

Sleep disorders and atopic dermatitis: A 2-way street?



Yung-Sen Chang, MD, MPH, PhD,^{a,b,c} and Bor-Luen Chiang, MD, PhD^{b,d} *Taipei, Taiwan*

Sleep disturbance is very common in patients with atopic dermatitis (AD) and is a major factor leading to impaired quality of life. Sleep disturbance is often viewed as one of the symptoms of AD and one of the measures of disease severity. In this review we describe a variety of sleep disorders associated with AD and a wide range of effect that sleep disorders have on patients with AD. We also discuss our current understanding of the mechanism of sleep disturbance in patients with AD. The relationship between sleep disorders and AD might be bidirectional and could form a vicious cycle. Therefore we suggest viewing sleep disorders as a comorbidity of AD for which regular screening and bidirectional management strategies are indicated, with equal focus on maintaining disease control and implementing specific strategies to improve sleep. (*J Allergy Clin Immunol* 2018;142:1033-40.)

Key words: Sleep disturbance, atopic dermatitis, eczema, melatonin, sleep disorder

Atopic dermatitis (AD) is a common allergic disease affecting 15% to 30% of children and 2% to 10% of adults.¹ It is a chronically relapsing pruritic inflammatory skin disease with complex pathophysiology that is still not fully understood.² It has long been known that sleep disturbance is very common in patients with AD and is a major factor leading to impaired quality of life.³⁻⁵ Sleep disturbance is often viewed as one of the symptoms of AD. For instance, the SCORAD index, the most commonly used symptom score for AD, includes a visual analog scale for subjective sleep loss,⁶ and studies assessing the effect of treatments for AD commonly evaluate whether the treatment improves sleep.⁷⁻⁹ However, more and more studies have found that sleep disturbances have complex interrelationships with AD and a wide range of effect on patients with AD. Therefore we suggest that sleep disorders in patients with AD should instead

Abbreviations used

AD: Atopic dermatitis
HR: Hazard ratio
OR: Odds ratio
OSA: Obstructive sleep apnea
PSG: Polysomnography
REM: Rapid eye movement

be viewed as a comorbidity of AD and as an individual category to be regularly assessed and managed.

SLEEP DISORDERS IN PATIENTS WITH AD

Sleep disturbance is reported in 47% to 80% of children with AD and in 33% to 87.1% of adults with AD (Table I).¹⁻²¹ The majority of studies in the literature describing sleep disturbance in patients with AD are based on questionnaires of subjective sleep problems. The most commonly reported sleep problems in both children and adults with AD include difficulty falling asleep, frequent nighttime awakenings, and excessive daytime sleepiness.^{4,10,13,14,16-20} Children with AD also reported more wake time after sleep onset and difficulty waking up in the morning.^{4,14,15,19-21} Chamlin et al¹¹ found that 30% of children with AD reported parent cosleeping, and cosleeping bothered 66% of these parents.

Only a few studies have taken objective measurements of sleep in patients with AD (Table I). Laboratory-based polysomnography (PSG), the gold standard assessment for sleep, has seldom been used to evaluate sleep in children with AD,²²⁻²⁴ possibly because of the inconvenience of having to be performed at a sleep center overnight. The attachment of multiple leads and equipment during the PSG examination might also result in more skin irritation for the patient with AD. Of the few studies that assessed the sleep of patients with AD by using PSG, Hon et al²⁴ found that sleep efficiency (the proportion of time in bed spent asleep) was reduced in children with AD compared with control subjects (72% vs 88%, $P = .04$). Stores et al²⁵ reported that sleep in children with AD was at least 4 times more disrupted than that in control subjects on both brief (<2 minutes) and long (>2 minutes) periods of waking. Our group found that patients with AD had lower sleep efficiency (71.2% vs 76.2%, $P = .004$) and less non-rapid eye movement (non-REM) sleep than control subjects.¹⁵

Actigraphy involves a small wrist-worn device that uses activity-based monitoring to estimate sleep-wake patterns. Because of its ease of use, it is increasingly applied to provide objective sleep assessments in patients with AD.³ Our group has validated that actigraphic measures had high correlation with the

From ^athe Department of Pediatrics, Taipei City Hospital Renai Branch; ^bthe Department of Pediatrics, National Taiwan University Hospital; ^cthe School of Medicine, National Yang-Ming University; and ^dthe Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication May 18, 2018; revised August 9, 2018; accepted for publication August 14, 2018.

