

## Obstructive sleep apnea and asthma\*

Apneia obstrutiva do sono e asma

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### Abstract

Symptoms of sleep-disordered breathing, especially obstructive sleep apnea syndrome (OSAS), are common in asthma patients and have been associated with asthma severity. It is known that asthma symptoms tend to be more severe at night and that asthma-related deaths are most likely to occur during the night or early morning. Nocturnal symptoms occur in 60-74% of asthma patients and are markers of inadequate control of the disease. Various pathophysiological mechanisms are related to the worsening of asthma symptoms, OSAS being one of the most important factors. In patients with asthma, OSAS should be investigated whenever there is inadequate control of symptoms of nocturnal asthma despite the treatment recommended by guidelines having been administered. There is evidence in the literature that the use of continuous positive airway pressure contributes to asthma control in asthma patients with obstructive sleep apnea and uncontrolled asthma.

**Keywords:** Apnea; Sleep apnea, obstructive; Asthma.

### Resumo

Tem-se observado que sintomas dos distúrbios respiratórios do sono, especialmente a síndrome da apneia obstrutiva do sono (SAOS), são comuns em asmáticos; além disso, associam-se com a gravidade da asma. Sabe-se que durante a noite tende a haver maior gravidade dos sintomas da asma, assim como uma maior proporção de mortalidade durante a noite e as primeiras horas da manhã. Sintomas noturnos ocorrem entre 60-74% dos pacientes com asma e são marcadores de controle inadequado da doença. Vários mecanismos fisiopatológicos são relacionados a esse agravamento. A SAOS está incluída entre os fatores mais importantes. A investigação da SAOS em pacientes com asma deve ser realizada sempre que não houver um controle adequado dos sintomas noturnos da asma com o tratamento recomendado por diretrizes. Há evidências da literatura que sugerem que o uso de pressão positiva contínua nas vias aéreas pode contribuir para o controle da asma, quando o paciente asmático tem apneia obstrutiva do sono e sua asma não está controlada.

**Descritores:** Apneia; Apneia do sono tipo obstrutiva; Asma.

### Asthma

Asthma is a chronic inflammatory disease with multiple phenotypes related to genetic predisposition and various environmental interactions, and there is still a major gap in the understanding of its complex causality and, consequently, in the primary prevention of the disease.<sup>(1)</sup> It is estimated that the annual cost of asthma in the USA is 11 billion dollars, and hospitalizations account for half of these expenditures in that country.<sup>(2)</sup> Although patients with severe asthma account for less than 20% of all asthma patients, they consume 80% of all funds allocated for the treatment of asthma.<sup>(2)</sup>

Asthma is the fourth leading cause of hospitalization via the Brazilian Unified Health Care System.<sup>(3)</sup> A multicenter study showed that Brazil ranks eighth, the mean prevalence of asthma in the country being 20%.<sup>(4)</sup> Approximately 45% of all adults with asthma have another chronic disease, such as hypertension, diabetes, and depression.<sup>(5)</sup> In addition, approximately 2,500 people die each year because of asthma.<sup>(6)</sup> In 2011, of the 177,800 patients who were hospitalized for asthma via the Brazilian Unified Health Care System, 77,100 were children.<sup>(6)</sup>

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## Obstructive sleep apnea syndrome

