

Pharmacologic approaches to daytime and nighttime symptoms of allergic rhinitis

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Allergic rhinitis is associated with sleep disturbances, daytime somnolence, and fatigue. The exact relationship between rhinitis and sleep disturbance is unknown; however, both the symptoms and underlying pathology of allergic rhinitis can interfere with sleep quality. Nasal congestion, which has been shown to cause sleep-disordered breathing, is thought to be primarily responsible for rhinitis-related sleep disorders. The severity of nasal congestion follows a circadian rhythm, being worst at night and in the early morning. Chronotherapy is the study of the effects of administration time on the safety and efficacy of drug therapy based on circadian influences on the pharmacokinetics and pharmacodynamics of medications. Chronotherapy studies in allergic rhinitis suggest there are benefits to nighttime dosing of antiallergy medications. For example, the antihistamine mequitazine has shown improved efficacy when administered in the evening compared with morning dosing. More study is needed to determine whether this is a class effect. Leukotriene receptor antagonists are indicated for evening administration; these drugs significantly improve nighttime rhinitis symptoms. Intranasal corticosteroids administered in the morning have demonstrated efficacy in improving nighttime symptoms; however, it is unknown whether evening administration would improve their effects on nocturnal rhinitis symptoms. Because of the significant detrimental effects of nocturnal rhinitis symptoms on quality of life, allergic rhinitis therapies should be evaluated for efficacy in ameliorating nighttime symptoms. (*J Allergy Clin Immunol* 2004;114:S146-53.)

Key words: *Quality of life, polysomnography, allergic rhinitis, antihistamine, leukotriene receptor antagonist, intranasal corticosteroid, decongestant, sleep, microarousals*

Approximately one third of our life is spent sleeping; nevertheless, little is known about sleep or disorders of sleep. Sleep disorders are highly prevalent: an estimated 35% of the population experiences acute sleep problems, and 10% to 20% of the population has chronic sleep disturbances.^{1,2} Allergic rhinitis (AR) is also a highly

Abbreviations used

AR:	Allergic rhinitis
ESS:	Epworth Sleepiness Scale
INS:	Intranasal corticosteroid
LTRA:	Leukotriene receptor antagonist
NRQLQ:	Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire
PSQI:	Pittsburgh Sleep Quality Index
REM:	Rapid eye movement
RQLQ:	Rhinoconjunctivitis Quality of Life Questionnaire

prevalent disease, occurring in up to 24% of adults and 40% of children in the United States.³ Both sleep disorders and AR are associated with increases in daytime somnolence, fatigue, irritability, absenteeism, and performance impairment.^{1,4,5} It is becoming increasingly clear that there is a high rate of comorbidity between these 2 conditions. What is less clear is exactly how they are related.

Both the symptoms (sneezing, rhinorrhea, nasal pruritus, and nasal congestion) and the underlying pathology of AR might contribute to sleep disturbance. Sneezing could delay onset of sleep, and anecdotally, some patients report being awakened from sleep by a sneeze. Nasal itching and runny nose certainly do not improve sleep quality; however, nasal congestion is thought to be the leading symptom responsible for rhinitis-related sleep problems.⁶

The nose is the primary route of breathing during sleep.¹ Nasal obstruction subsequent to nasal congestion can lead to pathologic changes in airflow velocity that can lead to nasal collapse and increased numbers of microarousals during sleep.⁷ Microarousals result in fragmented sleep and possible decreases in rapid eye movement (REM) sleep. Young et al⁸ investigated the role of chronic and acute nasal congestion in sleep-disordered breathing in a population-based study. Data on nasal congestion history and sleep problems were collected by questionnaire from almost 5000 subjects, and 911 subjects were evaluated by means of objective measurement in the laboratory. Those who reported experiencing rhinitis symptoms 5 or more nights per month were significantly ($P < .0001$) more likely to report habitual snoring, chronic daytime sleepiness, or chronic nonrestorative sleep than those who rarely or never had symptoms. Participants who reported nasal congestion caused by allergy were 1.8 times more likely to exhibit moderate-to-severe sleep-disordered breathing as subjects without nasal congestion. Similarly, the presence of allergy in children is associated with increased risk of obstructive sleep apnea.⁹

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Disclosure of potential conflict of interest—W. W. Storms has consultant arrangements with AstraZeneca, Novartis, Merck, Winston, and Sepracor-Investigation. He has received financial support from AstraZeneca, A Vennis, and Medpointe. He has received grants—research support from AstraZeneca, Novartis, Merck, Winston, and Sepracor-Investigational. He has received speaker's honoraria from AstraZeneca, Novartis, Merck, Winston, and Sepracor-Investigational.

