

# The correlation between allergic rhinitis and sleep disturbance

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Nasal congestion, a common symptom related to allergic rhinitis (AR), often is associated with poor sleep quality, leading to decreased learning ability, decreased productivity at work or school, and 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. Therefore it is important to treat AR with medications that improve congestive symptoms without exacerbating sedation. Second-generation antihistamines and anticholinergic drugs are well tolerated but have little effect on congestion and therefore are limited in their ability to reduce AR-associated daytime somnolence. However, intranasal corticosteroids reduce congestion, improve sleep and sleep problems, and reduce daytime sleepiness, fatigue, and inflammation. Recently, montelukast, a leukotriene receptor antagonist, has joined the approved therapies for AR. Montelukast significantly improves both daytime and nighttime symptoms. AR treatment should endeavor to improve daytime and nighttime symptoms, sleep, and productivity, thereby improving quality of life. (*J Allergy Clin Immunol* 2004;114:S139-45.)

**Key words:** Allergic rhinitis, antihistamines, inflammation, intranasal corticosteroids, leukotriene receptor antagonists, nasal congestion, nighttime symptoms, performance impairment, quality of life, sedation, sleep

Patients with allergic rhinitis (AR) often have a reduced quality of life (QOL)<sup>1-3</sup> directly caused by the primary AR symptoms (sneezing, nasal pruritus, rhinorrhea, and congestion).<sup>3</sup> Moreover, the pathophysiology of AR often disrupts sleep, leading to fatigue, irritability, memory deficits, excessive daytime somnolence, and depression, thereby further reducing QOL.<sup>4,5</sup>

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 effect on sleep quality.

## Abbreviations used

AR: Allergic rhinitis  
ARIA: Allergic Rhinitis and Its Impact on Asthma  
CysLT: Cysteinyl leukotriene  
INS: Intranasal corticosteroid  
LTRA: Leukotriene receptor antagonist  
QOL: Quality of life

Finally, therapies for AR are reviewed to evaluate their potential benefits on sleep and QOL.

## ALLERGIC RHINITIS PRODUCES SLEEP DISTURBANCE

AR can impair learning,<sup>6</sup> affect performance,<sup>7</sup> and often decrease productivity at work, during sports, and at school.<sup>8</sup> The daytime fatigue experienced by patients with AR is often attributed to medication side effects, although it might in fact be the result of nasal congestion and associated sleep fragmentation.<sup>9-11</sup> Some AR medications can be sedating, but AR itself might also contribute to sleepiness.<sup>6,12</sup> Compared with asymptomatic individuals, patients with chronic nighttime symptoms of rhinitis were significantly more likely to be snorers ( $P < .0001$ ), to have more daytime somnolence ( $P < .001$ ), or to feel unrested ( $P < .0001$ ).<sup>13</sup>

Rhinorrhea and congestion are the symptoms associated with AR that affect sleep the most. The increased nasal airway resistance resulting from congestion is a consequence of nasal discharge and edema of the nasal mucosa obstructing nasal passages. In addition, nasal airway resistance is greater when lying in a horizontal position than when upright.<sup>14</sup> Nasal airway resistance is already increased in allergic individuals compared with nonallergic individuals and almost triples when the patients lie down, whereas this increase is minimal in healthy individuals without AR.<sup>14</sup> Nasal obstruction associated with congestion is also a risk factor for sleep-disordered breathing events, including apnea, hypopnea, and snoring.<sup>13</sup> Obstructive apneas were longer and more frequent in patients with AR with nasal obstruction than in those without obstruction when sleep was measured by means of polysomnography ( $P < .01$ ).<sup>9</sup> Furthermore, allergic patients with nasal congestion had a 1.8 times greater chance of moderate-to-severe sleep-disordered breathing than those without congestion.<sup>13</sup> Compared with healthy control subjects, patients with AR had 10 times more

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microarousals from sleep in association with periodic breathing and hypopneic and hyperpneic episodes.<sup>5</sup> Of children who snored habitually, 36% were sensitive to allergens, approximately 3 times the rate in nonsnoring children.<sup>15</sup> Moreover, AR might be an important cause of sleep disturbance in asthmatic patients. By aggressively treating AR, asthmatic control and QOL are substantially improved.

