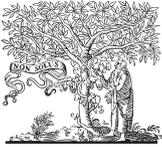


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Review Article

Treatment of upper airway resistance syndrome in adults: Where do we stand? ☆



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ARTICLE INFO

Article history:

Received 14 January 2015

Received in revised form

5 March 2015

Accepted 6 March 2015

Available online 20 March 2015

Keywords:

Upper airway resistance syndrome
flow limitation

Treatment

Arousal

Daytime sleepiness

ABSTRACT

Objective: To evaluate the available literature regarding Upper Airway Resistance Syndrome (UARS) treatment. **Methods:** Keywords “Upper Airway Resistance Syndrome,” “Sleep-related Breathing Disorder treatment,” “Obstructive Sleep Apnea treatment” and “flow limitation and sleep” were used in main databases. **Results:** We found 27 articles describing UARS treatment. Nasal continuous positive airway pressure (CPAP) has been the mainstay therapy prescribed but with limited effectiveness. Studies about surgical treatments had methodological limitations. Oral appliances seem to be effective but their efficacy is not yet established. **Conclusion:** Randomized controlled trials with larger numbers of patients and long-term follow-up are important to establish UARS treatment options.

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1. Introduction

The Upper Airway Resistance Syndrome (UARS) was first named by Guilleminault in 1993 [1] while investigating cases of excessive daytime sleepiness with no identified cause in adults. However, the respiratory pattern of increased upper airway resistance was previously identified in pre-pubertal children under the label “sleep-related respiratory resistive load” [2].

Since this first description, many authors have attempted to describe the clinical and polysomnographic features of UARS patients based on their experience, to find a definitive way to diagnose and finally treat them. In particular, during the last twenty years, the definition of UARS has varied (Table 1). Currently, UARS is subsumed under the diagnosis of Obstructive Sleep Apnea Syndrome (OSAS) by the American Academy of Sleep Medicine (AASM) (Berry AASM 2012) [3].

*Source of financial support: This work was supported by grants from Associação Fundo de Incentivo a Pesquisa (AFIP), Fundação de Amparo a Pesquisa do Estado de Sao Paulo (FAPESP), and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

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Peer review under responsibility of Brazilian Association of Sleep.

Table 1 – UARS definitions.

Authors	Clinical criteria	Polysomnographic criteria	
Kristo et al., 2005 [47]	Excessive daytime sleepiness (ESS > 10)	Pes ≤ - 12 cm H ₂ O	AHI < 5/hour, Arousal Index ≥ 10/hour, RERA ≥ 5/hour
Guilleminault et al. [7]	Excessive daytime sleepiness or fatigue	Pes and flow limitation by nasal cannula	AHI < 5/hour, RDI > 5/hour (RERA), Oxygen saturation > 92%
Loube et al., 2009 [48]	Excessive daytime sleepiness	Inductance plethysmography Pes ≤ - 12 cm H ₂ O	AHI < 5/hour and RERA ≥ 10/hour
Stoohs et al., 2009 [49]	Excessive daytime sleepiness or fatigue	Flow limitation by nasal cannula	AHI < 5/hour and presence of RERA
Pépin et al., 2012 [6]	Excessive daytime sleepiness	Pes, flow limitation by nasal cannula	RERA as more than 50% of respiratory events

ESS: Epworth Sleepiness Scale, Pes: Esophageal pressure, AHI: Apnea / Hypopnea Index, RERA: Respiratory Event-Related Arousal, RDI: Respiratory Disturbance Index

Its diagnostic criterion is still not defined and some authors believe that UARS is part of a continuum between primary snoring and OSAS whereas others believe that it is a distinct syndrome from OSAS. Some authors support that both UARS and OSAS have the same symptoms and as their pathophysiology do not significantly differ from each other, UARS is not a distinct disease [4,5]. Nevertheless, other authors believe that UARS patients present different features than other Sleep related Breathing Disorder (SRBD) [6,7,8]. The most frequent symptoms are excessive daytime sleepiness, fatigue and sleep fragmentation. However, UARS patients also present significantly more often with sleep-onset and sleep-maintenance insomnia, postural hypotension, headaches, gastroesophageal reflux, irritable bowel syndrome, anxiety and alpha-delta sleep [9,10,11]. The proportion of women with UARS is also significantly higher than for OSAS [12]. Besides having some different clinical presentation, it has been suggested that UARS and OSAS differ from each other in terms of their sleep EEG and autonomic nervous system responses. Some authors believe that UARS patients have an increase in alpha rhythm and an over-activation of the autonomic nervous system [13].