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0091-6749/\$30.00

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doi:10.1016/j.jaci.2004.08.045

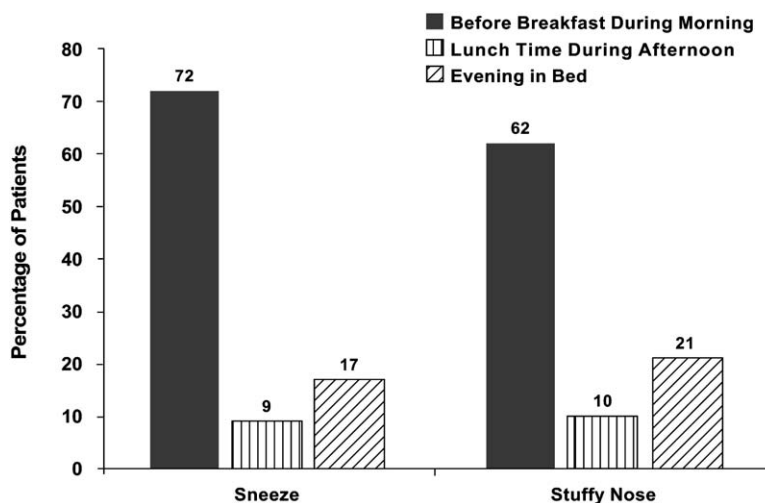


FIG 1. AR symptoms show significant circadian variability with peak symptom severity. *N* = 246. Adapted with permission from Smolensky et al. *J Allergy Clin Immunol* 1995;95:1084-96.¹²

The underlying pathology of AR symptoms might also be involved in sleep regulation. Degranulating mast cells release a variety of preformed (histamine, proteases, and TNF- α) and *de novo* synthesized (cysteinyl leukotrienes and prostaglandins) inflammatory mediators and cytokines. The early phase of the allergic response (within minutes of allergen exposure) is characterized by sneezing, rhinorrhea, pruritus, and congestion; histamine is the major mediator during this phase.³ The late-phase response (3-12 hours after allergen exposure) is characterized mainly by congestion and is associated with the infiltration of inflammatory cells (eg, eosinophils and T cells) into the tissue and the release of mediators, such as histamine, leukotrienes, and prostaglandins. Several of these mediators have also been implicated in the pathophysiology of sleep; for example, histamine receptors in the brain regulate the sleep-wake cycle, arousal, cognition, and memory.¹⁰ Similarly, prostaglandin D₂ enhances both REM and non-REM sleep in animal models.¹¹

Nighttime symptoms are an important component of the total morbidity associated with AR. The symptoms of AR at night are consistent with those during the day; however, there are temporal variations in the severity of some symptoms.

DIURNAL VARIATION IN ALLERGIC RHINITIS SYMPTOMS

Many chronic inflammatory diseases, such as rheumatoid arthritis and asthma, exhibit fairly predictable variations in occurrence and severity over a 24-hour period. Symptoms of these diseases are often worse during nocturnal sleep or in the morning on awakening, probably related, to some extent, to circadian shifts in cortisol levels.¹² In AR, also a chronic inflammatory disease, the intensity of nasal congestion, rhinorrhea, and sneezing are greatest early in the morning in approximately 70% of patients (Fig 1).¹² Reinberg et al¹³ reported that the amount of day-night variation in symptom severity is

TABLE I. Circadian variation in AR symptom severity¹³

Symptom	Circadian variation (worse during the night or early morning), %
Congestion	22.5
Rhinorrhea	18.1
Sneezing	23.3
Pruritus	No circadian variation

Adapted with permission from Reinberg et al. *J Allergy Clin Immunol* 1988;81:51-62.¹³

approximately 20% of the mean 24-hour severity level (Table I and Fig 2).