As a result, these data imply that treating AR symptoms to decrease nasal congestion will likely decrease sleep disturbances and subsequently lessen daytime fatigue, thereby improving QOL.<sup>10</sup>

## MECHANISM OF ALLERGIC RHINITIS AND SLEEP DISTURBANCES

In addition to the obvious effect of the symptoms of AR on sleep, the pathophysiologic elements, such as inflammatory cells and mediators, can also contribute to poor sleep. The early-phase response of AR, which is initiated within minutes of allergen exposure, follows mast cell release of chemical mediators. These mediators include histamine, cysteinyl leukotrienes (CysLTs), cytokines, chemotactic factors, and enzymes, all of which contribute to the early symptoms of AR (primarily sneezing, itching, and rhinorrhea).<sup>16,17</sup> The late-phase response of AR, which is essentially a cellular event, begins 2 to 4 hours after allergen exposure.<sup>16</sup> Early-phase chemical mediators stimulate the production, adhesion, and infiltration into local tissue of circulating leukocytes, especially eosinophils. These inflammatory cells then become activated, releasing their mediators into nearby tissue, thereby promoting local edema and tissue damage and perpetuating the overall inflammatory process.<sup>16</sup> Therefore late-phase AR is characterized by nasal congestion and obstruction rather than the sneezing and rhinorrhea characteristic of the early phase.<sup>17</sup>

A significant number of the mediators involved in AR inflammation also play vital roles in the pathophysiology of sleep disturbances. One of these shared mediators is histamine, which acts as a vasodilator<sup>17</sup> and a potent stimulator of vascular permeability<sup>16</sup> and mucus secretion.<sup>18</sup> These properties both directly and indirectly contribute to nasal obstruction and congestion, leading to decreased QOL.<sup>19</sup> Histamine is also involved in the regulation of the sleep-wake cycle, arousal, cognition, and memory.<sup>20</sup>

A second mediator of the inflammatory process in patients with AR is the CysLTs. CysLTs increase vascular permeability and mucus secretion, thereby increasing nasal airway resistance and obstruction and contributing to rhinorrhea.<sup>17,21,22</sup> CysLTs also act as chemoattractants for inflammatory cells, especially eosinophils, into the nasal tissues, which perpetuates the inflammatory cascade, leading to sleep disruption.<sup>23,24</sup>

Several cytokines released during early- and late-phase allergic reactions are involved in the regulation of sleep.<sup>25,26</sup> IL-1 $\beta$  and IL-4 can be considered allergy-

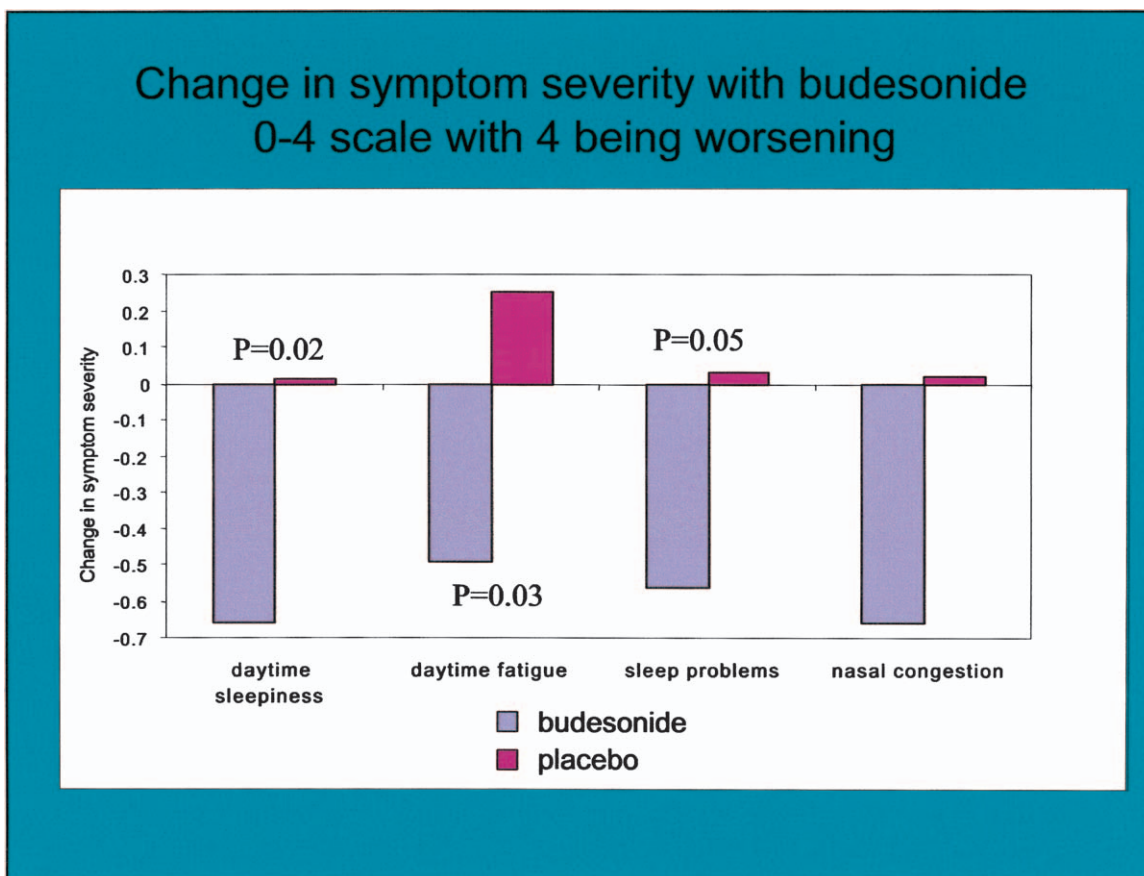
enhancing cytokines because their levels are higher in allergic patients than in nonallergic persons. Furthermore, they are associated with an increased latency to rapid eye movement sleep and decreased latency to sleep onset, resulting in a lower quality of sleep.<sup>25,26</sup> Among nonallergic individuals, IL-1 receptor antagonist, IL-2, and IL-12 levels are higher than those in allergic patients and can be viewed as allergy-inhibitory cytokines. Low levels of allergy-inhibitory cytokines correlate with increased allergic symptoms, suggesting that their lower levels, rather than increased levels of proallergic cytokines, lead to AR symptoms and subsequent reduced sleep quality and QOL.<sup>26</sup>

