Asthma and Sleep
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What is This?
Asthma and Sleep
Catherine Kier, MD, AE-C, Stephanie Hom, MD, and Faiza Qureshi MD

Abstract: Asthma significantly affects quality of sleep. Asthma physiology follows a diurnal pattern with peak flow at its lowest during early morning hours. The type and timing of release of inflammatory mediators also varies during the day and nighttime. Nocturnal symptoms are common in poorly controlled asthma. Hence, these nighttime symptoms play a significant role in the assessment of asthmatic patients as demonstrated in validated asthma control and quality of life questionnaires. Comorbid conditions may include allergic rhinitis, obesity, obstructive sleep apnea, and gastroesophageal reflux, all of which may worsen asthma symptoms, especially during sleep. In addition, exposure to greater loads of allergens in susceptible individuals during sleep is a significant problem and must be addressed to break the cycle of poor asthma control. Thus, asthma education for better symptom control should address these particular issues surrounding sleep.

Keywords: asthma; sleep; comorbid conditions; asthma education

Asthma is one of the most common chronic illnesses of childhood, affecting nearly 10 million children in the United States alone. Many of these children suffer significant morbidity and mortality from uncontrolled asthma, including frequent hospitalizations, emergency department visits, absences from school, and impaired quality of life (QOL). Common early respiratory symptoms include episodic coughing, shortness of breath, and wheeze, all of which may indicate an exacerbation. These same symptoms may cause frequent sleep disruptions, which can impair next day functioning.

Many studies have connected asthma symptoms with difficulty sleeping and troublesome childhood behavior. Fagnano and colleagues explored the link between sleep disordered breathing (SDB) and behavioral problems among inner-city children with asthma. Their study consisted of 194 children between the ages of 4 and 10 years, who were enrolled in an asthma intervention program at their school in Rochester, New York. SDB was assessed using the Sleep-related Breathing Disorder Questionnaire, which contains 3 subscales: (a) snoring, (b) sleepiness, and (c) attention/hyperactivity. Behavior was assessed by caregivers using the Behavior Problem Index, which consists of 8 behavioral subdomains. Both sleep scores and behavior scores were then analyzed. At the conclusion of the study, it was discovered that approximately one third of all urban children with asthma suffer from SDB and that a significant number of these children have behavioral problems severe enough to prompt further evaluation. Hence, making strides to improve SDB may help to improve these behavioral problems.

Asthma can result in frequent nighttime awakenings, disturbed sleep, and subsequent excessive daytime somnolence. The reason for this is the rhythmic, circadian nature of asthma symptoms, which often peaks just prior to morning awakening. Asthma severity follows a diurnal pattern with peak lung function in the afternoon and lower respiratory function (a trough) in the early morning. In addition, asthmatics have lower flow rates and greater variation in respiratory function.

The reason for these variations may be in the different levels of inflammatory mediators found in asthmatic patients. For instance, levels of exhaled nitric oxide may be increased in patients with nocturnal asthma symptoms, suggesting the presence of airway inflammation. However, interestingly enough, bronchial biopsies have not discovered significant differences in the degree of inflammation in patients with nighttime symptoms compared with those without—the precise difference and degree of inflammation in these 2 groups have yet to be elucidated. In addition, eosinophils and neutrophils
are found in increased numbers in the lower airways of asthmatics, further mediating inflammatory responses, particularly in patients who have nocturnal symptoms.\textsuperscript{25-27} Epinephrine also plays a role in the relaxation of bronchioles and suppression of histamine, which causes bronchospasms and mucus production. Epinephrine is at its lowest level in the morning just as histamine reaches its peak, also accounting for worsening of asthma symptoms during the nighttime.\textsuperscript{28} All these inflammatory mediators may account for why symptoms of asthma are frequently nocturnal.

In addition, some studies have discovered variations of receptors in patients with nocturnal asthma, helping to account for these symptoms. For example, glucocorticoid receptor binding affinity exhibits circadian variation in patients with nocturnal asthma—this variability is not observed in asthmatic patients without nighttime symptoms or in healthy controls. Also, leukocyte \(\beta_{2}\)-adrenergic receptors are decreased in density and have impaired response in patients with nocturnal asthma symptoms.\textsuperscript{29} Hence, these processes may further contribute to worsening nighttime airway inflammation that is not responsive to glucocorticoids or bronchodilators.

