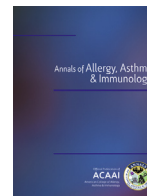




Contents lists available at SciVerse ScienceDirect



Review

Sleep impairment and daytime sleepiness in patients with allergic rhinitis: the role of congestion and inflammation

Alison Thompson, MS^{*}; Niti Sardana, MD[†]; and Timothy J. Craig, DO^{*}^{*} Penn State University, Hershey Medical Center, Hershey, Pennsylvania[†] New York Presbyterian Hospital, New York, New York

ARTICLE INFO

Article history:

Received for publication March 5, 2013.

Received in revised form May 18, 2013.

Accepted for publication May 21, 2013.

ABSTRACT

Objective: To investigate the association of rhinitis with stress, fatigue, decrease productivity, inflammation, and sleep disordered breathing.**Data Sources:** Medical literature obtained from OVID and PubMed searches in February 2013 using the search terms “sleep,” “rhinitis,” “allergic rhinitis,” “somnolence,” and “fatigue”.**Study Selection:** Studies were selected based on the US Preventive Services Task Force levels 1, 2, and 3.**Results:** Allergic rhinitis is a disease that severely affects patients' quality of life and is increasing in prevalence worldwide. Nasal congestion is reported as the most common and bothersome symptom; it is often associated with sleep-disordered breathing, a likely cause of sleep impairment in rhinitis-affected individuals. The end result is a reduced quality of life and productivity and an increase in daytime sleepiness, fatigue, and stress. Current treatment modalities include intranasal corticosteroids, which have been found to reduce nasal congestion. Clinical trials on intranasal corticosteroids have provided data on sleep-related end points, and these studies report that the improved nasal congestion is associated with improved quality of life with better sleep and reduced daytime fatigue. Alternate therapies, including montelukast, also decrease nasal congestion and positively influence sleep, but to a lesser extent.**Conclusion:** This review examines nasal congestion and cytokine changes and the associated sleep impairment in allergic rhinitis patients and the effect on daytime performance. It elaborates the adverse effects of disturbed sleep on quality of life and how therapies directed at reducing nasal congestion can relieve such effects.

© 2013 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Allergic rhinitis (AR) is thought to affect up to 40% of the population, and its prevalence is increasing worldwide.¹ In the United States alone, estimates suggest that 60 million people are affected by AR. Approximately 80% of people with AR are symptomatic before 20 years of age, and the overall prevalence of AR in children is reported to be 40%.^{2,3}

AR can be categorized as perennial or seasonal based on the allergen sensitivity and timing of the inflammatory stimulus. In addition, severity of symptoms, effect on productivity, and quality of life can affect the categorization. In addition, according to Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines, the duration of symptoms is important in determining classification and treatment.⁴ Symptoms include nasal congestion, rhinorrhea, sneezing,

and pruritus of the eyes, nose, and throat.² Typical sleep-related problems seen in AR include sleep-disordered breathing, sleep apnea, and snoring, all of which are associated with nasal obstruction and cytokine changes.⁵

Allergy-induced nasal congestion has a large effect on both children and adults. The 2009 Pediatric Allergies in America survey emphasized that congestion or stuffy nose is the most reported symptom that affects children.⁶ In adults, the 2009 Burden of Rhinitis in America survey indicated that sleep disturbance played a major negative role in rhinitis patients, with less than 5% of the almost 4000 AR patients surveyed experiencing 100% sleep adequacy.⁷ In a recent survey of individuals with AR, 68% of respondents with perennial allergic rhinitis (PAR) and 48% with seasonal allergic rhinitis (SAR) reported that their condition interfered with sleep.⁸ Overall, sleep impairment is a significant problem for patients with AR, and nasal congestion is one of the main causes.

Rhinitis also poses a significant socioeconomic burden. In 2000, it was estimated that more than \$6 billion was spent on prescription medications for AR.^{2,3,9} In 2005, these costs almost doubled according to a report by the Agency for Healthcare Research Quality. These socioeconomic costs include those for treatment, reduced productivity, and the use of inappropriate therapies. Both the

Reprints: Timothy Craig, DO, Penn State University, College of Medicine, Department of Allergy/Immunology, 500 University Dr 29 UME, Hershey, PA 17033; E-mail: tcraigpsu@yahoo.com.

Disclosures: Dr Craig has conducted research for GlaxoSmithKline, Schering, Novartis, Genentech, and Merck & Co and served as a speaker for Teva Pharmaceuticals, Genentech, Schering, Novartis, and Merck & Co. No potential conflicts of interest relevant to this article were reported.

Medical Outcomes Study Short Form Health Survey and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) have found that AR significantly affects patients' quality of life, which further contributes to the costs listed above.^{10,11}

Treatments directed at the symptomatic management of AR, particularly those that reduce nasal congestion and inflammation, have been found to improve patients' sleep and quality of life. Unfortunately, the data to prove a causal relationship between nasal congestion and inflammation and sleep disturbance are limited. Thus, further research is warranted.

We performed OVID and PubMed searches of the medical literature and selected studies based on the US Preventive Services Task Force levels 1, 2, and 3 in February 2013 using the search terms "sleep," "rhinitis," "allergic rhinitis," "somnolence," and "fatigue". This review explores the importance of congestion and inflammation in people with rhinitis and also addresses the adverse effects of disturbed sleep on quality of life, productivity, and performance. Finally, this review describes therapeutic modalities that can reduce these adverse effects by targeting the underlying problems that affect sleep.