Available online August 23, 2018.

Corresponding author: Bor-Luen Chiang, MD, PhD, Department of Medical Research, National Taiwan University Hospital, No. 7 Chung-Shan South Road, Taipei 100, Taiwan. E-mail: gicmbor@ntu.edu.tw.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/\$36.00

© 2018 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaci.2018.08.005>

TABLE I. Sleep disorders in patients with AD

| Sleep disorders in patients with AD | Prevalence/characteristics | Tool for assessment | References |
|-------------------------------------|---|--|-------------------|
| Subjective sleep problems | | | |
| Eczema-affected sleep | Children: 47% to 80%; 86% during eczema flare-up Adults: 33% to 87.1% | Questionnaire; interview | 1-7 |
| Difficulty falling asleep | Children: 10.2% to 51.4%; average sleep onset latency, 39.8 minutes Adults: 76.2% with mild disease, 89% with moderate disease, and 100% with severe disease | Questionnaire | 6-9 |
| Nighttime awakenings | Children: 43% to 73%; average, 2.7-3.5 awakenings per night during eczema flare-up Adults: 4.8% with mild disease, 76.2% with moderate disease, and 92.6% with severe disease | Interview | 1, 4, 5, 7, 9, 10 |
| More wake time after sleep onset | Children: 38% stayed awake for 0.25-1 hours per night, 20% between 1-2 hours, and 11% for >2 hours; average, 88.3 minutes | Questionnaire | 5, 10 |
| Difficulty awakening in the morning | Children: 58% to 62.5% | Questionnaire | 6, 8 |
| Excessive daytime sleepiness | Children: 43.1% to 61.9% Adults: OR, 2.66 (95% CI, 2.34-3.01) | Questionnaire | 6, 11, 12 |
| Parent cosleeping | Children: 30%; 66% parents bothered by cosleeping | Questionnaire | 2 |
| Objective sleep problems | | | |
| Prolonged sleep onset latency | Children: average, 45 minutes | Actigraphy | 6 |
| More wake time after sleep onset | Children: average, 73.2-103.4 minutes Adults: average, 57.3 minutes | Actigraphy | 6, 13, 14 |
| Lower sleep efficiency | Children: average, 72% to 76.8% Adults: average, 90.6% | Actigraphy; PSG | 6, 13-15 |
| Others | Children: less NREM sleep Children and adults: more sleep fragmentation, more arousals and awakenings, more scratching and movement in sleep | Actigraphy; PSG; infrared video | 6, 16, 17 |
| Specific sleep disorders | | | |
| Sleep-disordered breathing | Children with eczema had increased risk of snoring (OR, 1.80; 95% CI, 1.28-2.54); children with AD had higher risk of OSA (HR, 1.86; 95% CI, 1.43-2.42) Adults with OSA more likely to have AD (HR, 1.5; 95% CI, 1.15-1.95); hazard risk was greater in male and young OSA patients (0-18 and 19-34 years) | Questionnaire; population-based cohort study | 18-20 |
| Insomnia | Adult patients with AD are more likely to have insomnia (OR, 2.36; 95% CI, 2.11-2.64) | Questionnaire, population-based | 12 |
| Others | Children with AD had more bedtime resistance and parasomnias | Children Sleep Habits Questionnaire | 21 |

NREM, Non-REM.