UARS diagnosis is suspected in individuals with complaints of excessive daytime sleepiness or daytime tiredness, no OSAS and a polysomnographic study with respiratory parameters indicative of increased upper airway resistance, such as, flow limitation during sleep. They present arousals associated with increase in respiratory effort leading to sleep fragmentation and excessive daytime sleepiness. The polysomnographic studies of these patients also showed sequences of breaths with flow limitation, which were interrupted by abrupt arousals. Arousals were defined using American Sleep Disorders Center-American Academy of Sleep Medicine (AASM) [14,15] conventional criteria but were also described using the cyclic alternative pattern-CAP-atlas, [16] including the shorter duration arousals associated with

abnormal increases of “Phase A2” and “Phase A3” of the CAP scoring system and with RERA [17]. The arousals associated with flow limitations were described as “respiratory event related arousals” (RERA) by AASM [14,15]. The polysomnography (PSG) pattern of “flow limitation,” introduced in 1991 [18] was further investigated and defined particularly in New York [19,20] as a sign of increased upper airway resistance to airflow.

Untreated UARS individuals can present low quality of life and cardiovascular consequences. Sleep and daytime symptoms, such as fatigue, insomnia and depressive mood, in untreated UARS usually increase over time [7]. The syndrome's characteristic esophageal pressure (Pes) negativity can cause a diastolic leftward shift of the interventricular heart septum and a consequent ventricular “collapse”. [21] The longlasting flow limitation episodes can induce a small increase in end-tidal carbon dioxide (PetCO₂) that can stimulate the sympathetic nervous system activity. This could cause hypertension, and cardiovascular and metabolic consequences. [6] Even an increase in inflammatory markers can happen in non-treated UARS individuals. [22]

In order to avoid the consequences mentioned above, a proper treatment should be offered to UARS patients. There are some treatment studies available in the literature, but most of these are case reports and case series. Nasal continuous positive airway pressure (CPAP) is one treatment option that has been evaluated as a therapy for UARS, and the available studies demonstrated that it can improve different aspects of the condition. CPAP treatment was associated with significant improvements in the excessive daytime sleepiness, numbers of transient arousals and abnormal upper airway resistance.1 Other types of treatments evaluated included oral appliances, nasal and palatal surgeries and maxillomandibular advancement. Long-term studies to evaluate treatment response will be helpful to better define this SBD.

The following sections review the available literature describing UARS treatment.

2. Methods

A systematic search of articles covering 1982 to date using Medline (via PubMed), Scielo, Lilacs, The Cochrane Library and Web of Science was conducted to identify published articles regarding UARS treatment. The search terms used were: "Upper Airway Resistance Syndrome", "Upper Airway Resistance Syndrome AND treatment", "Sleep-related Breathing Disorder AND treatment", "Obstructive Sleep Apnea AND treatment" and "flow limitation AND sleep". "Sleep apnea, obstructive" is a MeSH (Medical Subject Heading) in PubMed, and we used the subheadings "diet therapy," "drug therapy," "surgery" and "therapy" to improve the search. Articles describing either adult or pediatric populations were included. Only articles published in English were considered.

The literature search and the screenings of headings and abstracts were made by two different authors (LG and LP) independently. Both of them read all 27 fulltext articles that were assessed for eligibility. If consensus was not achieved, ST was included for a final decision.