Other mediators, including prostaglandins, kinins, and neuropeptides, have been found to be important in AR and sleep. Prostaglandins, primarily prostaglandin D<sub>2</sub>, might cause congestion and rhinorrhea<sup>27</sup> and produce sleep disruption. Kinins are released after allergen challenge,<sup>28</sup> and bradykinin elicits congestion, rhinorrhea, and sore throat.<sup>29</sup> Nasal bradykinin concentrations are significantly ( $P < .05$ ) higher before and after sleep in patients with obstructive sleep apnea than in control subjects.<sup>30</sup> Neuropeptides can induce vasodilation and contribute to congestion,<sup>31,32</sup> and among the neuropeptides, substance P can increase rapid eye movement latency and arousal.<sup>33</sup>

## TEMPORAL VARIATION IN INFLAMMATION AND SLEEP DISTURBANCE

Many biologic processes exhibit a circadian rhythm. For example, lung functions in healthy persons have a circadian rhythm that peaks at 4 PM and is lowest at 4 AM.<sup>34</sup> Circadian variations are exaggerated by more than 15% in patients with nocturnal asthma compared with patients with nonnocturnal asthma, including nighttime increases of inflammatory eosinophils and basophils.<sup>34</sup> Likewise, the levels of these inflammatory cells in patients with AR are highest in the early morning ( $P < .05$  for 6 AM compared with 3 PM levels).<sup>35</sup> For patients with AR, symptoms can be more severe on waking, which is evidenced by 70% of patients having more intense sneezing and greater blocked nose, runny nose, or both in the morning than at other times. The day-to-night variation in symptom intensity is about 20% of the 24-hour mean level.<sup>36</sup>

CysLT levels were found to be higher in asthmatic patients than in healthy individuals ( $P < .05$ ), although it seems without circadian changes in their levels.<sup>36</sup> However, asthmatic patients with nocturnal symptoms had higher nighttime CysLT levels compared with those without nocturnal symptoms ( $P < .02$ ).<sup>36</sup> Diurnal rhythms also show up in other markers of airway inflammation: histamine levels, epinephrine levels, endogenous corticosteroid levels, and cholinergic tone all vary during the day, with cholinergic tone increasing at night and epinephrine and corticosteroid levels decreasing at night.<sup>34</sup> In addition, glucocorticoid receptor binding is reduced at night in nocturnal, but not in nonnocturnal, asthma.<sup>37</sup> This can also