The specific mechanisms underlying the chronobiology of AR are speculative; however, several factors might contribute to the occurrence of maximum nasal congestion in the morning: congestion is worse with recumbent position; secretions increase and accumulate overnight; there is allergen exposure to mites, mold, or dander; cortisol levels are lowest at night, and hence inflammatory mediators might be at high levels; and autonomic nervous system activity at night promotes vagal tone, favoring vasodilation.¹

Just as circadian rhythms influence disease symptomatology, they also affect the pharmacokinetics and pharmacodynamics of many drug classes.¹² Circadian rhythms of the gastrointestinal tract, liver, kidney, and other organs affect the absorption, distribution, and elimination of medications. There is growing interest in chronotherapy (administration of medication when it will be most beneficial) with respect to AR medications.

CHRONOTHERAPY

Chronotherapy with the second-generation antihistamine mequitazine was assessed in a large multicenter study conducted by Reinberg et al.¹⁴ Different mequitazine

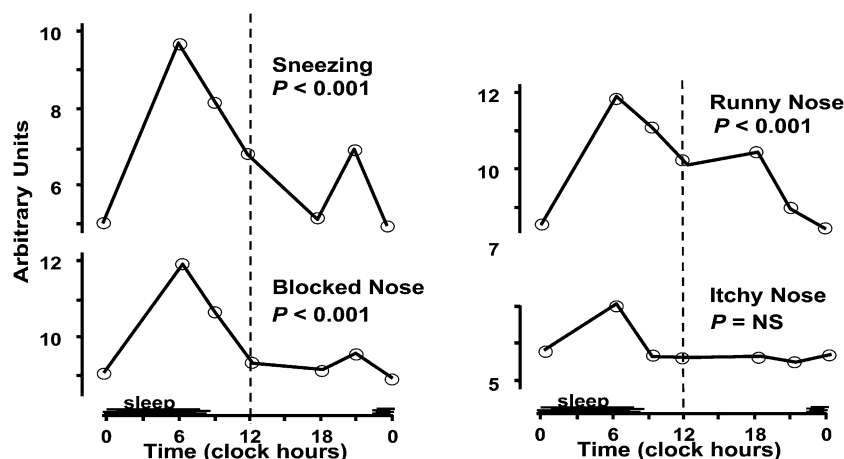


FIG 2. *P* values for circadian variation in symptom severity. *N* = 330 men. Adapted with permission from Reinberg et al. *J Allergy Clin Immunol* 1998;81:51-62.¹³

doses and regimens were administered in the morning and evening to comparable groups of adult patients with AR. Patients self-assessed symptom severity 4 times daily for 7 days. Mequitazine was most effective for moderating the morning symptom severity peak and controlling overall 24-hour symptom severity when taken at dinner time (Fig 3). The medication was least effective when administered in the morning around breakfast time. Additionally, dry mouth, one of the most common side effects of mequitazine, was minimized or eliminated when the dose was taken in the evening.^{14,15}

Differences in daytime and nighttime administration of mequitazine might represent a class effect. Administration time-dependent differences in the pharmacokinetics, specifically duration and time to peak effect, of the first-generation antihistamine cyproheptadine and the second-generation antihistamines terfenadine and clemastine have also been demonstrated.¹² Recent studies show loratadine, when administered in the evening, reduces nasal congestion and improves nighttime symptoms (see below); however, loratadine was not administered in the daytime in these studies, and therefore chronotherapeutic comparisons cannot be made.^{16,17}

ASSESSING EFFECTS OF MEDICATION ON NIGHTTIME ALLERGIC RHINITIS SYMPTOMS

Numerous quality-of-life (QOL) instruments are designed to test the effects of a disease or a therapeutic intervention on sleep quality.¹⁸ Most often, clinical studies use a generic instrument (ie, one that can be used in different disease states) or diary recordings to collect subjective assessments of sleep quality, fatigue, and/or daytime somnolence related to AR or its treatment. They include the Epworth Sleepiness Scale (ESS),¹⁹ which measures how likely a person is to fall asleep or doze off during different situations he or she would normally experience during the day; the Functional Outcomes of

Sleep Questionnaire,²⁰ which measures the effect of sleepiness on daily activities; and the Pittsburgh Sleep Quality Index (PSQI),²¹ which measures sleep quality.