3. Results

We found 457 articles in PubMed and 909 articles in Scielo, Cochrane, Bireme, Lilacs and Web of Science when the keywords "Upper Airway Resistance Syndrome" were used. Only 15 articles focused on UARS treatment, and all the articles included in Scielo, Cochrane, Bireme, Lilacs and Web of Science were also included in PubMed. We considered only once the articles that were identified twice because they were listed in two different sources. We also found 10 UARS systematic reviews that mentioned the syndrome's treatment along the article. Of the 349 articles found in PubMed using the keyword "Sleep-related Breathing Disorder AND treatment," none of them were about UARS treatment, and of the 493 articles found in Scielo, Cochrane, Bireme, Lilacs and Web of Science only 1 was about UARS treatment. In PubMed, 5051 articles were found using "Obstructive Sleep Apnea AND treatment" (with its respective MeSH) as the keyword, but only 1 was about UARS treatment. Of the 9147 articles found in Scielo, Cochrane, Bireme, Lilacs and Web of Science when the keyword "Obstructive Sleep Apnea AND treatment" was used, none focused on UARS treatments. Of the 222 articles found in PubMed and from the 678 articles in Scielo, Cochrane, Bireme, Lilacs and Web of Science using the keywords "flow limitation AND sleep," none described UARS treatments.

Seventeen (17) articles (Table 2) and ten (10) reviews were initially evaluated (Fig. 1). A summary of the original articles evaluated with year and journal of publication, study design, number and characteristics of the patients and conclusions are described in Table 2. The reports consisted mainly of case reports and case series. The main findings are discussed below.

From the 17 articles analyzed, 4 were about CPAP treatment [1,23,24,25], 1 about drug treatment [26], 1 about CPAP

and surgery [27], 1 was about rapid palatal expansion [28], 4 about surgery [22-32], 5 about oral device treatment [33-37] and 1 about external nasal device [38]. The definition of UARS also varied. Seven studies considered polysomnographic aspects associated to symptoms such as excessive daytime sleepiness, fatigue or snoring to diagnose UARS. Other studies only considered objective parameters from sleep study. The polysomnographic parameters considered were AHI less than 5-15 events/hour (10 studies) [24,25,27,28,31,32,34,35,37,38], RDI < 5-10 events/hour (3 studies) [29,30,33], RDI > 5 events/hour (2 studies) [31,35], Pes more negative than 10 or 20 mmH₂O (8 studies) [1,23,24,27,29,30,33,35], total arousal index (TAI) > 5-15 events/hour (7 studies) [1,24,25,33,34,35,38], the presence of excessive daytime sleepiness or fatigue or snoring (9 studies) [22,25,26,29,30,32,33,36,38] and presence of RERA or flow limitation (3 studies). [25,27,28]

In summary, therapeutic data about UARS treatment are few and consists of CPAP, oral device, surgery and external nasal device. There are no UARS cohorts with long-term treatment and follow-up available. Most studies about UARS treatment are observational and case reports. There were only two randomized double-blind, placebo-controlled studies published. Indeed, most studies have an inadequate methodology with a small number of patients and without precise sample estimation.

4. Discussion

Mild SBD criteria and events identification have been subject of discussion. The diagnosis of UARS is still controversial. Currently, UARS is considered part of Obstructive Sleep Apnea Syndrome (OSAS) by the AASM. OSAS is defined as the presence of more than 5 obstructive events per hour associated with symptoms or more than 15 events per hour independent of symptoms. Currently, there is no data with outcomes available defining the cut off limit for RERAs and Respiratory Disturbance Index (RDI) in SBD patients, as well as, on healthy individuals. Respiratory index, such as, apnea/hypopnea index (AHI) and RDI has been used with different definitions and considering different respiratory events. There are still several issues that need to be better defined and established regarding UARS, however, most authors today agree that sleep breathing disorders cannot be limited just to OSAS criteria.

CPAP is the UARS treatment modality better investigated. [1,23,24] One month of therapeutic trial with nasal CPAP can significantly change objective polysomnographic parameters [1] and subjective complaints. [1,23,24] CPAP treatment was associated to decrease in transient arousals, increase in percentage of NREM stages 3 and 4 and the sleep latency at MSLT. [1] Subjective daytime sleepiness, fatigue [1,23] and snoring [24] also can improve after CPAP treatment. Nevertheless, in some studies there were patients that did not have their excessive daytime sleepiness and fatigue decreased after CPAP treatment [24]. Consequently, these patients did not comply with CPAP due to the lack of beneficial effects [24]. Even though CPAP may be an effective treatment for UARS, the compliance is low in this patient population. Also, in follow up studies a significant part of patients did not use the

Table 2 – Articles included in the review.