Nasal Congestion and Sleep Impairment

Depending on methods used and populations surveyed, rhinitis has a prevalence of 15% to 40%, and more than 50% of these individuals have congestion as their main symptom. Even more concerning are the effects of congestion on those who experience it. Stull et al¹² concluded that congestion alone accounted for 73% of the adverse outcomes associated with allergic rhinitis, including poor sleep, missed work, and activity impairment. Congestion had a much greater effect on patients than any other symptom of rhinitis assessed. According to individuals in this cohort, 30% of impaired sleep was secondary to congestion. Congestion alone was calculated to have a direct cost of US \$3.4 billion and an indirect cost of US \$3.1 billion.

In the Pediatric Allergies in America survey, 52% of respondents reported that they experienced congestion most days of the week, making congestion the predominant symptom that affects children. Seventy-five percent of the respondents called congestion the most bothersome symptom. When health care professionals were polled with a similar question, 92% deemed congestion the worst symptom in their patients.⁶ Children in this cohort were described as less likely to be happy, energetic, peaceful, and full of life. Parents thought that their child's rhinitis had a negative effect on performance in school, sports, and activities. Furthermore, parents rated their rhinitis-affected children as being less healthy, less productive, limited in the ability to work, and more likely to have difficulty completing tasks. A total of 40% of parents believed allergies affected their child's sleep; 32% reported their children had difficulty falling asleep, 26% reported their children awakened at night due to sleep problems, and 29% reported their children had a lack of good sleep.⁶ As demonstrated here, both the pattern and quality of sleep were affected by allergies.

Adults with allergic rhinitis experience similar sleeping difficulties; AR patients were more likely to have poor sleep compared with those with nonallergic rhinitis or those without rhinitis symptoms. Only 3.6% of patients with AR symptoms in the previous month had 100% quality of sleep during this time vs 19.2% who had no symptoms of rhinitis.⁷ Overall, reports estimate that 57% of adults and 88% of children with AR have sleep problems and associated poor productivity and difficulties at work.¹³

Evidence of Sleep Impairment

As previously described, rhinitis is associated with sleeping difficulties, daytime somnolence, and fatigue. Because the symptoms of AR, particularly nasal congestion, adversely affect sleep, the

ARIA guidelines use the degree of sleep impairment to classify AR severity.⁶ Sleep disturbances associated with AR consist of both microarousals and sleep-disordered breathing (ranging from snoring to obstructive sleep apnea [OSA] and/or hypopnea).^{14–17} Individuals with frequent nighttime rhinitis symptoms have been found to be more likely to have chronic excessive daytime sleepiness or chronic nonrestorative sleep than those who rarely have such symptoms.¹⁸ Actigraphy studies have provided objective evidence for the discrepancy in the amount of sleep disturbance between adults with PAR and healthy control participants.¹⁹

Studies in children have reported that AR and allergic sensitization are associated with snoring.²⁰ Rhinitis has also been established as an independent risk factor for disordered sleep in children, as demonstrated by Bixler et al.²¹ A study in young adults with asthma found the presence of concomitant AR to be independently related to difficulties inducing sleep and also to daytime sleepiness.²² As indicated in this study, the evidence of sleep impairment is apparent across all age groups.

Mechanisms of Sleep Impairment

To reduce the effect of AR on patients' daily living, it is essential to identify the mechanisms that underlie sleep impairment and daytime fatigue. Multiple mechanisms have been addressed that may contribute to these adverse effects, particularly nasal congestion. Still, other rhinitis symptoms, such as ocular itch, may play a role.^{25,26} It is unclear whether fatigue is more a result of nasal congestion than other symptoms of rhinitis. Fatigue could also result from the direct effects of inflammatory cytokines. Current evidence suggests that underlying pathophysiologic changes of the AR, including cytokines, also contribute to decreased sleep quality and can affect latency to and duration in rapid eye movement (REM) sleep. In addition, cytokines, such as interleukin (IL) 1 and tumor necrosis factor (TNF), can result in daytime somnolence and fatigue.^{23,27} Figure 1 and Figure 2 illustrate the importance of cytokines in rhinitis and sleep impairment. Figure 1 highlights that cytokines are elevated in sleep apnea and that similar elevations are seen in patients with rhinitis and sleep disturbance. These cytokines can worsen sleep quality and cause daytime somnolence and fatigue. Figure 2 emphasizes the effect that cytokines can have on sleep.

Nasal congestion occurs when capacitance vessels dilate in the cavernous tissues of the nasal turbinates.²⁶ This leads to a smaller internal nasal diameter, which increases airway resistance to nasal airflow and results in nasal obstruction.²⁶ In addition to subjective clinical assessments of the severity of nasal congestion, objective measures of nasal airflow (eg, peak nasal inspiratory flow), airway resistance and conductance (rhinomanometry), and nasal cavity volume and area (acoustic rhinometry) have been used to determine the degree of congestion (nasal patency).²⁷

- | | |
|--|--|
| • Obese male with obstructive sleep apnea | • Young female with congestion and allergies |
| • Elevated pro-inflammatory cytokines IL-1, IL-6 and TNF | • Elevated pro-inflammatory cytokines IL-1, IL-6 and TNF |
| • Elevated T-helper 2 lymphocytes | • Elevated T-helper 2 lymphocytes |
| • Depressed T-helper 1 lymphocytes | • Depressed T-helper 1 lymphocytes |

Figure 1. Comparing cytokine changes from an obese male with obstructive sleep apnea to a young female with rhinitis and sleep disturbance

Cytokine	Effect on Sleep
IL-6, IL-1, TNF	Increases fatigue, mood disturbance
CysLT	Increases slow-wave sleep, congestion and sleep disturbance
Bradykinin	Increased in sleep apnea
IL-1, IL-4, IL-10	Increases latency to REM and decrease duration of REM
IL-6, TNF	Increased in sleep disturbance
Substance P	Increases latency to REM and increases arousals

Figure 2. Inflammatory mediators elevated in allergic rhinitis and effect on sleep and daytime symptoms.