Control of asthma symptoms, including nighttime symptoms, can be assessed by primary care providers. First, providers must classify the patient’s asthma severity and determine initiation of treatment based on the patient’s age. This can be done by referring to clinical guidelines set out by the National Institute of Health (NIH Asthma Guidelines Summary 2007, EPR3).\textsuperscript{30} Severity is divided into 2 domains: impairment (symptoms including daytime functioning and nighttime awakenings, short-acting \(\beta_{2}\)-agonist use, and interference with normal activity) and risk (exacerbations, decline in lung function, and side effects of medications). After management is initiated, asthma control needs to be assessed. Available validated asthma questionnaires that can be used are the Asthma Control Test, the Childhood Asthma Control Test, the Asthma Control Questionnaire (ACQ), and the Asthma Therapy Assessment Questionnaire control index.\textsuperscript{31} They are useful tools to standardize the assessment of asthma control. For instance, the ACQ asks patients to reflect on their asthma symptoms during the past week, looking at nighttime awakenings, shortness of breath, limitation of activity, and so on. The ACQ has been fully validated for clinical practice and has been shown to detect even small differences between different patients’ asthma control.\textsuperscript{32} The ACQ has been validated for use in children aged 6 to 16 years.\textsuperscript{30} Another useful tool is the TRACK (Test for Respiratory and Asthma Control in Kids) questionnaire, which was first introduced by Murphy and colleagues in 2009 for children younger than 5 years of age. This survey asks caregivers to review their child’s symptoms and how they have affected their lives during the past 4 weeks, 3 months, and 1 year. It has been proven to be easy to use and is validated for the assessment of respiratory symptoms in this young population.\textsuperscript{33}

There are numerous factors that may contribute to poor asthma control in patients. In addition to patient noncompliance, certain comorbid conditions may exacerbate symptoms. In particular, asthma symptoms may be triggered or worsened by a host of indoor allergens. Comorbid conditions such as allergic rhinitis, obesity, obstructive sleep apnea (OSA), and gastroesophageal reflux disease (GERD) are contributory factors to poor asthma control (see Figure 1). Each alone can negatively affect asthmatics, but in conjunction, the negative impact is even further amplified. Each of these comorbid conditions will be explored in greater detail in the following sections.

**Comorbidities**

**Allergic Rhinitis**

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines have stressed that both asthma and allergic rhinitis are common comorbid conditions. In patients with allergic rhinitis, airborne particles in the environment can activate mast cells, basophils, and other proinflammatory cells of the nasal mucosa resulting in impaired nasal function. Classic symptoms of rhinitis include sneezing, profuse rhinorrhea, and nasal congestion. Because of this, the ARIA proposes that allergic patients receive combined treatment of both upper and lower airway disease for improvement of symptoms.\textsuperscript{34}

There are many possible allergic triggers that can worsen asthma symptoms, many of which can be found in the bedroom where a majority of the night is spent. These include pollen, dust mites, pet dander, cockroach allergens, cigarette smoke, mold, and others. However, only dust mite allergen has reasonable evidence for being a causative factor for asthma. There remains insufficient or inadequate evidence to prove that...
molds and other environmental aeroallergens have a causal relationship with asthma development, although these allergens may exacerbate symptoms. Nonetheless, patients oftentimes discover that they suffer from multiple indoor allergens that can worsen their rhinitis symptoms and ultimately their sleep quality and QOL.33

Individuals suffering from allergic rhinitis often have impaired quality of sleep, which can lead to more nighttime asthma exacerbations and reduced QOL. Bousquet and colleagues studied the severity of allergic rhinitis in more than 3000 patients using the ARIA classification system.34 This study demonstrated that the severity of allergic rhinitis symptoms in regard to QOL factors, such as sleep, daily activities, and work performance, had a greater impact on QOL than the duration of symptoms. More than 80% of the patients with moderate to severe rhinitis reported impaired QOL compared with those with only mild rhinitis symptoms.