The disease-specific QOL instrument most often used in AR treatment studies is the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ),²² which comprises 7 domains, one of which measures the effects of disease, treatment, or both on sleep. Because Juniper et al⁶ believed nocturnal rhinitis-related impairments to QOL differ from problems associated with daytime AR symptoms, they recently developed the Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire (NRQLQ), which was designed to assess functional problems most troublesome to patients with nocturnal AR symptoms.

Rarely, objective tests of the effect of AR or its treatment on sleep quality are performed. Polysomnography measures microarousals, apnea, and hypopnea during sleep, and the Multiple Sleep Latency Test provides a physiologic measure of daytime sleepiness.⁸ Although informative, these tests are time consuming, require specialized equipment, and are very expensive to perform.

PHARMACOTHERAPY FOR DAYTIME AND NIGHTTIME ALLERGIC RHINITIS SYMPTOMS

AR therapies should reduce nasal congestion, sneezing, and rhinorrhea during the day, at night, and in the early morning to be optimally effective. A patient's difficulty falling asleep because of rhinitis symptoms, occurrence of awakenings caused by nasal problems, significant nasal congestion before sleep and on awakening, and/or sleep-disordered breathing (eg, snoring) are indications that starting, adding, or changing therapy might be warranted.

ANTIHISTAMINES

Antihistamines are not as effective for nasal congestion as other classes of AR drugs, such as intranasal steroids or

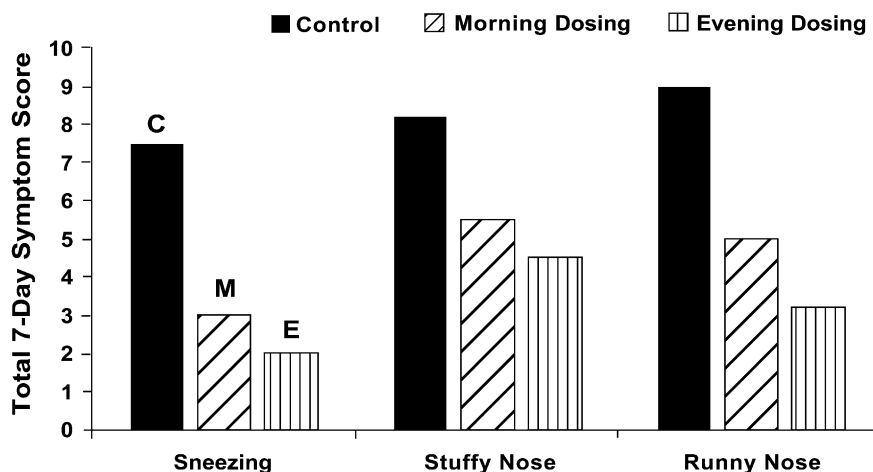


FIG 3. Chronotherapy with mequitazine: evening administration is more effective than morning dosing. $N = 98$; 10 mg mequitazine QD morning or evening for 7 days; $P < 0.005$ evening versus morning. Adapted with permission from Smolensky et al. *J Allergy Clin Immunol* 1995;95:1084-96.¹²

oral decongestants. However, newer antihistamines have demonstrated anti-inflammatory properties, and the results of clinical trials of their effects on nasal congestion are mixed.²³⁻²⁵

First-generation H_1 antihistamines effectively reduce AR symptoms but worsen daytime somnolence, decrease reaction time, and impair performance.²⁶ Diphenhydramine is widely used for insomnia treatment; it is the sixth most commonly used medication (considering both prescription and nonprescription drugs) in the United States (chlorpheniramine is the 12th most commonly used drug).⁵ Hypothetically, their sedating properties would make these drugs preferred for treating evening AR symptoms; however, some first-generation antihistamines have half-lives as long as 24 hours and, when taken at bedtime, might give patients an “antihistamine hangover” the next morning and for a considerable part of the day.^{5,27} Older antihistamines also worsen sleep architecture and disrupt the normal sleep process, and therefore patients wake up feeling unrested.⁵

Loratadine

The effects of loratadine taken at bedtime were assessed in 3 large clinical trials.^{16,17,28} Daytime symptoms (nasal congestion, rhinorrhea, nasal pruritus, and sneezing) and nighttime symptoms (difficulty going to sleep, nighttime awakenings, and nasal congestion on awakening) were evaluated. Daytime symptoms were improved in all 3 studies, and nighttime symptoms were improved in 2 of the 3 studies.^{16,17} Nasal congestion was also significantly improved compared with placebo ($P < .05$) in the latter 2 trials. There was no study arm in which loratadine was administered in the morning in these trials, and therefore it is impossible to determine a chronotherapeutic benefit to evening versus morning dosing of loratadine.