Nasal congestion varies in severity with the time of day; it is often worse at nighttime and during early morning hours. In healthy people, compensatory mechanisms normally reduce congestion in the supine position; however, these mechanisms are not sufficient in rhinitis patients.²⁸ One such mechanism that may contribute to nighttime worsening is the normal overnight decline in serum cortisol. Patients with asthma similarly demonstrate associations between greater airway obstruction and lower cortisol levels.²⁹ A large study in patients with AR confirmed that nasal congestion worsened overnight and peaked at approximately 6 AM, showing a clear, large-amplitude, circadian variation similar to that seen in asthma patients.³⁰

Research on the treatment of nasal congestion also supports that congestion is a significant process responsible for the disturbed sleep and daytime fatigue that occur with this condition.¹⁵ Early studies using objective assessments of sleep in patients with AR indicated that nasal congestion is related to an increase in the number of microarousals¹⁶ and apneic episodes.¹⁴ Large population-based studies confirm that congestion and poor sleep are associated.³¹ When developing the Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire (NRQLQ), Juniper et al³² found that patients with allergic rhinoconjunctivitis and sleep disturbance report stuffy nose and sinus congestion as 2 of the most disruptive symptoms.

A population-based study (n = 4927) investigating the role of acute and chronic nasal congestion in the development of sleep-disordered breathing provides additional support for the direct effect of congestion on sleep. Those with frequent nocturnal symptoms of rhinitis were more likely to report habitual snoring, chronic nonrestorative sleep, and excessive daytime fatigue compared with those who never had symptoms. Individuals with nasal congestion caused by AR were 1.8 times more likely to have moderate to severe sleep-disordered breathing than those with AR without nasal congestion.³³ The role of congestion as a risk factor for habitual snoring was confirmed in a population-based cohort study (n = 4916).³⁴ It is believed that the switch to oral breathing that occurs as a result of nasal congestion may be the key factor behind this association.

Other symptoms, such as sneezing, rhinorrhea, and nasal pruritus, may contribute to reduced sleep quality and sleep disturbance in individuals with AR. One study concluded that rhinorrhea was troublesome to patients with AR and interfered with sleep. Ocular itching has also been demonstrated as a cause of sleep disturbance.³² Two studies verified the relationship between AR-associated ocular itch and subjective sleep difficulty.^{35,36}

Histamine, cytokines, and other inflammatory mediators released during allergic reactions may directly affect the central nervous system and therefore contribute to disturbed sleep and daytime fatigue.^{37–39} Histamine is involved in the regulation of

arousal and the sleep-wake cycle.³⁷ Elevated levels of IL-1 β , IL-4, and IL-10 in allergic patients correlate with increased latency to REM sleep, decreased time in REM sleep, and decreased latency to sleep onset compared with healthy individuals.³⁹ REM sleep provides an important restorative function. Therefore, a disruption in REM sleep may contribute to daytime fatigue, difficulty concentrating, and worse performance in individuals with AR.³⁹ Peaking levels of inflammatory cells and mediators in the early morning hours correlate with increase of congestion in the early morning and the degree of sleep disturbance, making it difficult to determine which of the 2 have the greatest effect on sleep.⁴⁰

OSA has a cytokine milieu similar to that found in AR (Fig 1). The cytokine changes seen in sleep apnea are a T_H2 cell phenotype, and these cytokines result in inflammation and an increase in nasal congestion. Various cytokines, which are elevated in rhinitis, can affect sleep (Fig 2). In addition, elevated levels of TNF, IL-6, and IL-1, which are seen in both AR and OSA, can result in fatigue and other nonspecific constitutional symptoms, as well as stress, depression, and viral-like symptoms.⁴¹

Researchers are currently examining the potential role of autonomic dysfunction in sleep. The extent to which excessive cholinergic tone and diminished adrenergic activity correlate with congestion-induced sleep disturbance is unknown. However, autonomic disturbance has been associated with mild OSA. The autonomic abnormalities noted by Woodson et al⁴² may precede OSA, or they may contribute to the pathologic mechanism. Although we know the role of cholinergic activity in vasomotor rhinitis and nonallergic rhinitis, further research is warranted to determine what role this mechanism plays in AR and its associated nasal congestion and sleep dysfunction.

In summary, multiple mechanisms affect sleep quality in rhinitis. Nasal obstruction is the most researched and has a significant effect on sleep quality. However, as pointed out previously, other symptoms of rhinitis and components of the immune and inflammatory response can also influence sleep.