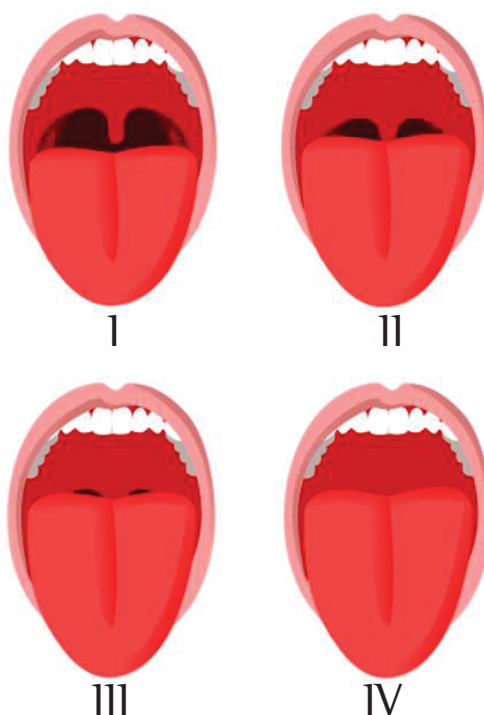
Obstructive sleep apnea syndrome (OSAS) is characterized by episodes of complete or partial upper airway obstruction during sleep.<sup>(7)</sup> It is known that OSAS induces hypoxemia, carbon dioxide retention, changes in the normal autonomic structure, and hemodynamic responses during sleep.<sup>(8)</sup> According to Young et al.,<sup>(9)</sup> OSAS affects 4% of males and 2% of females. In Brazil, it affects 32.9% of adults, affecting 40.6% of males and 26.1% of females.<sup>(10)</sup> According to Kapur et al.,<sup>(11)</sup> the average annual medical costs for patients with undiagnosed OSAS is US\$ 2,720, being approximately twice as high as those for patients diagnosed with and undergoing treatment for sleep-disordered breathing. If not diagnosed and treated appropriately, OSAS generates an additional annual expenditure of 3.4 billion dollars in the USA.<sup>(11)</sup> The lack of diagnosis in cases of severe OSAS is alarming because of the comorbidities and the risk of sudden death.<sup>(12)</sup>

Patients with OSAS tend to have circular upper airways, whereas normal individuals have elliptical upper airways.<sup>(13)</sup> In adult patients with upper airway obstruction, the most common types of obstruction are velopharyngeal narrowing, in 78%; oropharyngeal narrowing, in 35%; and hypopharyngeal narrowing, in 54%. Obstruction at a single level was observed in 48%, whereas obstruction at multiple levels was observed in 52%.<sup>(14)</sup> A disproportionate oral cavity anatomy due to increased soft tissue (in particular, increased tongue volume) or underdeveloped maxilla and mandible can be evaluated by applying the modified Mallampati classification.<sup>(15)</sup> The Mallampati classification was modified by Samssoon and Young (Figure 1).<sup>(16,17)</sup> The pharyngeal structures are now classified into four types: class I: the soft palate, palatine tonsils, uvula, and anterior and posterior pillars of the fauces are visible; class II: all class I structures are visible, except the pillars of the fauces; class III: only the base of the uvula is visible; and class IV: the uvula cannot be seen, and only the hard palate is visible.<sup>(16)</sup>

## OSAS-asthma

### Introduction

The first study examining asthma and OSAS was a case report by Hudgel & Shrucard, in 1979.<sup>(18)</sup> Ekici et al.<sup>(19)</sup> conducted a study involving 7,469 adults; of those, 2,713 had a history of



**Figure 1** – Modified Mallampati score.<sup>(17)</sup>

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asthma. The authors found that snoring (OR = 1.7) and self-reported apnea (OR = 2.7) were more prevalent in patients who had a history of asthma than in those who did not. Larsson et al.<sup>(20)</sup> evaluated 46 patients with a history of chronic cough, expectoration, or periodic wheezing. Of those 46 patients, 52% had a history of snoring and an apnea-hypopnea index (AHI)  $\geq 10$  events/hour of sleep. In that study, OSAS was associated with wheezing in 21% of the cases, and asthma was associated with OSAS in 17% of the cases.<sup>(20)</sup> Byun et al.<sup>(21)</sup> selected 176 adults with the following complaints: habitual snoring; excessive daytime sleepiness (EDS); choking during sleep; sleep fragmentation; nonrestorative sleep; daytime fatigue; and difficulty concentrating. Those patients were referred for clinical evaluation and polysomnography. Of the 176 patients, 111 (66%) had  $10 > \text{AHI} > 5$  events/h, and 72 (43%) had an  $\text{AHI} > 15$  events/h. Of the patients who had an  $\text{AHI} > 5$  events/h, 37 (33.6%) had been diagnosed with moderate to severe asthma.<sup>(21)</sup>

Both OSAS and asthma can result in fragmented sleep and EDS.<sup>(22)</sup> Calhoun et al.<sup>(22)</sup> studied 700 children and found that 13.3% of those who had EDS also had a diagnosis of asthma. The independent predictors of EDS were waist circumference (OR = 1.4), self-reported anxiety/depressive symptoms (OR = 2.9), difficulty falling asleep (OR = 1.7), and a history of asthma (OR = 2.4). In another study, impaired sleep quality was found to be far more common in children with asthma than in controls (33 vs. 0;  $p < 0.01$ ).<sup>(23)</sup> In addition, EDS was more common in the children with asthma than in those in the control group (19 vs. 14;  $p < 0.05$ ).<sup>(23)</sup> This EDS can be explained by recurrent episodes of coughing and dyspnea during sleep, which are characteristic of asthma.<sup>(23)</sup> It should be taken into consideration that both asthma and OSAS involve frequent awakenings associated with airflow limitation and increased respiratory effort, with consequent desaturation during sleep.<sup>(19)</sup>

