Allergic rhinitis and sleep: Implications for management

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Because nasal congestion can cause poor sleep and daytime fatigue and somnolence, allergic rhinitis is often associated with decreased learning and productivity at work and school and with a reduced quality of life. The release of inflammatory mediators and activation of inflammatory cells results in nasal congestion, causing disrupted sleep and subsequent daytime somnolence.

Some allergic rhinitis medications, such as the first-generation antihistamines, can be sedating and increase the daytime compromise on quality of life and productivity. It is therefore important to treat allergic rhinitis with medications that improve symptoms while producing few adverse effects. Medications such as the second-generation antihistamines and anticholinergic drugs are well tolerated, but they have little effect on congestion.

Intranasal corticosteroids reduce inflammation and therefore congestion. They also improve sleep quality, reduce daytime sleepiness, and reduce daytime fatigue. Recently, montelukast, a leukotriene receptor antagonist, has been added to the therapies approved for allergic rhinitis. Montelukast significantly improves both daytime and nighttime symptoms.

The goal of allergic rhinitis treatment should include improvement of the typical symptoms of allergic rhinitis—such as congestion, sneezing, rhinorrhea, itchy eyes, itchy nose and postnasal drip, but also sleep, productivity and quality of life.

A matter of quality

Sleep disturbances can reduce quality of life (QOL) and lead to fatigue, irritability, memory deficit, excessive daytime somnolence and depression. Patients with allergic rhinitis (AR) often have a reduced QOL not only because of the AR symptoms (sneezing, nasal pruritus, rhinorrhea and congestion), but also because the pathophysiology of AR itself can disrupt sleep.

This review presents evidence of the relationship between AR and reduced sleep quality. The symptoms and pathophysiology of AR and their diurnal variations are examined to evaluate their impact on sleep quality. Finally, therapies for AR are reviewed to evaluate their potential benefits on sleep and QOL.

AR symptoms cause sleep disturbance

AR can impair learning and often decrease productivity at work, during sports and at school (Figure 1). Patients with AR often attribute their daytime fatigue to medication side effects, when in fact the fatigue may be the result of nasal congestion and associated sleep fragmentation.

Although some AR medications can be sedating, AR itself can also produce sleepiness. Compared with asymptomatic individuals, patients with chronic nighttime symptoms of rhinitis were significantly more likely to be snorers (P < 0.0001), to have more daytime somnolence (P < 0.001) or to feel unrested (P < 0.0001). The symptoms of AR that impact sleep most are rhinorrhea and congestion. Nasal discharge and edema of the nasal mucosa obstruct nasal passages, leading to an increase in nighttime symptoms.
in nasal airway resistance. Furthermore, nasal airway resistance increases when a person reclines. In patients with AR, nasal airway resistance is already increased compared with nonallergic individuals and almost triples when patients lie down. In healthy individuals, this increase is minimal.

Nasal obstruction associated with congestion is also a risk factor for sleep-disordered breathing events, including apnea, hypopnea and snoring. In AR patients whose sleep was measured by polysomnography, obstructive apneas were longer and more frequent in those with nasal obstruction than in those without obstruction (P < 0.01). Furthermore, allergic patients with nasal congestion had a 1.8 greater chance of moderate to severe sleep-disordered breathing than those without congestion.

Compared with healthy people, AR patients had 10 times more “microarousals” from sleep in association with periodic breathing and hypopneic and hyperpneic episodes. Of children who snored habitually, 36% were sensitive to allergens, approximately three times the rate in non-snoring children. Moreover, in asthmatic patients, AR may be an important cause of sleep disturbance.

In one study, more than 70% of asthmatic patients had AR, which was independently related to difficulty inducing sleep and to daytime sleepiness.

These data suggest that treating AR symptoms to decrease nasal congestion will likely decrease sleep disturbances and subsequently lessen daytime fatigue and improve QOL.

The early-phase response of AR, which is initiated within minutes of allergen exposure, is primarily due to the release mediators by mast cell. These include histamine, cysteinyl leukotrienes (CysLTs), cytokines, chemotactic factors and enzymes—all of which produce the early symptoms of AR (primarily sneezing, itching and rhinorrhea). The late-phase response of AR, which begins two to four hours after allergen exposure, is essentially a cellular event. Mediators released during the early phase stimulate the production, adhesion and infiltration into local tissue of circulating leukocytes, especially eosinophils. When these inflammatory cells become activated, they release their mediators, thereby promoting local edema and tissue damage and perpetuating the overall inflammatory process. Therefore, late-phase AR is characterized by nasal congestion and obstruction rather than the sneezing and rhinorrhea characteristic of the early phase.

Several mediators involved in AR inflammation are also implicated in the pathophysiology of sleep disturbances. Among them, histamine, a vasodilator and a potent stimulator of vascular permeability and mucus secretion, contributes to nasal obstruction and congestion. Histamine also helps regulate the sleep-wake cycle, arousal, cognition and memory.

The CysLTs are important mediators of the inflammatory process in AR patients. CysLTs increase nasal airway resistance and obstruction and contribute to rhinorrhea by increasing vascular resistance.