Furthermore, Leger and colleagues discovered that more than 40% of patients with allergic rhinitis had feelings of fatigue despite believing they had a normal night’s sleep.35 Many of these patients reported symptoms of daytime somnolence, morning headache, anxiety, and depression when compared with healthy controls. The severity of rhinitis symptoms influenced the frequency of daytime sleepiness as well as the mean duration of nocturnal sleep. Hence, rhinitis can greatly influence sleep quality and must be controlled to avoid impairment of QOL.

It is apparent that both asthma and allergic rhinitis can be related and often coexist in patients with a history of allergies. Both these diseases may negatively affect sleep quality in addition to QOL, and as a result, both must be controlled to mediate this.

**Obesity**

A striking increase in the number of obese individuals has quickly made the obesity epidemic a prominent public health concern. Obese individuals can have more respiratory symptoms and pathology related to increased weight and body mass index (BMI). Excess body fat can easily affect both upper and lower airways. As a result, pulmonologists are becoming increasingly more involved in the management of these individuals.36 Physical inactivity is common in children who are either obese or who have asthma, and oftentimes these children limit their level of exertion when symptoms are invoked by intense physical activity.5 The precise connection between obesity and asthma still remains unclear; however, longitudinal studies regarding this link have suggested that obesity may precede asthma.36-40

Some studies have suggested that shared genetics might account for this relationship, hinting at a genetic predisposition for the development of asthma and obesity. Researchers have identified particular genes (angiotensin-1 converting enzyme, adrenergic receptor B2, and vitamin D receptor) that may play a role in both asthma and obesity.41,42 Furthermore, genes such as leptin, protein kinase C alpha, and tumor necrosis factor may have pleiotropic effects that allow them to influence both asthma and obesity simultaneously.43-45 Further studies must be done to precisely identify these genetic determinants.47

What is known is that obesity can affect the respiratory system in a variety of ways. First, excess body fat can cause mechanical effects on respiratory system performance, especially during sleep. For instance, fatty infiltration of muscles can directly narrow the upper airway, leading to altered mechanics of breathing. There is also reduced lung volume, including functional residual capacity and expiratory reserve volume.48-50 Reduced functional residual capacity can lead to decreased airway diameters49 and decreased lung volumes at the end of expiration, collapsing the smaller airways.50 Collectively, these factors may result in increased respiratory morbidity, particularly during sleep, which can be reduced or prevented with weight reduction.50

In addition, obesity affects asthma and sleep by causing a proinflammatory state that can progress to airway hyperactivity with abnormal levels of leptin and adiponectin.48 Leptin levels are elevated in obese patients and correlate positively with BMI, airway reactivity, and total IgE.51 In contrast, adiponectin is found in lower levels in the airway smooth muscle of obese individuals, counteracting their anti-inflammatory properties.52,53 Thus, the makeup of the airways on a molecular level is altered in obese patients, predisposing these individuals to airway inflammation.

Overall, the direct link between asthma, obesity, and sleep still remains unclear. Are asthmatics prone to becoming obese because of inactivity or are obese individuals more likely to develop asthma-type symptoms because of excess body fat? In the NHANES III study (the Third National Health and Nutrition Examination Survey), more than 16,000 subjects ages 17 and older were divided into quintiles based on BMI to clarify the relationship between weight and self-reported asthma, bronchodilator use, and degree of airflow obstruction. The most obese subjects were found to have the highest risk of self-reported asthma as well as bronchodilator use. However, this same population was found to have the lowest degree of airflow obstruction suggesting that the dyspnea experienced by obese patients was not likely to be secondary to asthma and that in reality, asthma may be overdiagnosed in these patients.54 In addition, elevated BMI in obese pediatric patients has also been associated with a lack of fitness that may contribute to feelings of dyspnea or breathlessness but may be interpreted as wheezing.55 Hence, these 2 studies demonstrate that asthma may actually be overdiagnosed in obese patients, and the exact relationship between these entities and how to differentiate them have yet to be elucidated.

