15(1):107–117.

10. Malloy-Diniz LF, da Cruz MdF, Torres VdM, Cosenza RM.O teste de aprendizagem auditivo-verbal de Rey: normas para uma população brasileira. *Rev Bras Neurol*. 2000;36(3):79–83.
11. Wechsler D. A standard memory scale for clinical use. *J Psychol*. 1945;19(1): 87–95.
12. Duncan MT. Obtenção de dados normativos para desempenho no teste de Stroop num grupo de estudantes do ensino fundamental em Niterói. *J Bras Psiquiat*. 2006;55(1):42–48.
13. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol*. 2004;19(2):203–214.
14. Joy S, Kaplan E, Fein D. Speed and memory in the WAIS-III Digit Symbol--Coding subtest across the adult lifespan. *Arch Clin Neuropsycho*. 2004;19(6): 759–767.
15. Lipp M, Guevara A. Validação empírica do inventário de sintomas de stress (ISS). *Estudos de Psicologia*. 1994;11(3):43–49.
16. Lipp M. [Lipp's inventory of symptoms of stress for adults (ISSL) in federal civil servants of São Paulo] O inventário de sintomas de stress para adultos de lipp (ISSL) em servidores da polícia federal de São Paulo; *Rev Bras Terapias Cognitivas*. 2008;4(2):108–119.
17. Iber C, Ancoli-Israel S, Chesson AL Jr, Quan SF; for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
18. Bao G, Guilleminault C. Upper airway resistance syndrome--one decade later. *Curr Opin Pulm Med*. 2004;10(6):461–467.
19. Lipp MN, Malagris LN. O Stress Emocional e Seu Tratamento. In: Range B, ed. *Psicoterapias Cognitivo-Comportamentais: Um Diálogo com a Psiquiatria*. Porto Alegre: Artmed.;2001:475–490.
20. Rossetti MO, Ehlers DM, Guntert IB, et al. O inventário de sintomas de stress para adultos de lipp (ISSL) em servidores da polícia federal de São Paulo. *Rev Bras Ter Cogn*. 2008;4(2):108–120.
21. Lipp MEN. *Manual do Inventário de Sintomas de Stress para Adultos de Lipp (ISSL)*. São Paulo: Casa do Psicólogo; 2000.
22. Arli B, Bilen S, Titiz AP, et al. Comparison of cognitive functions between obstructive sleep apnea syndrome and simple snoring patients: OSAS may be a modifiable risk factor for cognitive decline. *Appl Neuropsychol Adult*. 2015;22(4): 282–286.
23. Leng Y, McEvoy CT, Allen IE, Yaffe K. Association of sleep-disordered breathing with cognitive function and risk of cognitive impairment: a systematic review and meta-analysis. *JAMA Neuro*. 2017;74(10):1237–1245.
24. Cockshell SJ, Mathias JL. Cognitive functioning in chronic fatigue syndrome: a meta-analysis. *Psychol Med*. 2010;40(8):1253–1267.
25. Wearden A, Appleby L. Cognitive performance and complaints of cognitive impairment in chronic fatigue syndrome (CFS). *Psychol Med*. 1997;27(1):81–90.
26. Vrijkotte S, Meeusen R, Vandervaeren C, et al. Mental fatigue and physical and cognitive performance during a 2-bout exercise test. *Int J Sports Physiol Perform*. 2018;13(4):510–516.
27. Lipp ME, Pereira MM, Justo AP, de Matos TM. Cardiovascular reactivity in hypertensives: differential effect of expressing and inhibiting emotions during moments of interpersonal stress. *Span J Psychol*. 2006;9(2): 154–161.

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DISCLOSURE STATEMENT

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