gold standard PSG measures in patients with AD and suggest that actigraphy is a good and convenient method to assess the sleep of patients with AD in future studies.¹⁵ Benjamin et al²⁶ showed that children with AD spent a mean of 46 minutes less sleeping at night than control subjects (468 ± 3 vs 422 ± 37 minutes). Hon et al²⁷ reported that actigraphic measures of activity were correlated with disease severity ($r = 0.52$, $P < .01$) and occurred most in the first 3 hours of sleeping in children with AD. Our group assessed the sleep of 72 children with AD and 32 control subjects with actigraphy and showed that children with AD had lower sleep efficiency ($74.5\% \pm 9.2\%$ vs $81.2\% \pm 7.6\%$, $P = .001$), more wake time after sleep onset (73.2 ± 45.7 vs 50.7 ± 29.9 minutes, $P = .004$), longer sleep onset latency (45 ± 29.3 vs 27 ± 16.2 minutes, $P < .001$), and a higher sleep fragmentation index score.¹⁵

Some specific sleep disorders have been reported to be associated with AD. Sleep-disordered breathing has been found to be associated with AD in several studies: Chng et al²⁸ reported

that in preschool and primary school children in Singapore, habitual snoring was associated with AD (odds ratio [OR], 1.80; 95% CI, 1.28-2.54).²⁸ Population-based studies from Taiwan have shown that patients with obstructive sleep apnea (OSA) had a higher risk of AD (hazard ratio [HR], 1.5; 95% CI, 1.15-1.95), especially in male patients with OSA (HR, 1.53; 95% CI, 1.14-2.06), children less than 18 years old with OSA (HR, 4.01; 95% CI, 1.57-10.26), and young patients with OSA aged 19 to 34 years (HR, 1.75; 95% CI, 1.00-3.04; adjusted for allergic rhinitis and asthma).²⁹ In children less than 18 years old, patients with AD had a higher risk of OSA than those without AD (HR, 1.86; 95% CI, 1.43-2.42; adjusted for comorbidities of AD, such as rhinitis).³⁰ It is hypothesized that the association between AD and OSA could be due to common underlying pathways of oxidative stress and systemic inflammation.^{29,30} A high sympathetic tone in patients with AD and resultant sleep fragmentation could also contribute to upper airway instability during sleep.³¹ A US population-based study showed that in

adults eczema was associated with regular insomnia (OR, 2.36; 95% CI, 2.11-2.64).²⁰ Urrutia-Pereira et al¹⁸ reported that in Latin American children, patients with AD had more bedtime resistance, sleep-disordered breathing, and parasomnias compared with control subjects. Cicek et al³² reported that restless leg syndrome was more common in patients with AD than control subjects, although the underlying mechanism of this association is unclear. We suggest that patients with AD who complain of sleep problems should be carefully assessed for these associated sleep disorders to provide adequate treatment.

EFFECT OF SLEEP DISORDERS ON PATIENTS WITH AD

After itch, sleep disturbance has been ranked as the second highest factor leading to impaired quality of life in children with AD.¹² Children with AD have been reported to have lower quality of life than children with other chronic skin diseases, such as psoriasis, urticaria, and acne, and also other chronic diseases, such as renal disease, asthma, cystic fibrosis, epilepsy, and diabetes.³³

The quality of life and sleep of family members are also affected by childhood AD. In parents of children with chronic illnesses, sleep disruption is most highly reported in parents of children with AD, affecting 54% to 86% of parents.³⁴ Mean reduction in parental sleep time during flare-ups in children with AD ranged from 0.66 to 2.6 hours per night.^{13,35} Lawson et al³⁶ reported that 64% of parents of children with AD reported frustration and exhaustion caused by sleep problems, and 63% of siblings of children with AD were also losing sleep. Another study showed that the severity of sleep disturbance in the parents of children with AD was associated with the level of parental anxiety (maternal anxiety: $r = 0.58$, $P = .002$; paternal anxiety: $r = 0.59$, $P = .01$) and maternal depression ($r = 0.73$, $P < .001$).³⁵