Publications	Patients	Conclusion
Case reports		
Miller P et al. J Med Case Rep [28]	1 patient with UARS	Rapid palatal expansion may improve resistant adolescent depression with UARS
Venkat et al. Indian J Dent Res [36]	5 patients with UARS	Mandibular advancement device was better than four novel prosthodontic methods for UARS
Yoshida. J Prosthet Dent [37]	32 patients with UARS	Oral device therapy was effective in reducing objective and subjective daytime sleepiness
Guerreiro et al. Sleep Breath; 2001 [35]	1 patient with UARS with nocturnal asthma	Oral appliance can help control nocturnal asthma in patients with UARS and asthma
Ong et al. Ann Acad Med [23] Singapore; 2000	2 patients with UARS	Nasal CPAP improve excessive daytime sleepiness (Epworth)
Rose et al. Sleep Breath [34]	1 patient with UARS	An oral appliance improved daytime sleepiness in UARS
Loube et al. Sleep Breath [33]	1 patient with UARS	An oral appliance treatment decreased daytime sleepiness, snoring, transient arousals and Pes
Non-randomized studies		
Tschopp et al. Eur Arch Otorhinolaryngol [32]	35 patients with UARS and 109 with OSAS	After septoplasty, palatal surgery and hyoid suspension, preoperative AHI and tonsillectomy had a highly significant influence on the postoperative AHI
Lewis and Ducic. J Otolaryngol. [31]	4 UARS and 13 OSAS	After genioglossus muscle advancement, snoring and hypersomnolence were improved
Guilleminault et al. J Psychosom Res, 2002 [27]	62 patients with UARS x 68 chronic insomniacs	Treating the underlying breathing disorder with CPAP or nasal turbinectomy can improve complaints of post-menopausal women with chronic insomnia and UARS
Edwards et al. Am J Respir Crit Care Med [25]	11 women with severe preeclampsia	AutoCpap eliminated flow limitation
Watanabe et al. Psychiatry Clin Neurosci [24]	14 patients with UARS	Nasal CPAP and hormone replacement therapy improved snoring
Utley, Laryngoscope [30]	11 patients with UARS	Improvement of subjective daytime sleepiness after LAUP
Newman et al. Laryngoscope, [29]	9 patients with UARS	Nasal and palatal surgeries decreased subjective daytime sleepiness and snoring
Guilleminault et al. Chest [1]	15 patients with UARS	CPAP eliminated the daytime sleepiness, the transient arousals and abnormal upper airway resistance
Randomized double-blind studies		
Bahammam et al. Sleep [38]	18 patients with UARS	External nasal dilation reduced stage 1 sleep and desaturation time
Lofaso. Eur Respir J [26]	8 patients with UARS	Zolpiclone 7.5 mg improved sleep efficiency index and objective sleepiness (MSLT)
UARS: Upper Airway Resistance Syndrome, CPAP: Continuous Positive Airway Pressure, OSAS: Obstructive Sleep Apnea Syndrome, MSLT: Multiple Sleep Latency Test, LAUP: Laser-assisted Uvuloplasty, Pes: esophageal pressure		

recommended nasal CPAP treatment due to refusal by the insurance companies to cover its prescriptions, on the basis that according to their policies, UARS did not meet the criteria for a CPAP prescription [7].

Auto-CPAP was indicated to treat pregnant women with severe preeclampsia and flow limitation [25]. The mean overnight blood pressure was markedly reduced during the night of treatment with nasal CPAP when compared with the nontreatment night. The authors suggest that nasal CPAP may be considered as a therapy to improve blood pressure control in women with severe preeclampsia and flow limitation.