Sleep Impairment and Quality of Life

As noted, individuals with AR have impaired cognitive function and reduced work productivity and performance.^{43–45} AR can affect children's learning ability and performance at school and cause somnolence and inability to concentrate.⁴⁶ These effects may be a direct result of allergic symptoms, and they are likely exacerbated by sleep impairment.⁴⁷ Sleep-disordered breathing and sleep disturbance are directly associated with decreased quality of life in the general population⁴⁸; even experimentally induced sleep fragmentation in healthy individuals is associated with impaired mental flexibility and attention, increased daytime sleepiness, and impaired mood.^{49,50} Adolescents with AR have difficulty getting a good night's sleep and experience problems doing schoolwork.⁵¹ Children with rhinitis and snoring have poorer school performance than healthy individuals.⁵² Daytime fatigue, difficulty concentrating, and impaired psychomotor performance are commonly reported by individuals with AR. Furthermore, these difficulties may reduce the ability to perform the physical and social tasks of daily living.^{12,44,53} An Internet-based survey of 1322 people with self-reported rhinitis found that PAR and SAR interfered with sleep (68% and 51% of respondents, respectively) and the ability to perform their daily routine (58% and 48%, respectively).⁸

One of the largest surveys to examine the effect of rhinitis was performed by Meltzer et al⁷ using a self-reporting questionnaire. They surveyed 3831 people with rhinitis and 3193 without rhinitis. Quality-of-life instruments specific for rhinitis were used to assess sleep quality.⁵⁴ The results indicated that those with rhinitis missed more work or school, had poorer quality of life, and had decreased productivity. Other studies using subjective and objective

measurements of sleep impairment and its effect on patients' quality of life have emphasized the significance of this problem for those with AR. Numerous methods have been used to assess effect on sleep; however, most are not specific for rhinitis. Disease-specific quality-of-life measures (eg, the RQLQ) include a domain that measures the effects of disease and/or treatment on sleep.³² These questionnaires are more sensitive to changes in patients' quality of life than generic health status questionnaires because they focus on the problems for which patients seek help. The NRQLQ assesses the functional impairments that are most problematic for patients with nocturnal symptoms,³² including difficulty sleeping, rhinitis symptoms during nighttime and awakening, and problems during waking hours.

General surveys that subjectively assess daytime sleepiness and sleep quality include the Epworth Sleepiness Scale,⁵⁵ the Pittsburgh Sleep Quality Index,⁵⁶ the Calgary Sleep Apnea Quality of Life Index,⁵⁷ and the University of Pennsylvania Functional Outcomes of Sleep Questionnaire⁵⁸ plus others. However, poor sensitivity and specificity may limit the use of these questionnaires in assessing the mild to moderate sleep disturbance often noted in patients with rhinitis.

Only a few studies have objectively assessed sleep (using polysomnography) in AR.^{14,16,18,20,24,25,34,59,60} In one such study, 25 patients with SAR and 25 healthy volunteers underwent 2 consecutive nights of polysomnography before and during pollen season.²⁵ There were statistically significant differences in sleep parameters between the 2 groups, including increases in the apnea index (number of apneas per hour), hypopnea index (number of hypopneas per hour), apnea-hypopnea index, snoring time, amount of REM sleep, and sleep latency in the AR group. Although the authors considered the changes clinically irrelevant because the values remained within normal limits (<5 episodes of apnea hypopnea per hour), the sleep parameters worsened in accord with rhinitis symptoms. Of note, the authors did not assess for microarousals, which can fragment sleep. The study also found a statistically significant increase in daytime sleepiness (assessed subjectively using the Epworth Sleepiness Scale) in patients with SAR compared with healthy individuals, reinforcing the known poor correlation between subjective and objective measures of sleep disturbance.

Effects of Therapy

Therapies that target the mechanisms associated with sleep disturbance and daytime fatigue may improve quality of life in people with AR. Nasal congestion is a primary target because of the large amount of evidence linking it to these symptoms. In addition,

because inflammation can produce constitutional symptoms, therapies directed against inflammatory mediators, such as TNF, may positively influence quality of life. Figure 3 includes most of the available therapies for use in rhinitis.

Nonsedating oral antihistamines are widely used to treat AR. Although they relieve nasal symptoms, such as rhinorrhea, sneezing, and pruritus, they do not have a significant effect on nasal congestion or inflammatory mediators. This is despite some studies reporting an improvement in sleep and quality of life, as well as some anti-inflammatory effects, after therapy with an second-generation antihistamine or topical antihistamine.^{61,62} Although nonsedating antihistamines are tolerated well and often improve sleep and quality of life, data have suggested that first-generation antihistamines and topical antihistamines with sedating properties may exacerbate daytime somnolence. Histamine is important in the central nervous system for arousal, and inhibition of the histamine receptors in the central nervous system results in the sedation and somnolence discussed above.^{61,62} For this reason, sedating antihistamines are contraindicated in those experiencing daytime sedation, fatigue, and functional impairment and thus should be avoided.