**FIG 1.** Significant change in symptom severity with nasal steroid. Twenty-two subjects were enrolled in a double-blind, placebo-controlled trial in which patients received either 128  $\mu\text{g}/\text{d}$  budesonide or placebo. Subjective data were collected from the Epworth Sleepiness Scale, Functional Outcomes Questionnaire, Rhinoconjunctivitis Quality of Life Questionnaire, and daily diary recordings of nasal symptoms, sleep problems, and daytime fatigue. The results demonstrated that the topical nasal corticosteroid significantly improved daytime fatigue ( $P = .03$ ), daytime somnolence ( $P = 0.02$ ), and quality of sleep ( $P = .05$ ) when compared with placebo. The scale rated symptoms from 0 (being free of symptoms) to 4 (having severe symptoms). Reprinted with permission from Hughes et al. *Allergy* 2003;58:380-5.<sup>11</sup>

lead to increases in inflammation during the night and subsequent sleep disturbance. Furthermore, the decrease in affinity was also observed in atopic asthmatic subjects, in whom allergen exposure significantly reduced the binding of glucocorticoids to their receptor.<sup>38</sup> The mechanistic links between these circadian cycles and inflammation are not fully understood.<sup>34</sup>

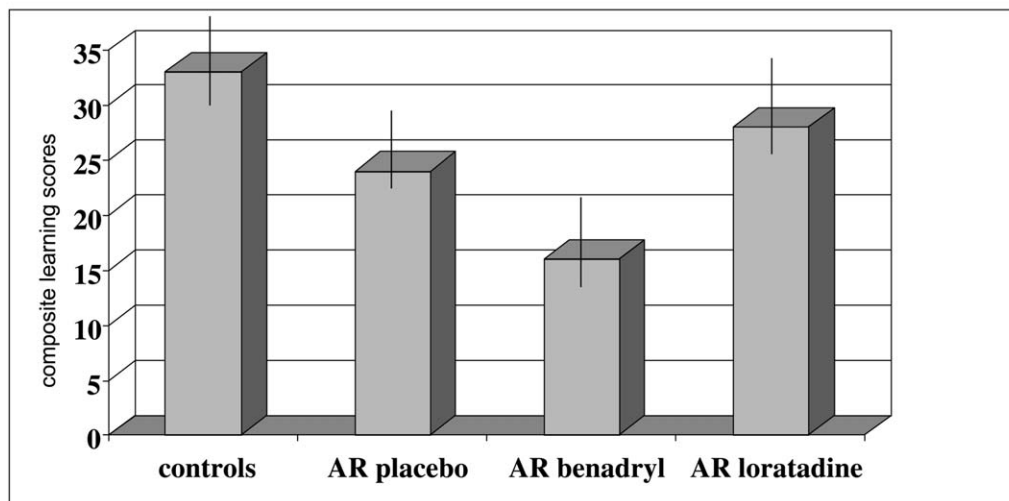
### THERAPY OF ALLERGIC RHINITIS IMPROVES ASSOCIATED SLEEP DISTURBANCES

Therapy aimed at reducing AR symptoms, particularly congestion, should significantly improve sleep quality and directly improve an individual's QOL. Medications available to aid in managing AR include intranasal corticosteroids (INs), intranasal or oral decongestants, intranasal or oral antihistamines, anticholinergic medications, and leukotriene antagonists.

The mainstay of therapy for AR should focus on the use of INs. INs have been shown to reduce congestion ( $P = .001$ ) and improve sleep ( $P = 0.01$ )<sup>10</sup>; furthermore, they reduce daytime sleepiness ( $P = .02$ ), daytime fatigue ( $P = .03$ ), and sleep problems ( $P = .05$ , Fig 1).<sup>11</sup> INs are considered safe,<sup>39</sup> with minimal influence on adrenal suppression with topical administration because of low systemic bioavailability.<sup>40</sup> However, in individuals being treated for multiple disease processes requiring additional steroids, care should be taken to avoid unwanted effects, including adrenal suppression.<sup>41</sup>

The use of intranasal or oral decongestants can effectively reduce nasal obstruction and congestion. Intranasal formulations act within 10 minutes, and many are efficacious up to 12 hours. Adverse effects might include nasal burning, dryness, or mucosal ulceration and even septal perforation if used incorrectly. With oral formulations, activity starts within 30 minutes and lasts up to 6 hours or for 8 to 24 hours with sustained-release

