

*Editorial***Sleep disorders in patients with asthma, atopic dermatitis, and allergic rhinitis**Bruce G. Bender, PhD,^{a,b} and Donald Y. M. Leung, MD, PhD^{a,c} *Denver, Colo*

The best bridge between despair and hope is a good night's sleep.

—E. Joseph Cossman

The worst thing in the world is to try to sleep and not to.

—F. Scott Fitzgerald

Sleep, the long-recognized victim of obstructive sleep apnea, also suffers in patients with asthma, atopic dermatitis, and allergic rhinitis. As many as 75% of patients with asthma awaken weekly with symptoms of their disease, and about half of these awaken nightly.¹ Rhinitis sufferers also tend to sleep poorly, often because of sleep-disordered breathing secondary to nasal obstruction^{2,3} and with the consequence of decreased quality of life and increased daytime somnolence.^{4,5} Adults⁶ and children⁷ with atopic dermatitis are more restless in their sleep, awaken more often, spend fewer minutes in sleep, and report more daytime fatigue than those without.

In this issue of the Journal, 4 contributions help advance our understanding of the relationships among sleep, immune function, and respiratory disease. Madje and Krueger⁸ integrate a large literature that examines immune function in normal and abnormal sleep. Bergeron et al⁹ cite recent evidence that systemic and airway inflammation may contribute to daytime sleepiness associated with obstructive sleep apnea syndrome. It follows that implementing appropriate anti-inflammatory treatment may facilitate improved sleep. The substantial evidence for airway changes and differential response to β_2 -receptor agonists and glucocorticoids at night is reviewed by Sutherland.¹⁰ Combining data from 3 studies of perennial rhinitis, Craig et al¹¹ demonstrate that treatment with intranasal corticosteroids reduces nasal congestion, sleep disturbance, and daytime somnolence. These collective contributions remind the reader that both sleep and immunology are

governed by complex circadian patterns, and that the treatment of patients with respiratory, allergic, and immune disorders must take into account the quality of their sleep.

Sleep disruption can bring significant daytime consequences. Poor sleep has a well documented deleterious effect on mood, cognition, and motor performance. Further, individuals deprived of sufficient sleep are at markedly increased risk of causing a motor vehicle accident. Crashes or near-crashes are increased among truck drivers,¹² airline pilots,¹³ shift workers,¹⁴ and medical residents,¹⁵ all of whom are exposed to irregular and reduced sleep. While sleep science has long recognized the dramatic changes in human performance that accompany multiple nights of total sleep deprivation,¹⁶ more recent research has provided insight into the consequences of partial sleep deprivation, or the poor night's sleep often accompanying atopic and respiratory diseases, but also commonly associated with the stress and demands of daily life. Even as little as 4 nights of partial sleep restriction resulting in less than 7 hours of sleep causes measurable increases in daytime sleepiness and impaired cognitive performance.^{17,18} In a comprehensive study of sleep deprivation, 2 weeks of sleep restricted to 4 hours created deficits in attention and memory equivalent to 2 nights of total sleep deprivation.¹⁹ A systematic review of intermittent hypoxia in children concluded that even at mild levels of desaturation, children with sleep-disordered breathing demonstrate lower levels of performance on tests of attention and verbal intelligence.²⁰ Readers interested in learning more about neurocognitive consequences of sleep deprivation are directed to an excellent review by Durmer and Dinges.²¹

The causes of poor sleep in these patients may not be as obvious as they first appear. The discomforts experienced by patients with asthma, allergic rhinitis, and atopic dermatitis are clear, and the implications for sleep seem evident. The increased nasal airway resistance accompanying allergic rhinitis nearly triples when a patient lies down,²² and many with atopic dermatitis report unbearable itching at night. For some with asthma, circadian variations in airway physiology deliver a marked increase in sleep-disordered breathing between midnight and 8:00 AM. Yet the origins of disordered sleep in these patients may also be traced to altered inflammatory processes. Studies of individuals with diseases causing systemic inflammation²³ and healthy volunteers in sleep deprivation studies^{24,25} reveal that a variety of cytokines are implicated in sleep regulation. Majde and Krueger²³ cite some that include IL-4, IL-6, IL-1 β , and TNF- α . For example, IL-4