Oral decongestants reduce nasal congestion, but they also cause adverse effects, such as tachycardia, sexual dysfunction, and urinary retention, that may negatively affect sleep. Topical decongestants seem to improve sleep in patients with nasal obstruction,⁶³ yet they are not a good long-term option for symptomatic relief because the risk of rhinitis medicamentosa ("rebound" congestion) limits the use of topical decongestants to short periods. Although the anticholinergic agent ipratropium bromide is not considered effective in relieving nasal congestion, there are limited data suggesting that its use in AR treatment may improve sleep and daily living.⁶⁴

Leukotriene receptor antagonists⁶⁵ or a combination of an antihistamine and a leukotriene receptor antagonist⁶⁶ have shown some efficacy in improving sleep and quality of life in patients with AR and sleep-disordered breathing. The mechanisms responsible for improved sleep and decreased daytime somnolence may include congestion reduction, a decline in inflammatory mediators, or a combination of these. Montelukast, for instance, is an effective intervention in young children with large adenoids, especially in those with increased levels of inflammatory mediators and daytime somnolence and sleep disturbance.⁶⁷

According to the ARIA guidelines persistent AR is best treated with intranasal corticosteroids, and intranasal corticosteroids are considered first-line therapy when patients predominantly have nasal congestion. They relieve nasal symptoms and decrease inflammatory mediators secreted from activated lymphocytes, epithelial cells, mast cells, and other inflammatory cells.^{4,68} All intranasal corticosteroids currently available effectively reduce nasal congestion. The improvement in nasal congestion is both subjective and objective; objective evidence is assessed by an increase in peak nasal inspiratory flow in AR patients treated with intranasal corticosteroids.⁶⁹

Alleviation of nasal congestion using intranasal corticosteroids may have beneficial effects on sleep, daytime fatigue, and quality of life in patients with inflammatory nasal conditions. Three small studies in adults and children with PAR found that intranasal budesonide reduces nasal congestion, subjective daytime somnolence, and fatigue, thus improving sleep quality and patients' quality of life.^{59,70,71} Another intranasal corticosteroid, flunisolide, improved subjective assessments of nasal congestion and sleep problems in patients with PAR compared with placebo. Daytime fatigue and sleepiness, however, did not produce significant improvement.²⁴ Berlin et al⁷² found that flunisolide was superior to azelastine nasal spray in improving nasal congestion, sleep, and daytime sleepiness in patients with PAR. In another study with PAR patients, intranasal fluticasone significantly improved subjectively

	Decreases congestion	Anti-inflammatory	Improves eye symptoms	Improves sleep	Improves daytime somnolence
Non-sedating AH	+	+	++++	+	+
Sedating AH	0	0	++++	+++++	-
Nasal CS	++++	+++++	++	+++	++++
Oral DC	+++	0	0	-	+++
Topical-IN DC	+++++	0	0	+	0
IN-Cromones	+	+	0	0	+
Topical AH	++	++	+	+	-
Anti-LT	++	++	++	++	++

Figure 3. Effects of therapies for allergic rhinitis on congestion, sleep, daytime somnolence and inflammation. AH = antihistamines, DC = decongestion, CS = corticosteroid, IN = intranasal, LT = anti-leukotriene, - = negative effect, + to +++++ is improving positive effect.

assessed sleep compared with placebo; it reduced daytime sleepiness and fatigue by more than 10%.⁶⁰ Mansfield and Posey⁷³ replicated these findings in children and likewise demonstrated improved daytime sleepiness, improved cognitive function, and decreased mood disturbance. The study was placebo-controlled and double-blinded, adding significance to the results.

Fluticasone propionate nasal spray improved nasal symptoms, quality of life, and verbal memory in children with SAR.⁷⁴ Furthermore, intranasal fluticasone improved AR associated with OSA syndrome; treatment resulted in a significantly lower frequency of apnea and hypopnea. Subjective improvements in nasal congestion and daytime alertness were also noted, although snoring noise and sleep quality were unchanged compared with placebo.⁷⁵

Data indicate that all intranasal corticosteroids improve quality of life in patients with AR. Milgrom et al.⁶⁴ reported that beclomethasone dipropionate controlled nasal congestion and improved quality of life in children with PAR or nonallergic rhinitis, reducing the negative effects of rhinorrhea on mood, concentration on school or work, and sleep. Two recent studies in AR patients found that intranasal triamcinolone acetonide relieved nasal congestion and improved health-related quality of life (including sleep) as assessed using the RQLQ,⁷⁶ the NRQLQ, and the Pittsburgh Sleep Quality Index.⁷⁷

Further research is warranted on the use of immunotherapy to improve sleep quality and daytime somnolence. Data associated with the benefit of immunotherapy on these symptoms and outcomes are extremely limited. Such trials should use sleep-related measures as primary end points and include subjective and objective assessments of sleep parameters. Furthermore, studies are needed that investigate the effectiveness of the instruments used to measure subjective and objective evidence of sleep disturbance in patients with rhinitis. This information would help determine which instruments to use moving forward in studies that assess sleep quality in these patients.

A very fruitful area of research is the effect of cytokines on sleep and the effect of sleep disturbance on cytokines.⁷⁸ As suggested by Figure 2, multiple cytokines can influence sleep. In turn, Figure 1 suggests that sleep disturbance can influence cytokine production. Either way, cytokines can worsen the quality of life and research directed at defining the “chicken or the egg” paradigm are essential.

Another area of needed research is to assess the effect of the combination of fluticasone and azelastine on sleep. The combination has been demonstrated to be effective at reducing symptoms and signs of rhinitis; however, the sedating characteristic of azelastine may reduce the ability of fluticasone to improve daytime somnolence and fatigue.⁷⁹

Conclusions

Sleep impairment associated with rhinitis has a significant effect on patients' quality of life. Nasal congestion, one of the most common and bothersome symptoms of rhinitis, is thought to be a major cause of sleep impairment and sleep-disordered breathing. Recent research has suggested that the poor sleep associated with nasal congestion is an important therapeutic target. However, evidence also indicates that other rhinitis symptoms, as well as the inflammatory mediators released because of rhinitis, can disturb sleep and lead to an increase in daytime somnolence. As pointed out in the introduction, data to prove a causal relationship between nasal congestion and inflammation and sleep disturbance are limited. Further research is warranted and may be a fruitful endeavor for other investigators.