## Learning: Conceptual Knowledge Scores



**FIG 2.** Effect of AR and its therapies on learning. Children ( $n = 52$ ) with seasonal AR and matched healthy children ( $n = 21$ ) received one of the 3 following treatments for 2 weeks: a sedating antihistamine (ie, diphenhydramine;  $n = 18$ ), a nonsedating antihistamine (ie, loratadine;  $n = 17$ ), or placebo ( $n = 17$ ). Composite learning scores for the healthy children were significantly ( $P = .007$ ) 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 ( $P = .002$ ) lower, demonstrating that seasonal AR plus sedating antihistamines (but not nonsedating antihistamines) had a negative effect on learning. Reprinted with permission from Vuurman et al. *Ann Allergy Asthma Immunol* 1993;71:121-6.<sup>6</sup>

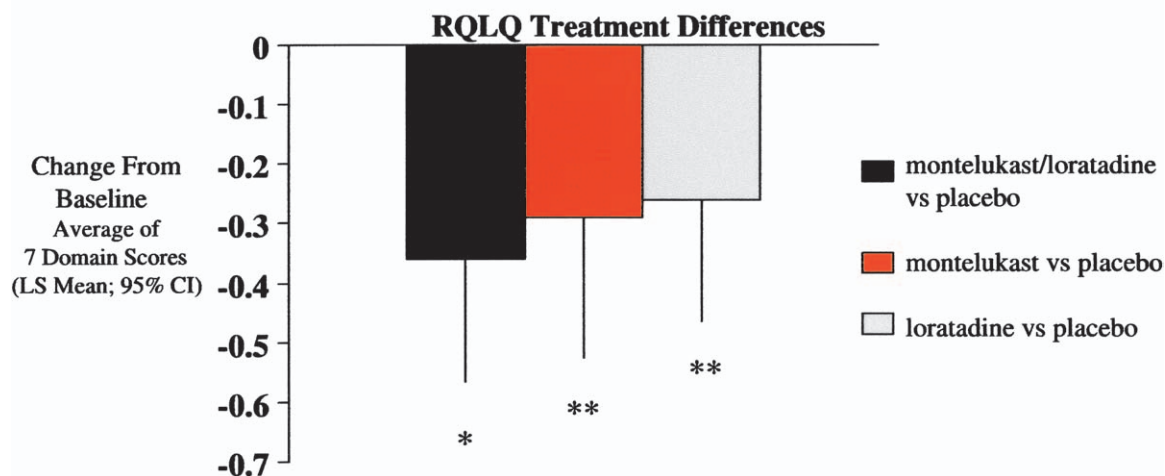
formulations. Systemic effects can include irritability, dizziness, headache, tremor, tachycardia, and insomnia, which, in turn, can result in daytime somnolence. With topical use, tachyphylaxis and a rebound of symptoms (rhinitis medicamentosa) can result from prolonged decongestant use, and therefore the chronic use of these medications is not recommended.<sup>41</sup>

Antihistamines have long been a mainstay of treatment in allergic diseases. Antihistamines are very effective at reducing the pruritus, sneezing, and watery rhinorrhea associated with AR; however, nasal obstruction is not reduced significantly (although desloratadine and cetirizine might improve congestion to some degree).<sup>41,42</sup> First-generation antihistamines (eg, chlorpheniramine, diphenhydramine, and promethazine) have a proven track record; however, they have numerous undesirable side effects, including significant anticholinergic properties and marked sedation.<sup>41</sup> Although these antihistamines might help at night and lead to a better sleep, during the day, patients might experience fatigue or sleepiness. Furthermore, these antihistamines can impair learning, especially in children (Fig 2),<sup>6</sup> and they can have effects like those caused by alcohol, making skilled activities more difficult or dangerous.<sup>43</sup>

Newer second-generation antihistamines (eg, cetirizine, loratadine, fexofenadine, and desloratadine) have higher potencies and longer durations of action than first-generation antihistamines, with the additional benefit of minimal or no sedating properties. It has been shown that the 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 H<sub>1</sub> receptors in the brain.<sup>20</sup> Because these antihistamines are less or non-sedative, their effect on learning and drowsiness is similar to that of placebo (Fig 2).<sup>6,43</sup>