Medications that decrease sleep fragmentation could be also helpful for UARS patients. 7.5 mg Zolpiclone during 1 week produced significant improvements in the sleep efficiency index and average sleep latency in MSLT [26]. Nevertheless, it had no effect on respiratory parameters during sleep and daytime sleepiness in patients with UARS. Despite some improvements demonstrated objectively in the polysomnography, Zolpiclone use did not decrease UARS symptoms. It was concluded that medications that consolidate

sleep could be an adjuvant medicine used during the main treatment of UARS patients.

Sleep fragmentation persists in many patients with insomnia despite an adequate insomnia treatment. The sleep fragmentation associated with UARS can cause daytime fatigue and enhance anxiety, factors that can increase the difficulty in treating chronic insomnia. Postmenopausal women with chronic insomnia and UARS had their daytime fatigue decreased after nasal treatment (nasal radio-frequency ablation of turbinate or septoplasty with turbinectomy) and nasal CPAP-treatment [27]. This study reinforce the idea that SDB should be investigated in patients with chronic insomnia to guarantee an adequate insomnia treatment result.

Psychiatric patients may also present SDB. A case report about a young man with treatment-resistant depression and with sleep symptoms (insomnia, fatigue and daytime sleepiness) was investigated for SDB [28]. As his psychiatric symptoms were not well controlled despite an adequate medical treatment and he had sleep complaints he underwent a sleep

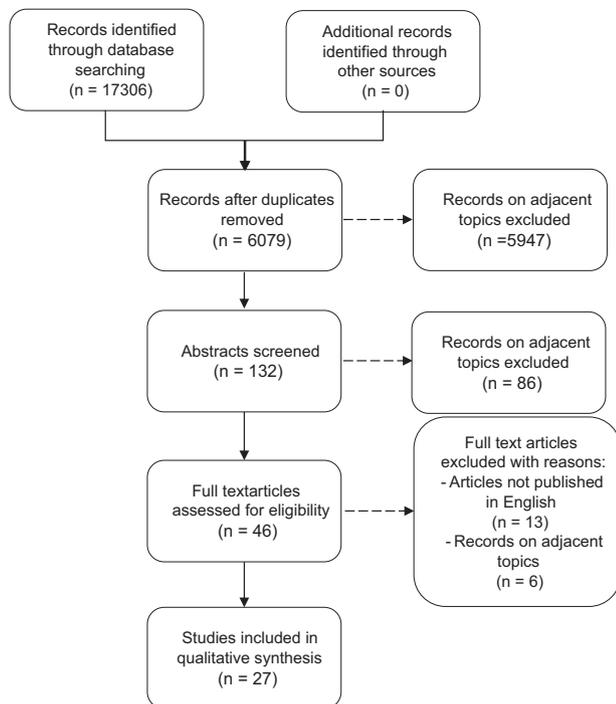


Fig. 1 – Flow diagram for identification of articles that were evaluated, excluded and included in the review.

study that showed UARS. The patient was submitted to rapid palatal expansion and during the two-year follow-up remained free from symptoms of depression, anxiety, sleepiness or fatigue in the absence of any psychotropic medication, although there were no statistically significant changes in the polysomnographic parameters. This article reinforces the idea that a sleep study should be included and SDB should be investigated in psychiatric patients who have persistent sleep complaints and whose psychiatric symptoms are not controlled despite an adequate medical treatment.

Upper airway surgeries have also been evaluated as UARS treatment option. Craniofacial abnormalities that may increase upper airway resistance are often present in UARS. Dental malocclusion and elevated ogival hard palate as well as a narrow posterior airway space can be frequent findings in upper airway examination [39]. Surgical treatment were studied as an option for patients who cannot tolerate or are unwilling to adhere to CPAP therapy [29]. Some authors studied UARS patients that preferred surgery (such as septoplasty, turbinate reduction, laser-assisted uvuloplasty – LAUP, uvulopalatopharyngoplasty, genioglossus bone advancement, mandibular osteotomy with tongue advancement and hyoid myotomy with suspension) rather than CPAP [29–31]. Sleep studies were performed from 3 to 6 months after treatment [29–31]. The only outcome evaluated in these studies were subjective sleepiness [29–31] and snoring [30–31] and the follow-up was not long enough to consider surgery a long-term effective management for this group of patients.