Pathophysiology of AR causes sleep disturbances

Besides the obvious impact of AR symptoms on sleep, elements of the AR pathophysiology, such as inflammatory cells and mediators, can contribute to poor sleep.

The Allergy-Specific Work Productivity and Activity Impairment Questionnaire (WPAI-AS) was used to assess the impact of AR on patients’ ability to work and carry out regular daily activities. Questions were also modified to assess productivity impairment in the classroom (some patients were both employed and students; age range, 11 to 68 years). Data obtained from 1,425 employed patients and 556 students with moderate-to-severe seasonal AR confirmed the detrimental effect of AR in the workplace, in the classroom and on daily activities. More than 90% of the 1,885 patients believed their ability to perform daily activities was impaired because of seasonal AR. Similarly, more than 90% of the employed patients and students believed their work or classroom productivity was negatively affected by seasonal AR. Moreover, approximately one-quarter of patients reported missing some work or school due to allergy symptoms in the seven days preceding the assessment.

Allergic rhinitis has negative effects on learning ability, and some AR therapies may affect learning as well. Children (n = 52) suffering from seasonal AR and matched healthy children (n = 21) received one of the three following treatments for two weeks: a sedating antihistamine (i.e., diphenhydramine, n = 18), a nonsedating antihistamine (i.e., loratadine, n = 17), or placebo (n = 17). Composite learning scores for the healthy children were significantly (P = 0.007) better than for children with seasonal AR treated with placebo, suggesting that seasonal AR, by itself, caused learning impairment. The scores for children with seasonal AR who received loratadine were not significantly different from those of healthy children, but the scores for those who received diphenhydramine were significantly (P = 0.002) lower, demonstrating that seasonal AR plus sedating antihistamines (but not non-sedating antihistamines) had a negative effect on learning.


Diurnal variation in inflammation and sleep disorders

Many biological processes have a circadian rhythm. For example, lung functions in healthy people have a circadian rhythm that peaks at 4 pm and is lowest at 4 am.34 In nocturnal asthma (but not in non-nocturnal asthma), circadian variations are increased by more than 15% and include nighttime increases of inflammatory eosinophils and basophils.34 Similarly, in AR patients, the levels of these cells are highest in the early morning (P <0.05 for 6 am compared to 3 pm levels).35

In AR patients, symptoms can be more severe upon waking. Seventy percent of patients have more intense sneezing, blocked nose, and runny nose in the morning than at other times. The variation in intensity between day and night is about 20% of the 24-hour mean level.36

In asthmatic patients, CysLT levels were higher than in healthy individuals in nocturnal, but not in non-nocturnal asthma.40 Therefore, there is a potential
for inflammation to increase during the night and subsequently lead to sleep disturbance. Furthermore, the decrease in affinity was also observed in atopic asthmatics, in whom allergen exposure significantly reduced the binding of glucocorticoids to their receptor. The mechanistic links between these circadian cycles and inflammation are not fully understood.

Management of AR improves associated sleep disturbances

Any therapy that can reduce AR symptoms—especially congestion—should help improve sleep quality and subsequently the QOL of patients with sleep disturbances associated with AR. Agents in a variety of classes are available to help manage AR. Among them, intranasal or oral decongestants can effectively reduce nasal obstruction and congestion, subsequently improving the sleep quality of AR sufferers. Intranasal formulations act within 10 minutes and many work up to 12 hours. Adverse effects may include nasal burning, dryness, mucosal ulceration and even septal perforation. With oral formulations, activity starts within 30 minutes and lasts up to 6 hours, or for 8 to 24 hours with sustained-release formulas. Systemic effects can include irritability, dizziness, headache, tremor, tachycardia and insomnia, which in turn can result in daytime somnolence. Tachyphylaxis and a rebound of symptoms (rhinitis medicamentosa) can result from prolonged decongestant use. Thus, their chronic use is not recommended.

Antihistamines are the oldest drugs used to treat allergic diseases. First-generation antihistamines (e.g., chlorpheniramine, diphenhydramine, promethazine, tripolidine) have an unfavorable risk/benefit ratio overall, with poor selectivity and a high rate of anticholinergic and sedative effects. Although these antihistamines may help at night and lead to better sleep, during the day patients may experience fatigue or sleepiness.

Furthermore, these antihistamines can impair learning, especially in children (Figure 2), and they can have effects like those caused by alcohol, making skilled activities more difficult or dangerous (Figure 3). Low or nonsedating second-generation antihistamines (e.g., cetirizine, loratadine, fexofenadine, desloratadine) have higher potency and longer durations of action than sedating antihistamines. It has been shown that sedative effects of these antihistamines correlate with the level of antihistamine that crosses the blood-brain barrier. For example, fexofenadine, which does not cross the blood-brain barrier, tends to be less sedative than cetirizine, which occupies 30% of the H1 receptors in the brain.