Topical antihistamines, delivered by means of nasal spray, avoid or minimize systemic side effects. Azelastine used topically reduced rhinorrhea but failed to reduce congestion in one study,<sup>44</sup> although not in another.<sup>45</sup> Thus the debate on the benefits of antihistamines on nasal congestion continues. Because antihistamines are not historically very effective against congestion, they are often combined with a decongestant. However, because of the side effects of both drugs, caution should be used, especially with other over-the-counter combinations that contain a sedating first-generation antihistamine and a

## Montelukast for Seasonal Allergic Rhinitis: *Fall Study Results*



**FIG 3.** QOL improvement with montelukast and loratadine versus placebo in seasonal AR. The use of LTRAs has been shown to be effective in the treatment of AR. In this study 907 male and female patients were randomized to one of 4 treatment arms: 10 mg of montelukast (n = 155), 10 mg of loratadine (n = 302), combination therapy (n = 302), or placebo (n = 149). For each of the 3 treatment arms, significant improvement from baseline compared with placebo ( $P \leq .001$ ) was documented. The researchers concluded that montelukast alone or in combination with loratadine provides QOL improvement, which includes questions on sleep and daytime sleepiness, in those individuals with seasonal AR. Montelukast/loratadine versus loratadine: not significant. Montelukast/loratadine versus montelukast: not significant. \* $P < .001$ . \*\* $P < .05$ . Reprinted with permission from Nayak et al. *Ann Allergy Asthma Immunol* 2002;88:592-600.<sup>51</sup>

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.<sup>41</sup>

Anticholinergic medications, such as ipratropium bromide, have antisecretory properties and a high safety profile, with minimal crossing of the nasal and gastrointestinal mucosa, as well as the blood-brain barrier.<sup>46</sup> When delivered locally to the nasal mucosa, they inhibit mucus secretion and the subsequent rhinorrhea in both adults and children with perennial AR.<sup>46</sup> In children with perennial AR, ipratropium bromide administered topically significantly ( $P < .05$ ) improved rhinorrhea, congestion, and sneezing compared with baseline. Responses to QOL questionnaires showed also that after 6 months of treatment, ipratropium improved sleep by almost 50%.<sup>47</sup> However, because it does not relieve nasal congestion or sneezing associated with seasonal AR,<sup>46</sup> it is recommended by the ARIA guidelines as first-line therapy only when rhinorrhea is the primary symptom.<sup>41</sup>

The use of leukotriene receptor antagonists (LTRAs) has recently been proved to be effective in the treatment of AR. 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. When compared with placebo, the LTRAs

provide effective symptomatic relief. Pranlukast reduced nasal mucosal swelling ( $P < .01$ ),<sup>48</sup> and zafirlukast reduced congestion ( $P < .01$ ), rhinorrhea, and sneezing ( $P \leq .05$  for both).<sup>49</sup> Currently, montelukast is the only LTRA approved for treatment of AR in the United States. Significant ( $P < .05$ ) improvement in both daytime (congestion, rhinorrhea, pruritus, and sneezing) and nighttime (difficulty going to sleep, nighttime awakenings, and congestion on awakening) symptoms has been demonstrated in patients with allergies in the spring<sup>24,50</sup> and fall. QOL has also been demonstrated to improve in those treated with montelukast (Fig 3).<sup>51</sup> Furthermore, montelukast significantly ( $P \leq .001$ ) reduced the number of peripheral blood eosinophils, suggesting that montelukast reduces allergic inflammation systemically.<sup>24</sup> These data demonstrate that not only were there subjective improvements in symptoms, but also objective improvement on the basis of a decrease in a marker of allergic disease.

### CONCLUSION

Patients with AR symptoms, most importantly nasal congestion, frequently have disturbed sleep, daytime somnolence, and fatigue. Complaints of excessive fatigue and poor sleep should immediately trigger consideration

of AR as a culprit. Close monitoring of an individual's sleep pattern and daytime alertness should be used to establish the diagnosis of AR and potential treatment strategy. In asthma and AR, inflammation increases at night, often leading to disturbed sleep and early-morning symptoms. Treatment with INs reduces nighttime inflammation, and as a result, patients report less congestion and better sleep. Recently, an LTRA, montelukast, has been shown to effectively reduce not only daytime but also nighttime symptoms of AR.<sup>24,50,51</sup> 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. Furthermore, with improved sleep, patients should experience increased productivity and a better QOL.

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