### ***Sleep-disordered breathing vs. asthma control***

In patients with asthma, OSAS acts as a mechanism that contributes to the lack of asthma control,<sup>(24)</sup> because the reduction in airway caliber in nocturnal asthma is often associated with sleep fragmentation, early morning awakening, difficulty maintaining sleep, and EDS.<sup>(25)</sup> Increased abdominal pressure during periods of OSAS contributes to gastroesophageal reflux (GER), bronchial hyperreactivity, and bronchial inflammation.<sup>(26)</sup> Patients with difficult-to-control asthma can have an increase in the number of episodes of OSAS and oxyhemoglobin desaturation, especially during rapid eye movement sleep.<sup>(24)</sup> Because of the aforementioned reasons, the US National Asthma Education and Prevention Program recommends that patients with difficult-to-control asthma be screened for OSAS.<sup>(27)</sup>

Teodorescu et al.<sup>(28)</sup> found that individuals with OSAS were 3.6 times as likely to have uncontrolled asthma. Janson et al.<sup>(29)</sup> found an association of bronchial hyperreactivity with daytime fatigue, EDS, early awakening, higher percentage of time awake during the night, and decreased sleep efficiency. The use of theophylline was associated with an increased prevalence of difficulty initiating sleep and decreased sleep efficiency.<sup>(29)</sup> A negative

correlation was found between FEV<sub>1</sub> and daytime fatigue, and a positive correlation was found between PEF and duration of insomnia and between PEF and sleep efficiency.<sup>(29)</sup>

Julien et al.<sup>(30)</sup> found that greater asthma severity translated to a higher AHI; that is, patients with severe asthma had an AHI of 23.6 events/h, those with moderate asthma had an AHI of 19.5 events/h, and those with mild asthma had an AHI of 9.9 events/h ( $p < 0.001$ ). When the authors investigated OSAS in those with an AHI  $\geq 15$  events/h, they found that 23 (88%) of the 26 patients with severe asthma had been diagnosed with OSAS, as had 15 (58%) of the 26 patients with moderate asthma and 8 (31%) of the 26 controls without asthma. Mean nocturnal SaO<sub>2</sub> was significantly lower in the patients with severe asthma than in the controls.<sup>(30)</sup> The high prevalence of OSAS in patients with severe asthma suggests that recognition and treatment of OSAS play an important role in improving asthma control.<sup>(30)</sup> Approximately 63% of children with severe asthma have OSAS.<sup>(31)</sup>

Teodorescu et al.<sup>(32)</sup> found that asthma patients who were using low-dose inhaled corticosteroids regularly, those who were using medium-dose inhaled corticosteroids regularly, and those who were using high-dose inhaled corticosteroids regularly were, respectively, 2.29 times, 3.67 times, and 5.43 times as likely to develop OSAS as were those who were not using inhaled corticosteroids. In addition, an inverse association was found between OSAS and FEV<sub>1</sub>.<sup>(32)</sup> Teodorescu et al.<sup>(32)</sup> reported that the association between OSAS and the doses of inhaled corticosteroids can be associated with the known adverse effects of corticosteroids. The authors reported that inhaled corticosteroids can compromise the upper airway dilator muscles in asthma patients and therefore act as facilitators of OSAS.<sup>(32-34)</sup>