**Obstructive Sleep Apnea**

There has been a significant rise in the prevalence of OSA, obesity, and asthma during the past several years.56 In the United States, there was a 12-fold increase in the annual number of patients diagnosed with OSA between 1990 and 1998, with that number rising from 108,000 to more than 3 million adults, 4.5% are between 20 and 29 years of age, and
60% of patients are between 40 and 59 years of age. During this same time the prevalence of asthma has significantly increased. OSA has been identified as a risk factor for poorly controlled asthma, and patients with difficulty to control asthma should be screened for OSA. Prevalence of pediatric OSA is about 1% to 4%. In children, history of wheezing is associated with more frequent tonsillar hypertrophy. Likewise, obesity is also significantly associated with asthma and wheezing in children, and unrecognized OSA may partly explain this association. Like the comorbidities previously discussed, OSA in children, and unrecognized OSA may partly explain this association. The association.61

Like the comorbidities previously discussed, OSA may complicate the course of asthma in a patient with both these processes.64 Hence, OSA may complicate the course of asthma in a patient with both these processes. Hence, OSA may complicate the course of asthma in a patient with both these processes.64 Hence, OSA may complicate the course of asthma in a patient with both these processes. Hence, OSA may complicate the course of asthma in a patient with both these processes.64

OSA is characterized by repeated episodes of upper airway occlusion, resulting in brief episode of breathing cessation (apnea) and a marked reduction in tidal volume (hypopnea) during sleep. This leads to oxy-hemoglobin desaturations, persistent inspiratory effort against an occluded airway, and frequent nighttime arousals, all of which contribute to excessive daytime sleepiness and cardiovascular, pulmonary, neurocognitive, and metabolic abnormalities. Decreased sleep quality in OSA shares many characteristics with nocturnal asthma symptoms, including reduced sleep time, snoring, early morning awakenings, and excessive daytime sleepiness. Hence, OSA may complicate the course of asthma in a patient with both these processes.64

Studies have implicated both local and systemic inflammation in the pathophysiology of OSA, originally thought to be simply a mechanical problem. It is postulated that inflammatory changes occur because of snoring, which evokes precise vibration frequencies capable of soft tissue damage and local inflammation. Even C-reactive protein, a nonspecific marker for systemic inflammation, is increased in patients with OSA compared with normal, healthy subjects.65

The primary treatment for OSA in children is typically tonsillectomy and adenoidectomy. However, for patients with only mild disease, recent studies have shown that pharmacologic treatment may be of some benefit. In a study by Kheirandish-Gozal and colleagues, intranasal budesonide was found to be helpful in improving mild OSA, with this effect lasting at least 8 weeks after treatment has been discontinued. In a separate article, these same authors stated that for residual OSA disease following tonsillectomy and adenoidectomy, intranasal budesonide and oral leukotriene modifier therapy may be beneficial. Hence, surgery is no longer the only option for treating OSA in pediatric populations—pharmacotherapy can be helpful in treating mild or residual OSA.

Thus, OSA is characterized by a state of inflammation, which may worsen asthma symptoms. And if both of these disease states are present, then they each must be controlled to alleviate symptoms and improve sleep quality.

Gastroesophageal Reflux Disease

GERD is a common condition affecting 20% to 30% of adult populations and is commonly found in patients with both obesity and asthma. GERD refers to the reflux of gastric contents through the esophagus, with or without signs of mucosal lesions on endoscopic exam. Sleep can contribute to GERD since there is relaxation of lower esophageal sphincter tone and prolongation of gastric acid clearance. Upper airway obstruction in patients with OSA can also change the transdiaphragmatic pressure gradient and lead to reflux of gastric contents into the esophagus. A link between GERD and asthma has also been suggested. Studies have shown increased airway hyperresponsiveness and bronchial hyperreactivity with esophageal acid exposure in patients with both asthma and GERD. Three mechanisms for this have been proposed by Stein and colleagues: first, small amounts of aspirated gastric contents may contribute to airway inflammation; second, GERD may increase vagal tone and stimulate vagal reflexes, ultimately causing bronchoconstriction; and finally, neuroinflammatory reflexes may play a role in airway response through tachykinin release. Together, these 3 mechanisms may lead to airway hyperresponsiveness.