Many authors agreed that procedures should address anatomical regions that cause upper airway obstruction and that UARS treatment consists of approaching the causes of

the upper airway anatomical problems such as treatment of nasal allergies, usage of palatal soft-tissue surgeries, orthognatic surgery or use of dental devices [6,40,41,42,43,44]. Some authors had even tried to formulate a statistical model for postoperative AHI after multilevel surgery in UARS patients [32]. It was concluded that tonsillectomy had a highly significant influence on postoperative AHI.

Concluding, few studies evaluating surgical treatment for UARS are available. Most studies about surgery treatment only consider subjective outcomes and the number of patients has been too low to lead to conclusive results. Many methodological problems in published literature did not allow a proper analysis [45,46]. Randomized prospective protocols of surgical procedures should be conducted.

Another treatment option for SDB is the use of oral devices. Oral devices move the mandible and tongue forward in order to minimize the oropharyngeal obstruction. Patients with UARS present a narrow posterior airway space behind the base of the tongue. Oral devices increase upper airway dimensions and are often indicated for mild SDB. There are some case reports [33–36] and a prospective study [39] published about oral device as UARS treatment. Some authors noticed polysomnographic differences, such as a decrease in the total arousal index (TAI) [33,34,37], a less negative mean Pes [33,34], an improvement in sleep efficiency [37] and lower oxygen saturation [37]. A significant increase in the mean sleep latency in the MSLT [34,35] and an absence of sleep during the Maintenance of Wakefulness Test (MWT) was also observed [34]. Oral appliance also decreased subjective daytime sleepiness [33,37] and snoring [33]. Another study report a case of oral appliance indicated for an asthmatic patient with UARS that had poorly controlled asthma symptoms despite high-doses steroids [35]. The post-treatment polysomnography showed normalization of the Pes and decrease in the TAI. Even the asthma symptoms were better controlled and lower doses of drugs were required after the oral device treatment.

The side effects of oral devices observed (excessive salivation and transient tooth discomfort) were minor and tolerable, and no major complications were reported [37]. Objective and subjective aspects of the treatment response were evaluated during a longer follow up. The results demonstrated that oral appliance was effective in decreasing sleep fragmentation and objective and subjective daytime sleepiness and was also well tolerated.

Other types of oral devices besides the mandibular advancement device were also published as case reports but the study did not report clinical or polysomnographic changes pre- and post-treatment [36].

Nasal obstruction is another cause of flow limitation and can lead to occlusion of the pharyngeal airway. The decrease in nasal resistance might also reduce the inspiratory effort. A double-blind, randomized, controlled trial with a cross-over design study was performed to evaluate the effect of external nasal dilatation in UARS patients [38]. The external nasal dilator significantly increased nasal cross-sectional area, reduced stage 1 sleep and decreased desaturation time when comparing to the placebo treatment. These were the only changes observed after treatment. There were no significant effects on the MSLT, AHI or TAI or on the clinical complaints.

The absence of significant clinical changes after treatment, despite the polysomnographic differences, demonstrated that this device, currently, cannot be recommended for the treatment of UARS. Future studies with a larger number of patients and with a longer follow-up should be conducted to better analyze this device's effects on UARS patients.

5. Conclusion

Currently, there are few well designed studies available of UARS treatment, CPAP has been the primary therapy prescribed, but its effectiveness has been limited because of low patient compliance and there are no randomized controlled trials evaluating this type of treatment in UARS patients. The available studies that have evaluated surgical treatments of UARS patients have methodological limitations and low numbers of patients evaluated. Oral appliances seem to be an effective option, but only case reports and small case series have been reported, and the efficacy of these devices is not yet established for this group of patients. Randomized controlled trials comparing different modalities of treatment with larger numbers of patients and including long-term follow-up are important to better define and establish treatment options in UARS patients.

Conflict of interest

The authors had no conflict of interest in this article.

Acknowledgments

The authors would like to thank for the support by grants from Associação Fundo de Incentivo a Pesquisa (AFIP), Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP), and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

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