It has been reported that 60-74% of patients with asthma have nocturnal symptoms, which function as markers of inadequate control of the disease.<sup>(25)</sup> In 1988, Guilleminault et al.<sup>(35)</sup> studied patients with nocturnal asthma and OSAS and noted that episodes of nocturnal asthma exacerbation were inhibited by the recommended treatment for OSAS, i.e., continuous positive airway pressure (CPAP). The authors suggested that patients with OSAS have an increased vagal

tone during sleep, which can increase the chance of having nocturnal bronchoconstriction, which in turn can be inhibited by CPAP. Subsequently, Ciftci et al.<sup>(36)</sup> conducted polysomnographic studies in asthma patients who had nocturnal symptoms despite using the medications recommended by the Global Initiative for Asthma. In addition to nocturnal symptoms, those patients had a history of snoring for at least 6 months. Polysomnography showed that 21 (48.83%) of the 43 patients had OSAS, i.e., an AHI  $\geq 5$  events/h, and 19 of the 21 patients with OSAS had an AHI  $\geq 15$  events/h; therefore, they were referred for CPAP treatment, the recommended treatment having improved the symptoms of nocturnal asthma.<sup>(36)</sup>

## Hypotheses for the interaction between OSAS and asthma

### *OSAS-obesity-asthma*

Obesity is considered one of the causal factors for OSAS. Peppard et al.<sup>(37)</sup> evaluated adults at two different time points (at baseline and 4 years later). Initial data showed that individuals with body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> (n = 268) had an AHI of 7.4 events/h; those with  $30 < \text{BMI} \leq 25$  kg/m<sup>2</sup> (n = 241) had an AHI of 2.6 events/h; and those with BMI  $< 25$  kg/m<sup>2</sup> (n = 181) had an AHI of 1.2 events/h. After 4 years, 39 of the patients who did not have moderate to severe OSAS (AHI  $\geq 15$  events/h) had a 3.9 kg increase in weight. Of the 46 participants who had moderate to severe OSAS, 17 gained an average of 3.1 kg, although there was no significant change in the AHI; among those whose AHI was normal, there was an average increase in weight of 2.2 kg. The authors found that the increase in weight was positively correlated with the AHI; that is, patients who gain 10% of their body weight tend to show an increase of approximately 32% in the AHI, and a 10% reduction in weight resulted in a 26% reduction in the AHI. A 10% increase in body weight increased the chance of developing moderate to severe OSAS by 6 times.<sup>(37)</sup>

The high prevalence of OSAS in patients with asthma appears to be associated with obesity. Cottrell et al.<sup>(38)</sup> conducted a cross-sectional study involving 17,994 children (in the 4-12 year age bracket), 14% of whom had a diagnosis of asthma. The prevalence of asthma was directly proportional to the BMI percentile. The prevalence

of asthma is higher in obese children and even higher in morbidly obese children. It has been suggested that, beyond a certain threshold of obesity, metabolic factors become involved in the pathophysiology of upper airway inflammation, as well as in bronchial hyperreactivity, being able to interfere with the clinical manifestations of asthma.<sup>(38)</sup> It seems that the association between asthma and OSAS worsens the clinical picture of asthma, given that OSAS can stimulate weight gain, playing a significant role in the severity of asthma.<sup>(39)</sup> It is known that OSAS interferes with lipid homeostasis and systemic inflammation and, when associated with obesity, affects glycemic regulation, interfering with insulin sensitivity, independently of the BMI.<sup>(40)</sup> Komakula et al.<sup>(41)</sup> found an association of BMI, leptin levels, and adiponectin levels with decreased levels of exhaled nitric oxide in patients with asthma.

### *OSAS-systemic inflammation-asthma*

It is known that OSAS has a negative effect on proatherogenic lipid levels and promotes inflammatory responses, which are evidenced by a reversible increase in C-reactive protein (CRP).<sup>(40)</sup> Gozal et al.<sup>(40)</sup> noted that triglyceride levels decreased after adenotonsillectomy, although only in the group of obese children. In both groups, serum levels of apoB decreased remarkably after adenotonsillectomy, and the effect was slightly higher in the group of nonobese children. Similarly, serum levels of CRP, which were higher in the pre-adenotonsillectomy period, decreased proportionally to the AHI, the reduction being more significant in the group of nonobese children. By means of hypoxemia, hypercapnia, and sleep fragmentation, OSAS can cause or aggravate proinflammatory states through effects on sympathetic hyperreactivity, oxidative stress, or both.<sup>(42)</sup>