Treatment with intranasal corticosteroids has been found to significantly reduce nasal congestion in AR patients. These medications are considered the drug of choice in patients with

congestion as a predominant symptom. Montelukast may be a second-line therapy for those intolerant to intranasal corticosteroids. Finally, sedating antihistamines should be avoided because they may amplify sedation and decrease productivity in those already compromised.

References

- [1] Settippane RA. Demographics and epidemiology of allergic and nonallergic rhinitis. *Allergy Asthma Proc.* 2001;22:185.
- [2] Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J.* 2004;24:758–764.
- [3] Derebery J, Meltzer E, Nathan RA, et al. Rhinitis symptoms and comorbidities in the United States: Burden of Rhinitis in America survey. *Otolaryngol Head Neck Surg.* 2008;139:198–205.
- [4] Bousquet J, van Cauwenberge P, Khaltaev N. ARIA Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma (ARIA). *J Allergy Clin Immunol.* 2001;108:S147–S334.
- [5] Rappai M, Collop N, Kemp S. The nose and sleep-disordered breathing: what we know and what we do not know. *Chest.* 2003;124:2309–2323.
- [6] Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. *J Allergy Clin Immunol.* 2009;124(3 suppl):S43–S70.
- [7] Meltzer EO, Nathan R, Derebery J, et al. Sleep, quality of life, and productivity impact of nasal symptoms in the United States: findings from the Burden of Rhinitis in America survey. *Allergy Asthma Proc.* 2009;30:244–254.
- [8] Blaiss M, Reigel T, Philpot E. A study to determine the impact of rhinitis on sufferers' sleep and daily routine [abstract]. *J Allergy Clin Immunol.* 2005;115: S197.
- [9] Stempel DA, Woolf R. The cost of treating allergic rhinitis. *Curr Allergy Asthma Rep.* 2002;2:223–230.
- [10] Leynaert B, Neukirch C, Liard R. Quality of life in allergic rhinitis and asthma: a population-based study of young adults. *Am J Respir Crit Care Med.* 2000;162:1391–1396.
- [11] Meltzer EO. Quality of life in adults and children with allergic rhinitis. *J Allergy Clin Immunol.* 2001;108:S45–S53.
- [12] Stull DE, Roberts L, Frank L, Heithoff K. Relationship of nasal congestion with sleep, mood, and productivity. *Curr Med Res Opin.* 2007;23:811–819.
- [13] Nathan RA. The burden of allergic rhinitis. *Allergy Asthma Proc.* 2007;28:3–9.
- [14] McNicholas WT, Tarlo S, Cole P, et al. Obstructive sleep apneas during sleep in patients with seasonal allergic rhinitis. *Am Rev Respir Dis.* 1982;126:625–628.
- [15] Staevska MT, Mandajieva MA, Dimitrov VD. Rhinitis and sleep apnea. *Curr Allergy Asthma Rep.* 2004;4:193–199.
- [16] Lavie P, Gertner R, Zomer J, Podoshin L, et al. Breathing disorders in sleep associated with “microarousals” in patients with allergic rhinitis. *Acta Otolaryngol.* 1981;92:529–533.
- [17] Kramer MF, De La Chaux R, Derher A, Pfrogner E, Rasp G. Allergic rhinitis does not constitute a risk factor for obstructive sleep apnea syndrome. *Acta Otolaryngol.* 2001;121:494–499.
- [18] Young T, Finn L, Kim H, The University of Wisconsin Sleep and Respiratory Research Group. Nasal obstruction as a risk factor for sleep-disordered breathing. *J Allergy Clin Immunol.* 1997;99:S757–S762.
- [19] Rimmer J, Downie S, Bartlett DJ, Gralton J, Salome C. Sleep disturbance in persistent allergic rhinitis measured using actigraphy. *Ann Allergy Asthma Immunol.* 2009;103:190–194.
- [20] Sogut A, Altin R, Uzun L, et al. Prevalence of obstructive sleep apnea syndrome and associated symptoms in 3–11 year-old Turkish children. *Pediatr Pulmonol.* 2005;39:251–256.
- [21] Bixler EO, Vgontzas AN, Lin HM, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. *Sleep.* 2009;32: 731–736.
- [22] Janson C, De Backer W, Gislason T, et al. Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: a population study of young adults in three European countries. *Eur Respir J.* 1996;9:2132–2138.
- [23] Craig TJ, McCann JL, Gurevich F, Davies MJ. The correlation between allergic rhinitis and sleep disturbance. *J Allergy Clin Immunol.* 2004;114:S139–S145.
- [24] Craig TJ, Teets S, Lehman EB, Chinchilli VM, Zwillich C. Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids. *J Allergy Clin Immunol.* 1998;101:633–637.
- [25] Stuck BA, Czajkowski J, Hagner AE, et al. Changes in daytime sleepiness, quality of life, and objective sleep patterns in seasonal allergic rhinitis: a controlled clinical trial. *J Allergy Clin Immunol.* 2004;113:663–668.
- [26] Corey JP, Houser SM, Ng BA. Nasal congestion: a review of its etiology, evaluation, and treatment. *Ear Nose Throat J.* 2000;79:690–693, 696, 698.
- [27] Nathan RA, Eccles R, Howarth PH, Steinsvag SK, Tagias A. Objective monitoring of nasal patency and nasal physiology in rhinitis. *J Allergy Clin Immunol.* 2005;115:S442–S459.
- [28] Rundcrantz H. Postural variations of nasal patency. *Acta Otolaryngol.* 1969;68: 435–443.
- [29] Landstra AM, Postma DS, Boezen HM, van Aalderen WMC. Role of serum cortisol levels in children with asthma. *Am J Respir Crit Care Med.* 2002;165: 708–712.