Fexofenadine, desloratadine, and cetirizine

These second-generation antihistamines have been shown to relieve nasal congestion compared with placebo in some studies.^{23,25} These medications have a rapid onset of action and are not known to interfere with sleep.⁵ Whether their effectiveness on nighttime AR symptoms could be improved by evening administration warrants investigation.

Intranasal azelastine

The effect of the intranasal antihistamine azelastine on sleep and daytime somnolence was tested in a double-blind, placebo-controlled crossover study in 24 subjects with perennial AR.²⁹ Patients were randomized to azelastine or placebo for 8 weeks. Of 4 patients who discontinued prematurely while taking azelastine, 3 did so because of sedation (no patient discontinued while receiving placebo for this reason). Compared with placebo, only rhinorrhea was significantly improved with azelastine ($P = .03$). Patients rated sleep with azelastine significantly better than with placebo ($P = .041$), despite no significant improvement in nasal congestion, daytime sleepiness, or ESS scores with active treatment.

INTRANASAL CORTICOSTEROIDS

Intranasal corticosteroids (INSs) are considered first-line therapy for moderate-to-severe seasonal and perennial AR.³ INSs suppress many of the inflammatory mediators implicated in the allergic reaction; they have been shown to significantly reduce nasal congestion with a concomitant improvement in sleep compared with placebo.³⁰ Because they are applied topically and have low systemic bioavailability, they are generally considered safe in adults and children.³¹ In the studies listed below, the INSs were

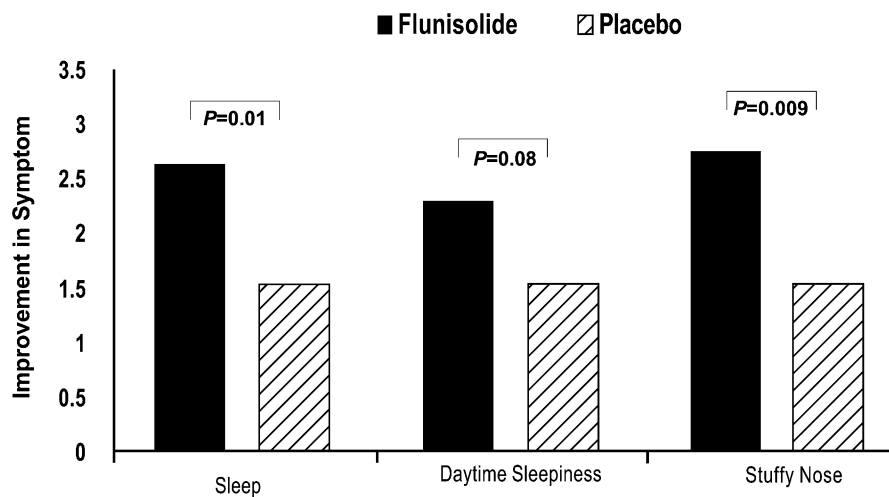


FIG 4. Intranasal flunisolide improves daytime and nighttime AR symptoms. $N = 20$; 2 sprays twice daily for 8 weeks. Reprinted with permission from Craig et al. *J Allergy Clin Immunol* 1998;101:633-7.⁷

administered in the morning, or administration time was not reported.

Budesonide

Intranasal budesonide was tested for effects on sleep quality and daytime somnolence in 22 patients with perennial AR.³² The double-blind, placebo-controlled crossover study compared budesonide with placebo for 8 weeks. Subjective assessments were made with the ESS, Functional Outcomes of Sleep Questionnaire, RQLQ, and daily recording of nasal symptoms, sleep problems, and daytime fatigue. Intranasal budesonide treatment significantly improved daytime fatigue, somnolence, and quality of sleep compared with placebo.