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and IL-1 β , both of which are elevated in patients with allergy, are associated with increased latency to rapid eye movement sleep and lower overall quality of sleep.²⁶ The causal pathway may be that cytokine changes resulting from these diseases contribute to sleep changes by affecting the role of these substances in the brain neurochemistry of sleep regulation. Equally plausible is the possibility that sleep disturbance resulting from the discomfort of allergic rhinitis or atopic dermatitis promotes further changes in cytokines, hormones, or other neuropeptides, which in turn influence the course of the disease. Majde and Krueger²³ review studies demonstrating that sleep deprivation alters IL-6 and growth hormone production and increases susceptibility to infection. A growing body of electrophysiological, biochemical, and genetic evidence indicates that IL-1 and TNF- α play a role in supporting sleep.^{27,28} When injected into animals peripherally, or microinjected directly into the brain, IL-1 and TNF- α increase nonrapid eye movement sleep while suppressing rapid eye movement sleep.²⁹⁻³¹ Daytime sleepiness is decreased in patients with sleep apnea given intravenous TNF- α receptor antagonist.³² In healthy volunteers, injection of IL-1 or TNF- α alters rapid eye movement sleep.²⁷

Disease, inflammation, and sleep are thus linked in a complex set of relationships. The possibilities are intriguing, and the continuing task of teasing apart the causal sequences promises important discoveries. Treatments for asthma, allergic rhinitis, and atopic dermatitis should slow or stop the interaction between disease and sleep while improving both. For example, a group of children with atopic dermatitis treated with pimecrolimus cream demonstrated improvement in their skin that in turn was correlated with improvement in sleep.³³ As Sutherland and colleagues²⁵ note, understanding the circadian cycles of inflammation and symptoms may direct choice and timing of specific treatments. In the case of asthma, this includes dosing strategies to optimize therapeutic effects during periods of nocturnal worsening. The role of sleep-promoting medications for these groups of patients is unclear and should be approached cautiously. In the case of atopic dermatitis, the possibility of treating sleep with such medications as a way to interrupt the itch-scratch-itch cycle is a strategy that warrants further exploration.