- [30] Reinberg A, Gervais P, Levi F, et al. Circadian and circannual rhythms of allergic rhinitis: an epidemiologic study involving chronobiologic methods. *J Allergy Clin Immunol*. 1988;81:51–62.
- [31] *Impact of Nasal Congestion Amongst Allergic Rhinitis Sufferers: An Internet Survey of 2002 People*. New York, NY: Roper Public Affairs Group of NOP World; 2004.
- [32] Juniper EF, Rohrbach T, Meltzer EO. A questionnaire to measure quality of life in adults with nocturnal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2003;111:484–490.
- [33] Canova CR, Downs SH, Knoblauch A, Andersson M, Tamm M, Leuppi JD. Increased prevalence of perennial allergic rhinitis in patients with obstructive sleep apnea. *Respiration*. 2004;71:138–143.
- [34] Young T, Finn L, Palta M. Chronic nasal congestion at night is a risk factor for snoring in a population-based cohort study. *Arch Intern Med*. 2001;161:1514–1519.
- [35] Pitt AD, Smith AF, Lindsell L, Voon LW, Rose PW, Bron AJ. Economic and quality-of-life impact of seasonal allergic conjunctivitis in Oxfordshire. *Ophthalmic Epidemiol*. 2004;11:17–33.
- [36] Sack R, Conradi L, Beaton A, Sathe S, McNamara N, Leonardi A. Antibody array characterization of inflammatory mediators in allergic and normal tears in the open and closed eye environments. *Exp Eye Res*. 2007;85:528–538.
- [37] Tashiro M, Mochizuki H, Iwabuchi K, et al. Roles of histamine in regulation of arousal and cognition: functional neuroimaging of histamine H1 receptors in human brain. *Life Sci*. 2002;72:409–414.
- [38] Mullington JM, Hinze-Selch D, Pollmacher T. Mediators of inflammation and their interaction with sleep: relevance for chronic fatigue syndrome and related conditions. *Ann N Y Acad Sci*. 2001;933:201–210.
- [39] Krouse HJ, Davis JE, Krouse JH. Immune mediators in allergic rhinitis and sleep. *Otolaryngol Head Neck Surg*. 2002;126:607–613.
- [40] Aoyagi M, Watanabe H, Sekine K, et al. Circadian variation in nasal reactivity in children with allergic rhinitis: correlation with the activity of eosinophils and basophilic cells. *Int Arch Allergy Immunol*. 1999;120:95–99.
- [41] Vgontzas AN, Zoumakis E, Bixler EO, Lin H, Follett H, Kales A. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *J Clin Endocrinol Metab*. 2004;89:2119–2126.
- [42] Woodson BT, Brusky LT, Saurajen A, Jaradeh S. Association of autonomic dysfunction and mild obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2004;130:643–648.
- [43] Marshall PS, O'Hara C, Steinberg P. Effects of seasonal allergic rhinitis on selected cognitive abilities. *Ann Allergy Asthma Immunol*. 2000;84:403–410.
- [44] Wilken JA, Berkowitz R, Kane R. Decrements in vigilance and cognitive functioning associated with ragweed-induced allergic rhinitis. *Ann Allergy Asthma Immunol*. 2002;89:372–380.
- [45] Kessler RC, Almeida DM, Berglund P, Stang P. Pollen and mold exposure impairs the work performance of employees with allergic rhinitis. *Ann Allergy Asthma Immunol*. 2001;87:289–295.
- [46] Lack G. Pediatric allergic rhinitis and comorbid disorders. *J Allergy Clin Immunol*. 2001;108:S9–S15.
- [47] Simons FE. Learning impairment and allergic rhinitis. *Allergy Asthma Proc*. 1996;17:185–189.
- [48] Flemons WW, Tsai W. Quality of life consequences of sleep-disordered breathing. *J Allergy Clin Immunol*. 1997;99:S750–S756.
- [49] Martin SE, Engleman HM, Deary IJ, Douglas NJ. The effect of sleep fragmentation on daytime function. *Am J Respir Crit Care Med*. 1996;153:1328–1332.
- [50] Martin SE, Wraith PK, Deary IJ, Douglas NJ. The effect of nonvisible sleep fragmentation on daytime function. *Am J Respir Crit Care Med*. 1997;155:1596–1601.
- [51] Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. *J Allergy Clin Immunol*. 1994;93:413–423.
- [52] Fisher L, Ghaffari G, Davies M, Craig T. Effects of poor sleep in allergic rhinitis. *Curr Opin Allergy Clin Immunol*. 2005;5:11–16.
- [53] Kremer B, den Hartog HM, Jolles J. Relationship between allergic rhinitis, disturbed cognitive functions and psychological well-being. *Clin Exp Allergy*. 2002;32:1310–1315.
- [54] Juniper EF, Stahl E, Doty RL, Simons FE, Allen DB. Clinical outcomes and adverse effect monitoring in allergic rhinitis. *J Allergy Clin Immunol*. 2005;115:S390–S413.
- [55] Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991;14:540–545.
- [56] Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28:193–213.
- [57] Flemons WW, Reimer MA. Measurement properties of the Calgary Sleep Apnea Quality of Life Index. *Am J Respir Crit Care Med*. 2002;165:159–164.
- [58] Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep*. 1997;20:835–843.