Flunisolide

Craig et al⁷ conducted a double-blind, placebo-controlled 8-week crossover study of intranasal flunisolide in patients ($n = 20$) with perennial AR. Patients rated improvement with sleep, daytime sleepiness, daytime fatigue, and stuffy nose. Sleep and stuffy nose were significantly improved with flunisolide compared with placebo ($P \leq .01$), and improvement in daytime sleepiness approached statistical significance ($P = .0838$, Fig 4).

Fluticasone propionate

A double-blind, randomized, 8-week crossover study compared the effects of intranasal fluticasone propionate and placebo in 32 patients with perennial AR who experienced chronic sleep problems.³⁰ One objective of the study was to determine whether subjective assessments of nasal congestion, sleep, and daytime somnolence correlated with results of objective sleep testing by means

of polysomnography. Subjective assessments of nasal congestion were collected in a daily diary, and subjective ratings of sleep and daytime somnolence were made by using the daily diary, the RQLQ, and the ESS. Diary data showed fluticasone improved subjective sleep quality ($P = .04$) compared with placebo. Daytime somnolence, daytime fatigue, sleep-related RQLQ items, and ESS scores were also improved but not to a statistically significant extent compared with that after placebo. Furthermore, subjective findings did not correlate with results of objective testing; polysomnography indicated no significant difference in the number of arousals, awakenings, hypopneas, and apneas between fluticasone and placebo treatment.

Mometasone furoate

In a double-blind, placebo-controlled parallel-group trial, 245 patients with seasonal AR were randomized to receive placebo or intranasal mometasone for 2 weeks.³³ Mometasone significantly reduced most nighttime nasal symptoms of AR (congestion, nasal itching, and sneezing), although to a lesser extent than reductions in daytime symptoms.

Triamcinolone acetonide

The effects of intranasal triamcinolone acetonide on changes in nocturnal QOL, as determined by using the NRQLQ, and in sleep quality, as determined by using the PSQI, were evaluated in an open-label study in more than 500 patients with AR treated in a primary care setting.³⁴ No assessment of AR symptom severity was made during the trial. Triamcinolone was associated with significant improvements in overall and individual domain scores on both the NRQLQ and PSQI ($P < .001$ for all comparisons), with strong correlations between the results of both instruments. Although the trial had an inherent weakness

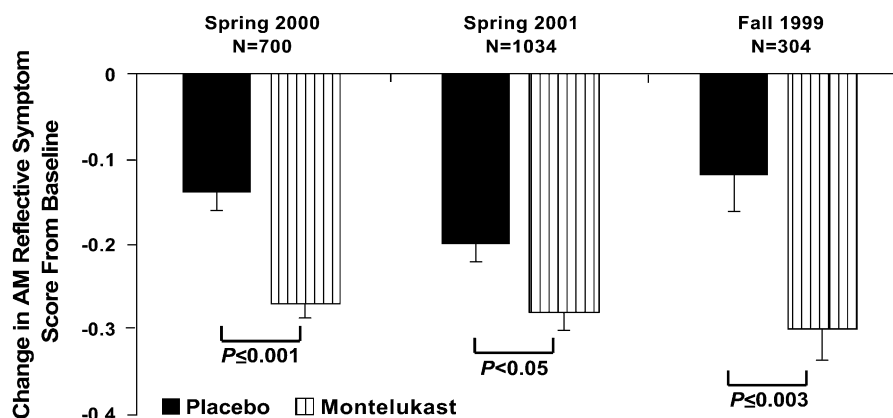


FIG 5. Montelukast for nighttime AR symptoms. Nighttime symptoms are difficulty going to sleep, nighttime awakenings, and congestion on awakening. 10 mg montelukast or placebo QD at bedtime for 2 weeks. Baseline data: Spring 2000, 1.43 placebo and 1.46 montelukast; Spring 2001, 1.47 placebo and 1.51 montelukast; and Fall 1999, 1.32 placebo and 1.52 montelukast. Adapted with permission from Philip et al. Clin Exp Allergy 2002;32:1020-8; van Adelsberg et al. Ann Allergy Asthma Immunol 2003;90:214-22; Nayak et al. Ann Allergy Asthma Immunol 2002;88:592-600.¹⁶

in that it was nonrandomized and had an open-label design, the goal was to assess the effects of the INSs in a real-world scenario.