Sleep disturbance itself can have many negative consequences for children, including higher rates of behavioral problems, impaired neurocognitive function, and changes in mood.^{37,38} A study found that 54% of parents of children with AD reported behavioral disturbances, such as irritability, bad temper, and being hurtful to other family members during flare-ups of AD.³⁶ A large cohort study including 1658 children showed that infant eczema with concurrent sleeping problems predicted emotional (OR, 2.63; 95% CI, 1.20-5.76) and conduct (OR, 3.03; 95% CI, 1.01-9.12) problems at 10 years of age.³⁹

It has also been found that AD is associated with attention deficit hyperactivity disorder and short stature only when accompanied by sleep problems.^{40,41} Because sleep is essential for growth and development and sleep disruption can result in poor concentration and disruptive behavior, it was suggested that sleep disturbance in patients with AD is an important link for these associations (Fig 1).^{40,41}

Several studies also reported a significant effect of sleep problems on adults with AD. A US population-based study showed that sleep disturbances in adults with AD were significant predictors of poorer overall health status, number of sick days, and doctor's office visits.²⁰ In adults with AD, those with sleep disturbance and fatigue have also been reported to be more likely to have difficulty with instrumental activities of daily living (including concentrating, remembering, performing hobbies, doing finances, and driving), impaired quality of life, and negative effects on mental health and social functioning (Fig 1).¹⁶

MECHANISM OF SLEEP DISORDERS IN PATIENTS WITH AD

The pathogenesis of sleep disturbance in patients with AD is complex and not fully understood but likely involves several contributing factors.⁴² Several studies have shown that disease severity is associated with sleep disturbance in children with AD.^{3,15} Pruritus and scratching movements disrupting sleep seem to be the most straightforward reason for sleep disturbance in children with AD because the itch in these patients is often worse at night. The cause of itch in patients with AD has been suggested to be neuropeptide-mediated vasodilation and change in skin temperature³ and sensory hypersensitivity caused by eosinophil-induced cutaneous nerve growth or increased skin levels of nerve growth factor.⁴³⁻⁴⁵ IL-31, brain-derived neurotrophic factor, and substance P have also been suggested to have a role in the pruritus seen in patients with AD.^{1,46} However, studies to establish an association of itch or pruritogenic factors with sleep disturbance in patients with AD are either lacking or produced conflicting results.⁴² It was also reported that scratching accounted for only 15% of arousals and awakenings in children with AD.²² Therefore itch and scratching movements are contributing factors but are unlikely the only reason for sleep disturbance in patients with AD.

The circadian rhythm regulates immune function and cytokine production, cortisol secretion, and skin physiology, and these mechanisms could play a role in sleep disturbance in patients with AD. Various immune cell counts, immune cell function, and cytokine levels exhibit diurnal patterns.⁴² Levels of proinflammatory cytokines, such as IL-1 β , IL-2, TNF- α , IFN- γ , and IL-6, are increased at night and generally promote sleep, whereas anti-inflammatory cytokines, such as IL-4 and IL-10, are induced after awakening and could inhibit sleep.^{47,48}

The pathogenesis of AD is complex. In acute lesions AD is characterized by profound increases of T_H2 and T_H22 responses. IL-4 and IL-13 seem to play key roles, but IL-5, IL-31, CCL18, and IL-22 levels are also increased. T_H17-associated molecules, such as IL-17A, peptidase inhibitor 3/elafin, and CCL20, are up-regulated in both patients with acute and those with chronic AD. In chronic AD lesions T_H2 and T_H22 responses are intensified, but activation of the T_H1 axis is also found, with increased levels of IFN- γ , CXCL9, and CXCL10.⁴⁹ Histamine, thymic stromal lymphopoietin, IL-33, IL-31, IL-4, and IL-13 have been suggested to be key mediators of pruritus in patients with AD.⁵⁰ Serum IL-31, CCL17, CCL22, and CCL27 levels have been found to be correlated with AD disease activity.⁴⁹