- [59] Mansfield LE, Diaz G, Posey CR, Flores-Neder J. Sleep disordered breathing and daytime quality of life in children with allergic rhinitis during treatment with intranasal budesonide. *Ann Allergy Asthma Immunol*. 2004;92:240–244.
- [60] Craig TJ, Mende C, Hughes K, et al. The effect of topical nasal fluticasone on objective sleep testing and the symptoms of rhinitis, sleep, and daytime somnolence in perennial allergic rhinitis. *Allergy Asthma Proc*. 2003;24:53–58.
- [61] Murray JJ, Nathan RA, Bronsky EA, Olufade AO, Chapman D, Kramer B. Comprehensive evaluation of cetirizine in the management of seasonal allergic rhinitis: impact on symptoms, quality of life, productivity, and activity impairment. *Allergy Asthma Proc*. 2002;23:391–398.
- [62] Golden S, Teets SJ, Lehman EB, et al. Effect of topical nasal azelastine on the symptoms of rhinitis, sleep, and daytime somnolence in perennial allergic rhinitis. *Ann Allergy Asthma Immunol*. 2000;85:53–57.
- [63] McLean HA, Urton AM, Driver HS, et al. Effect of treating severe nasal obstruction on the severity of obstructive sleep apnea. *Eur Respir J*. 2005;25:521–527.
- [64] Milgrom H, Biondi R, Georgitis JW, et al. Comparison of ipratropium bromide 0.03% with beclomethasone dipropionate in the treatment of perennial rhinitis in children. *Ann Allergy Asthma Immunol*. 1999;83:105–111.
- [65] Goldbart AD, Goldman JL, Veling MC, Gozal D. Leukotriene modifier therapy for mild sleep-disordered breathing in children. *Am J Respir Crit Care Med*. 2005;172:364–370.
- [66] Moinuddin R, deTineo M, Maleckar B, Naclerio RM, Baroody FM. Comparison of the combinations of fexofenadine-pseudoephedrine and loratadine-montelukast in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2004;92:73–79.
- [67] Santos CB, Hanks C, McCann J, Craig T. The role of montelukast on perennial allergic rhinitis and associated sleep disturbances and daytime somnolence. *Allergy Asthma Proc*. 2008;29:140–145.
- [68] Ciprandi G, Cirillo I, Vizzacarro A, et al. Seasonal and perennial allergic rhinitis: is this classification adherent to real life? *Allergy*. 2005;60:882–887.
- [69] Bende M, Carrillo T, Vóna I, Castel-Branco MG, Arheden L. A randomized comparison of the effects of budesonide and mometasone furoate aqueous nasal sprays on nasal peak flow rate and symptoms in perennial allergic rhinitis. *Ann Allergy Asthma Immunol*. 2002;88:617–623.
- [70] Hughes K, Glass C, Ripchinski M, et al. Efficacy of the topical nasal steroid budesonide on improving sleep and daytime somnolence in patients with perennial allergic rhinitis. *Allergy*. 2003;58:380–385.
- [71] Craig TJ, Gurevich F, Glass C. The effect of intranasal steroid budesonide on sleep disturbance and daytime somnolence in patients with perennial allergic rhinitis [abstract]. *J Allergy Clin Immunol*. 2004;113:S332.
- [72] Berlin JM, Golden SJ, Teets S, Lehman EB, Lucas T, Craig T. Efficacy of a steroid nasal spray compared with an antihistamine nasal spray in the treatment of perennial allergic rhinitis. *J Am Osteopath Assoc*. 2000;100:8–13.
- [73] Mansfield LE, Posey CR. Daytime sleepiness and cognitive performance improve in seasonal allergic rhinitis treated with intranasal fluticasone propionate. *Allergy Asthma Proc*. 2007;28:226–229.
- [74] Bender BG, Milgrom H. Comparison of the effects of fluticasone propionate aqueous nasal spray and loratadine on daytime alertness and performance in children with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2004;92:344–349.
- [75] Kiely JL, Nolan P, McNicholas WT. Intranasal corticosteroid therapy for obstructive sleep apnoea in patients with co-existing rhinitis. *Thorax*. 2004;59:50–55.
- [76] Potter PC, Van Niekerk CH, Schoeman HS. Effects of triamcinolone on quality of life in patients with persistent allergic rhinitis. *Ann Allergy Asthma Immunol*. 2003;91:368–374.
- [77] Mintz M, Garcia J, Diener P, Liao Y, Dupclay L, Georges G. Triamcinolone acetate aqueous nasal spray improves nocturnal rhinitis-related quality of life in patients treated in a primary care setting: the Quality of Sleep in Allergic Rhinitis study. *Ann Allergy Asthma Immunol*. 2004;92:255–261.
- [78] Craig TJ, Ferguson BJ, Krouse JH. Sleep impairment in allergic rhinitis, rhinosinusitis, and nasal polyps. *Am J Otolaryngol*. 2008;29:209–217.
- [79] Ratner PH, Hampel F, Van Bavel J, Amar NJ, Daftary P, Wheeler W, Sacks H. Combination therapy with azelastine hydrochloride nasal spray and fluticasone propionate nasal spray in the treatment of patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2008;100:74–81.