REFERENCES

- Turner-Warwick M. Epidemiology of nocturnal asthma. *Am J Med* 1988;85:6-8.
- Young T, Finn L, Kim H. Nasal obstruction as a risk factor for sleep-disordered breathing. *J Allergy Clin Immunol* 1997;99(suppl):S757-62.
- Craig TJ, McCann JL, Gurevich F, Davies MJ. The correlation between allergic rhinitis and sleep disturbance. *J Allergy Clin Immunol* 2004;114:S139-45.
- Blaiss M, Reigel T, Philpot E. A study to determine the impact of rhinitis on sufferers' sleep and daily routine. *J Allergy Clin Immunol* 2005;115(suppl 2):S197.
- Stuck BA, Czajkowski J, Hagner A, Klimek L, Verse T, Hörmann K, 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;113:663-8.
- Bender B, Leung SB, Leung D. Actigraphy assessment of sleep disturbance in patients with atopic dermatitis: an objective life quality measure. *J Allergy Clin Immunol* 2003;111:598-602.
- Reuveni H, Chapnick G, Tal A, Tarsiuk A. Sleep fragmentation in children with atopic dermatitis. *Arch Pediatr Adolesc Med* 1999;153:249-53.
- Majde JA, Krueger JM. Links between the innate immune system and sleep. *J Allergy Clin Immunol* 2005;116:1188-98.
- Bergeron C, Kimoff J, Hamid Q. Obstructive sleep apnea syndrome and inflammation. *J Allergy Clin Immunol* 2005;116:1393-6.
- Sutherland ER. Nocturnal asthma. *J Allergy Clin Immunol* 2005;116:1179-86.
- Craig TJ, Hanks CD, Fisher LH. How do topical nasal corticosteroids improve sleep and daytime somnolence in allergic rhinitis? *J Allergy Clin Immunol* 2005;116:1264-6.
- McCartt AT, Rohrbaugh JW, Hammer MC, Fuller SZ. Factors associated with falling asleep at the wheel among long-distance truck drivers. *Accid Anal Prev* 2000;32:493-504.
- Bourgeois-Bougrine S, Casbron P, Gounelle C, Mollard R, Coblenz A. Perceived fatigue for short- and long-haul flights: a survey of 739 airline pilots. *Aviat Space Environ Med* 2003;74:1072-7.
- Folkard S, Monk TH. Shiftwork and performance. *Hum Factors* 1979;21:483-92.
- Steele MT, Ma OJ, Watson WA, Thomas HA, Muelleman RL. The occupational risk of motor vehicle collisions for emergency medicine residents. *Acad Emerg Med* 1999;6:1050-3.
- Kleitman N. Sleep and wakefulness. Chicago: University of Chicago Press; 1963.
- Drake CL, Roehrs TA, Burduvali E, Bonahoom A, Rosekind J, Roth T. Effects of rapid versus slow accumulation of eight hours of sleep loss. *Psychophysiology* 2001;38:979-87.
- Belenky G, Wesensten NJ, Thorne DR. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *J Sleep Res* 2003;12:1-12.
- Van Dongen H, Maislin G, Mullington JM. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 2003;26:117-26.
- Bass JL, Corwin M, Gozal D, Moore C, Nishida H, Parker S, et al. The effect of chronic or intermittent hypoxia on cognition in childhood: a review of evidence. *Pediatrics* 2004;114:805-16.
- Durmer JS, Dinges DF. Neurocognitive consequences of sleep. *Semin Neurol* 2005;25:117-29.
- Lavie P, Gertner R, Zomer J, Podoshin L. Breathing disorders in sleep associated with "microarousals" in patients with allergic rhinitis. *Acta Otolaryngol* 1981;92:529-33.
- Majde JA, Krueger JM. Neuroimmunology of sleep. In: D'haenen H, editor. *Textbook of biological psychiatry*. London: John Wiley & Sons, Ltd; 2002. p. 1247-57.
- Redwine L, Hauger RL, Christian GJ, Irwin M. Effects of sleep and sleep deprivation on interleukin-6, growth hormone, cortisol, and melatonin levels in humans. *J Clin Endocrinol Metab* 2000;85:3597-603.
- Sutherland ER, Ellison MC, Kraft M, Martin RJ. Elevated serum melatonin is associated with the nocturnal worsening of asthma. *J Allergy Clin Immunol* 2003;112:513-7.
- Krouse HJ, Davis JE, Krouse JH. Immune mediators in allergic rhinitis and sleep. *Otolaryngol Head Neck Surg* 2002;126:607-13.
- Krueger JM, Ferenc OJ, Fang J. The role of cytokines in physiological sleep regulation. *Acad Sci* 2001;933:211-21.
- Opp MR. Cytokines and sleep. *Sleep Med Rev* 2005;9:355-64.
- Manfridi A, Grambilla D, Bianchi S, Mariotti M, Opp MR, Imeri L. Interleukin enhances non-rapid eye movement sleep when microinjected into the dorsal raphe nucleus and inhibits serotonergic neurons in vitro. *Eur J Neurosci* 2003;18:1041-9.
- Kubota T, Li N, Guan Z, Brown RA, Krueger JM. Intrapreoptic microinjection of TNF- α enhances non-REM sleep in rats. *Brain Res* 2002;932:37-44.
- Alam M, McGinty D, Bashir T, Kumar S, Imeri L, Opp MR. Interleukin-1 β modulates state-dependent discharge activity of preoptic area and basal forebrain neurons: role in sleep regulation. *Eur J Neurosci* 2004;20:207-16.
- Vgontzas A, Zoumakis E, Lin HM, Bixler EO, Trakada G, Chrousos GP. Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor- α antagonist. *J Clin Endocrinol Metab* 2004;89:4409-13.
- Leo HL, Bender B, Leung S, Vu Tran Z, Leung D. Effect of pimecrolimus cream 1% on skin condition and sleep disturbance in children with atopic dermatitis. *J Allergy Clin Immunol* 2004;114:691-3.