LEUKOTRIENE RECEPTOR ANTAGONISTS

Leukotriene receptor antagonists (LTRAs) are the most recent class of drugs to be added to the AR armamentarium. Evidence of a significant role of cysteinyl leukotrienes in nasal congestion was provided by a demonstration of significant increase in nasal mucosal blood flow and nasal airway resistance in healthy subjects after nasal challenge with leukotriene D₄.³⁵ Compared with histamine, nasal challenge with leukotriene D₄ was approximately 5000 times more potent for evoking nasal congestion.³⁵

Montelukast

Montelukast is the LTRA approved for the treatment of AR. It is indicated for evening administration. The efficacy of montelukast was evaluated in 3 large, double-blind, randomized, placebo-controlled clinical studies (2 in the spring and 1 in the fall) that included more than 3400 patients with seasonal AR.^{16,17,28} Effects of montelukast and loratadine monotherapy were compared with those of placebo in the 2 spring studies,^{17,28} and monotherapy with montelukast or loratadine and combination montelukast and loratadine therapy compared with placebo were measured in the fall study.¹⁶ Efficacy outcomes included patient-assessed daytime nasal symptom scores (mean of nasal congestion, rhinorrhea, sneezing, and nasal pruritus scores) and nighttime symptom scores (mean of difficulty going to sleep, nighttime awakenings, and nasal congestion on awakening scores). Compared with placebo, montelukast monotherapy and combination montelukast and loratadine therapy significantly improved

daytime and nighttime symptoms (Fig 5). In 2 of the studies, montelukast monotherapy was associated with significant improvement in the sleep domain of the RQLQ.^{17,28} Montelukast significantly reduced peripheral blood eosinophil counts compared with placebo in all of these studies.

Zafirlukast

Zafirlukast, another LTRA, is not approved for use in AR, but results of early clinical trials have shown mixed results.³⁵ More study is needed to evaluate the utility of zafirlukast in AR.

MAST CELL STABILIZERS

Intranasal cromolyn sodium inhibits the degranulation of sensitized mast cells, reducing the release of mediators that trigger inflammation and the allergic response. Cromolyn is more effective than placebo but less effective than an INS for relieving allergy symptoms.³⁶ The drug has weak anti-inflammatory properties and is not highly effective against nasal congestion.³⁷ However, it has a sterling safety profile and might be useful in patients for whom safety and tolerability are of primary importance, such as pregnant women, elderly patients with significant comorbidity, very young children (≤ 2 years of age), or those who cannot tolerate an INS.³⁶

DECONGESTANTS

Decongestants are sympathomimetic drugs that constrict capacitance vessels in the turbinates.¹⁰ Despite their efficacy in relieving nasal congestion, they have stimulatory properties and can produce insomnia, restlessness, agitation, and other conditions not conducive to relaxation

or sleep. Decongestants and antihistamine-decongestant combinations are not recommended for use by persons with AR-related sleep difficulties.

CONCLUSION

Sleep disturbances and microarousals related to nasal congestion detrimentally affect daytime energy, mood, and function.⁷ A single night of fragmented sleep can compromise daytime wakefulness and alertness.³⁸ Persons with sleep disturbances are more accident prone and likely to have higher rates than average of general work-related and motor vehicle accidents.¹

Daytime somnolence and fatigue might be surrogate markers of untreated nighttime AR symptoms. Do physicians adequately assess these symptoms when taking the medical history of a patient or the patient's parent? Patients often do not report the existence or extent of symptoms fully to a physician. The physician might also underestimate the severity of the problem because when asked about symptoms, patients are most likely to describe them as mild.³⁹ Yet recent Allergic Rhinitis and Its Impact on Asthma classifications include sleep disturbance as a criterion that differentiates mild AR from moderate-to-severe disease.⁴⁰

Treatment of AR must control daytime and nighttime symptoms of the disease. Further investigation into the pathology of sleep disturbances related to AR and of the effects of available medications on nighttime AR symptoms are needed.

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