TNF- $\alpha$  is considered a marker of sleep-disordered breathing.<sup>(42)</sup> Vgontzas et al.<sup>(43)</sup> demonstrated that TNF- $\alpha$  inhibition can decrease the severity of OSAS. Gozal et al.<sup>(44)</sup> noted that children with moderate to severe OSAS had elevated levels of TNF- $\alpha$  in the early hours of the morning and that children with adenotonsillar hypertrophy showed a reduction in the levels of TNF- $\alpha$  after surgical treatment. In patients with OSAS, CPAP therapy results in an improvement in the levels of CRP, TNF- $\alpha$ , and IL-6.<sup>(45)</sup> TNF- $\alpha$  is a potent proinflammatory cytokine that plays an important

role in the pathogenesis of asthma; that is, it interferes with airway smooth muscle contractility.<sup>(45)</sup>

### ***OSAS-leptin-asthma***

The treatment of OSAS can reduce circulating leptin levels as a result of the reduction in the AHI.<sup>(46)</sup> Sanner et al.<sup>(46)</sup> noted that adults with OSAS treated with CPAP showed a reduction in the AHI, from 29 events/h before CPAP treatment to 1.6 events/h after CPAP treatment, as well as showing a reduction in leptin levels, from 8.5 ng/mL before CPAP treatment to 7.4 ng/mL after CPAP treatment. Circulating leptin levels are directly proportional to the amount of adipose tissue; therefore, obese children and adults have elevated circulating leptin levels.<sup>(46)</sup> Mai et al.<sup>(47)</sup> showed that leptin levels are higher in obese children than in nonobese children (mean, 18.1 ng/mL vs. 2.8 ng/mL). In addition, children with asthma are twice as likely to have elevated leptin levels as are those without. Guler et al.<sup>(48)</sup> compared children with asthma and healthy children in terms of leptin levels, which were found to be 3.53 ng/mL and 2.26 ng/mL, respectively. A logistic regression showed that leptin acted as a predictive factor for asthma.

### ***OSAS-GER-asthma***

It is believed that the significant increase in negative intrathoracic pressure caused by upper airway obstruction can predispose to retrograde movement of gastric contents.<sup>(49)</sup> One study showed that 71.4% of patients with OSAS had GER (as measured by pH monitoring); of those, 10.4% reported no symptoms.<sup>(50)</sup> Guda et al.<sup>(51)</sup> suggested that patients with GER have more episodes of OSAS than do those without symptoms of GER. It has been reported that OSAS-induced GER can play an important role in asthma symptoms.<sup>(39)</sup> Kiljander et al.<sup>(52)</sup> studied 90 patients with asthma and reported that 32 (36%) had a diagnosis of GER. However, this prevalence can be as high as 84%.<sup>(53,54)</sup> Sontag et al.<sup>(53)</sup> studied 62 patients with asthma and GER; of those, 24 were on antacids (control group), 22 were on ranitidine (150 mg), and 16 underwent fundoplication. Those who underwent surgical treatment showed an immediate reduction in nocturnal exacerbation of wheezing, cough, and dyspnea. After 2 years, there was an improvement in asthma in 74.5% of the patients who underwent surgical treatment,

in 9.1% of those in the ranitidine group, and in 4.2% of those in the control group. In the group of patients who underwent surgical treatment, asthma symptom scores increased by 43%, whereas, in the ranitidine and control groups, asthma symptom scores increased by less than 10%.<sup>(53)</sup>

### ***OSAS-upper airways-asthma***

The current trend is to regard the nose and bronchi as parts of a single airway.<sup>(55)</sup> Rhinitis is considered an independent risk factor for asthma.<sup>(56)</sup> The proportion of asthma patients who have symptoms of rhinitis can be as high as 100%.<sup>(57)</sup> Kiely et al.<sup>(58)</sup> noted that, after four weeks of treatment with a corticosteroid (fluticasone propionate), the AHI was lower in the group of patients who used fluticasone than in the control group. Kheirandish-Gozal et al.<sup>(59)</sup> used intranasal budesonide for six weeks in children with moderate OSAS and noted a significant improvement in the polysomnographic variables, 54.1% of the children having reached the normal range. There was also a reduction in adenoid size. The discontinuation of the nasal corticosteroid did not affect the results. However, in the placebo group, there were no changes in the investigated data.<sup>(59)</sup>