This link is further exemplified in a study by Khoshoo and colleagues. Their study examined the prevalence of bronchial hyperreactivity in nonallergic children with asthma and GERD using methacholine challenge testing before and after antireflux medication treatment. The results of this study suggest that a majority of children with both asthma and GERD have evidence of bronchial hyperreactivity, which decreases after prolonged antireflux medication treatment. These patients had fewer asthma exacerbations following treatment. GERD may also severely affect sleep quality. Gallup, on behalf of the American Gastroenterological Society, conducted a telephone survey of 1000 adults with heartburn symptoms at least once a week. This study discovered that 75% of surveyed adults had nocturnal heartburn symptoms, and the vast majority believed that their symptoms negatively affected sleep quality, oftentimes hampering next-day functioning. Identified predictors for GER during sleep are overweight/obesity, increased intake of carbonated drinks, snoring, daytime sleepiness, insomnia, benzodiazepine use, hypertension, and asthma. Nocturnal GERD, like nocturnal asthma, can severely affect quality of sleep, leading to increased patient morbidity and decreased QOL.

Treatment of GERD can improve nocturnal asthma. A clinical trial using esomeprazole in patients with both nighttime asthma and GERD showed improvement in peak expiratory flow rates. This study provides evidence that GERD treatment potentially improve asthma during sleep. However, the use of proton pump inhibitors (PPIs) in all patients with asthma is not routinely recommended. In a meta-analysis of 11 trials consisting of randomized, placebo-controlled trials, it was discovered that there was a small but statistically significant improvement in morning peak expiratory flow rate. However, the magnitude of improvement was found unlikely to be of strong clinical significance. Hence, the routine use of PPIs is not recommended in all patients with asthma.

Thus, GERD and asthma may occur simultaneously in a patient, with GERD ultimately worsening airway hyperactivity.
Gastroesophageal reflux often occurs during sleep, leading to sleep disruption and daytime sleepiness. Therefore, sleep problems are often exacerbated in the presence of both asthma and GERD components. The only way to treat patients suffering from these ailments is to treat both components. If not, then true asthma control can never be achieved.

Education

Providers can help asthmatic patients with these comorbid conditions in a variety of ways. For patients with allergic symptoms, antihistamines, topical nasal corticosteroids, nasal decongestants, and leukotriene inhibitors may be prescribed or purchased to improve rhinitis, asthma, and sleep quality. It is important to note, however, that the routine use of nasal decongestants is not recommended for pediatric patients because of limited published data regarding the benefits of therapy and the potential for adverse effects. Small household changes can also be made to reduce the presence of indoor allergens and, thus, reduce rhinitis and allergic asthma symptoms. For instance, impermeable encasements for bedroom mattresses and pillows can reduce the presence of dust mites. Some studies have suggested that feather-filled pillows are associated with fewer wheeze episodes than synthetic-filled pillows because of their tightly woven casing. Special air filtration units may be recommended in the home to reduce the presence of indoor air allergens. Education, supervision, and a strong relationship with providers are important for asthma management and optimal sleep. Finally, for obese asthmatic patients, long-term asthma education and nutritional education is desperately needed. A multistep approach of healthy diets and physical activity must be undertaken in conjunction with treatment of asthma in order to decrease patient morbidity and mortality. Primary care providers must work cooperatively with patients to develop this foundation for long-term improvement.

Conclusion

In conclusion, asthma is one of the most common chronic illnesses in the world. Because of the circadian nature of asthma symptoms, oftentimes these symptoms are worst at night. Comorbid conditions including allergic rhinitis, obesity, OSA, and GERD can influence the severity of asthma symptoms, leading to increased morbidity and mortality. Hence, early diagnoses of asthma as well as comorbid conditions are important for asthma management and optimal sleep. Education, supervision, and a strong relationship with providers are needed to control asthma, improve sleep, and improve QOL for those suffering from these diseases.

References