Certain medications for the treatment of AR may carry potential risks, including drowsiness and impairment of everyday tasks. During the ragweed season, the effects of fexofenadine (60 mg), a nonsedating antihistamine; diphenhydramine (50 mg), a sedating antihistamine; alcohol (estimated blood alcohol concentration of 0.1% [21.7 mmol/L]); and placebo were compared in 40 adults allergic to ragweed pollen. The experiment was of crossover design with four treatments on four successive sessions one week apart. Participants taking diphenhydramine felt significantly (P < 0.05) drowsier than did those on any other treatment. These results show that depending on the chosen agent, therapy can have a negative impact on alertness.

Patients with AR symptoms, particularly congestion, often have disturbed sleep, daytime somnolence and fatigue. Therefore, records of patients’ sleep patterns and daytime alertness should be part of the medical history used to diagnose AR and to establish a treatment plan.
Azelastine used topically reduced rhinorrhea but failed to reduce congestion in one study,44 but not in another.45

Because antihistamines are not very effective against congestion, they are often combined with a decongestant. Because of the side effects of both drugs, however, caution should be used, especially with other over-the-counter combinations that contain a sedating first-generation antihistamine and a decongestant. Such combinations can cause insomnia and subsequently daytime fatigue.

According to the recent “Allergic Rhinitis and Its Impact on Asthma (ARIA) Guidelines,” these combinations should no longer be used.42

Anticholinergic drugs, such as ipratropium bromide, have antisecretory properties and a high safety profile with minimal crossing of the nasal and gastrointestinal mucosae as well as the blood-brain barrier. When delivered locally to the nasal mucosa, they inhibit mucus secretion and the subsequent rhinorrhea in both adults and children with perennial AR.

In children with perennial AR, ipratropium bromide given topically significantly (P <0.05) improved rhinorrhea, congestion and sneezing compared with baseline. Responses to QOL questionnaires also showed that after 6 months of treatment, ipratropium improved sleep by almost 50%. However, because it does not usually relieve nasal congestion or sneezing associated with seasonal AR, it is recommended by the ARIA guidelines as first-line therapy only when rhinorrhea is the primary symptom.42

Intranasal corticosteroids have proven efficacy in AR patients, compared with placebo. They reduce congestion (P = 0.01) and improve sleep (P = 0.01) (Figure 4);11 furthermore, they reduce
daytime sleepiness (P = 0.02), daytime fatigue (P = 0.03) and sleep problems (P = 0.05).12 Because of their topical application and low systemic bioavailability, INS are generally considered safe and have a minimal influence on adrenal suppression.46 In treating concomitant diseases such as asthma, however, the amounts of nasal, inhaled or oral steroids should be adjusted to avoid unwanted effects, including adrenal suppression.42

CysLTs are mediators of AR symptoms, and of congestion in particular, and it is rational to use an antileukotriene to alleviate both daytime and nighttime symptoms. For example, after an allergen challenge in AR patients, zileuton, a leukotriene synthesis inhibitor, reduced congestion (P <0.02).47 Similarly, the leukotriene receptor antagonists (LTRAs) provide effective symptomatic relief, compared with placebo. Pranlukast reduced nasal mucosal swelling (P <0.01),48 and zafirlukast reduced congestion (P <0.01), rhinorrhea and sneezing (P <0.05 for both).49 Montelukast is the only LTRA currently approved for treatment of AR in the United States. It significantly improves nighttime symptoms (difficulty going to sleep, nighttime awakenings and congestion on awakening) as well as daytime symptoms (congestion, rhinorrhea, pruritus and sneezing), compared with placebo.

Montelukast significantly (P <0.05) improved both daytime and nighttime symptoms (Figure 5) in patients with allergies in the spring33,50 and fall. Furthermore, montelukast significantly (P <0.001) reduced the number of peripheral blood eosinophils, suggesting that montelukast reduces allergic inflammation systemically.31 In these studies, the effects of montelukast on congestion were evaluated subjectively using nasal symptom scores that were obtained from answers to questions about congestion.

Final notes
Patients with AR symptoms, particularly congestion, often have disturbed sleep, daytime somnolence and fatigue. Therefore, records of patients’ sleep patterns and daytime alertness should be part of the medical history used to diagnose AR and to establish a treatment plan. In asthma and AR, inflammation increases at night, often leading to disturbed sleep and early-morning symptoms.

Treatment with INS reduces nighttime inflammation; as a result, patients report less congestion and better sleep. Recently, the LTRA montelukast was shown to effectively reduce not only daytime but also nighttime symptoms of AR.

With these effective treatments available, patients have additional incentives to manage their AR actively, because good AR treatment improves not only the AR symptoms, but also sleep. With improved sleep, patients should experience increased productivity, alertness, responsiveness, vigilance and better quality of life, and they should hope to become more successful competitors.

Using a symptom diary, patients rated their nighttime symptoms, including nasal congestion on awakening, difficulty falling asleep, and nighttime awakening. Nighttime symptoms were rated on a 4-point scale, with “0” representing the absence of symptoms and “4” representing the most severe symptoms. Patients who received montelukast 10 mg per day (purple bars), significantly (P < 0.05) reduced nighttime symptom score from baseline, compared with placebo (blue bars).


Figure 5 Montelukast reduces nighttime symptoms in spring seasonal AR

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Resources

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