In children with OSAS, the most common upper airway obstruction sites are as follows: adenoid, in 57%; hard palate, in 29%; and palatine tonsils, in 14%.<sup>(60)</sup> Donnelly et al.<sup>(61)</sup> studied the upper airways using magnetic resonance imaging and found hypopharyngeal collapse in 81% of the children with OSAS, having found no collapse in the control group (composed of healthy children). Fregosi et al.<sup>(62)</sup> noted that the palatine tonsils, pharyngeal tonsils, and hard palate account for 74.3% of all cases of upper airway obstruction in children. However, Guilleminault et al.<sup>(63)</sup> noted that OSAS persisted in 45% of the children who underwent adenotonsillectomy. Therefore, adenotonsillar hypertrophy is only one of the causes of OSAS in children. Other triggering factors, such as rhinopathy, turbinate hypertrophy, septal deviation, and micrognathia, should be taken into consideration.<sup>(64)</sup>

Regarding the inflammatory process of the upper airways, Almendros et al.<sup>(65)</sup> conducted an experimental study in rats submitted to recurrent episodes of negative pressure alternating with positive pressure and inducing upper airway

collapse and reopening, similar to what occurs in OSAS. They concluded that there was a high expression of pro-inflammatory biomarkers, such as TNF- $\alpha$ , IL-1, and macrophages, in the laryngeal and soft palate tissue. Puig et al.<sup>(66)</sup> examined human bronchial epithelial cells placed on a vibrating platform. After 12 h and 24 h of exposure to vibration, the cells exhibited high levels of IL-8 in comparison with those in the control group. The authors concluded that vibration applied to epithelial cells can trigger inflammatory processes, similar to what occurs in snoring and OSAS.<sup>(66)</sup>

Trudo et al.<sup>(67)</sup> used magnetic resonance imaging in order to evaluate the upper airways of 15 healthy adults during induced sleep and noted changes in and around the upper airways. The air space at the level of the retropalatal region was reduced by 19% during sleep, with an anteroposterior and laterolateral reduction in the pharynx. In the retroglottal region, no significant reduction was observed. Schwab et al.<sup>(68)</sup> compared patients with OSAS and healthy individuals in terms of the dimensions of the upper airways. The chance of upper airway structures being associated with OSAS was 6.01 for the lateral pharyngeal wall, 4.66 for tongue volume, and 6.95 for soft tissues. The volume of the tongue and lateral pharyngeal walls proved to be an independent factor for OSAS. Studies have shown fat deposition in upper airway tissues in patients with OSAS.<sup>(69,70)</sup>

## Prospects for intervention in OSAS-asthma

Patients with severe uncontrolled asthma seek emergency room treatment 15 times as often as do those with moderate asthma and are hospitalized 20 times as often.<sup>(71-73)</sup> It is speculated that OSAS plays an important role in asthma exacerbations and that the use of CPAP can decrease exacerbations, improve quality of life, and reduce the number of cases of difficult-to-control asthma.<sup>(74)</sup> Chan et al.<sup>(75)</sup> noted that the mean pre-bronchodilator and post-bronchodilator FEV<sub>1</sub> were higher during CPAP therapy than during two control periods (i.e., without CPAP therapy). The authors reported that CPAP treatment improved asthma control, and, in particular, nocturnal exacerbations of asthma. Guillemineault et al.<sup>(35)</sup> studied patients with asthma and craniomandibular abnormalities, with a narrow

retrolingual space. They found that the use of CPAP eliminated snoring, apnea, hypopnea, and nocturnal asthma exacerbations. Nasal CPAP had no effect on daytime asthma.<sup>(35)</sup> The use of CPAP, when appropriate, is beneficial for asthma-OSAS, having favorable effects on bronchial and systemic inflammation, reducing bronchial hyperreactivity, improving sleep architecture, reducing body weight, suppressing lecithin production by adipose tissue, improving cardiac function, and significantly reducing GER.<sup>(74)</sup> Therefore, bronchial asthma and OSAS are two public health problems, whose interrelationship is being recognized.<sup>(76)</sup> It is expected that an understanding of this process can provide the basis for the development of new treatment strategies.<sup>(76)</sup>

## Final considerations

Although the association between OSAS and asthma is common, it is poorly investigated. If left untreated, OSAS can contribute to the lack of control of asthma, especially nocturnal asthma symptoms. In patients with asthma, OSAS should be investigated whenever there is inadequate control of nocturnal asthma symptoms despite the treatment recommended by guidelines having been administered. There is evidence in the literature that CPAP therapy is effective in terms of symptom remission and contributes to asthma control in asthma patients with OSAS and uncontrolled asthma.

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