Because of the involvement of a wide range of cytokines and chemokines in patients with AD, it is possible that dysregulated levels of cytokines, such as IL-4, could contribute to sleep disturbance.^{42,51} However, direct relationships between cytokine levels or immune cell activity during sleep in patients with AD have rarely been studied. Bender et al⁵² reported that an increased differential between morning and evening IL-6 production by PBMCs stimulated with anti-CD3 was correlated with better sleep efficiency in adults with AD. Hon et al²⁷ reported that wrist activity during sleep was correlated with plasma concentrations of cutaneous T cell-attracting cytokine, thymus and activation-regulated chemokine, and macrophage-derived chemokine but did not correlate with subjective pruritus or sleep loss. Our group found that in children with AD, a higher morning serum IL-4 level was correlated with better sleep efficiency, and the ratio of

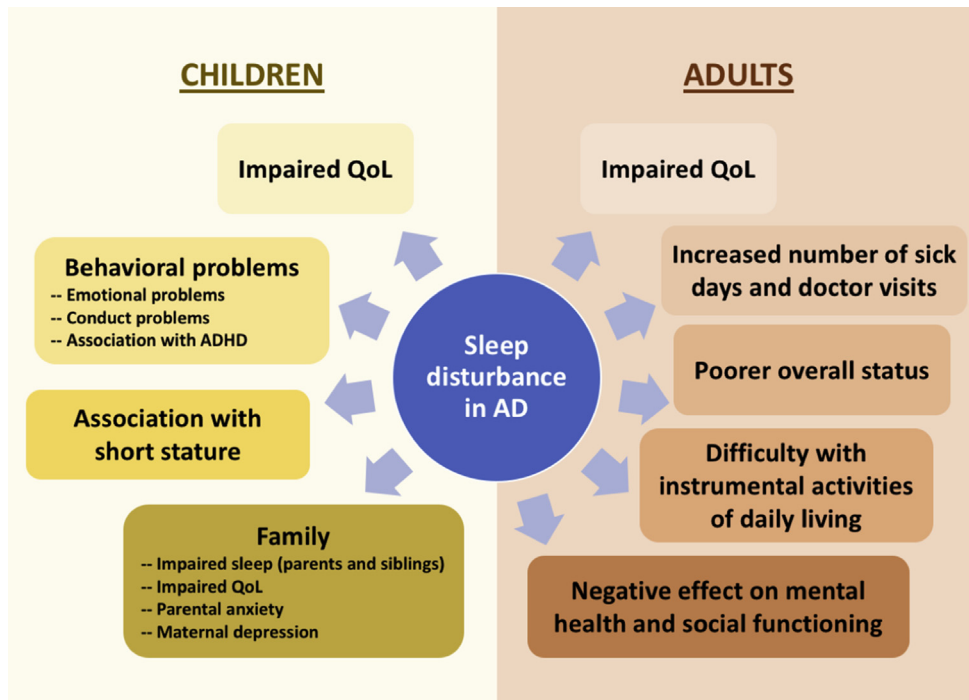


FIG 1. Effect of sleep disorders in patients with AD. Sleep disorders have a wide range of effects on both children and adults with AD. *ADHD*, Attention deficit hyperactivity disorder; *QoL*, quality of life.

IFN- γ /IL-4 was lower in those with poor sleep efficiency. We also found that morning serum IL-31 levels were correlated with a lower percentage of stage N1 sleep.¹⁵

Skin cells express circadian clock genes, such as circadian locomotor output cycles kaput (*CLOCK*) and brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (*BMAL1*), and skin barrier function is also regulated by the circadian rhythm. Skin blood flow rate is greater in the afternoon and early evening and has a second peak in the late evening before sleep onset.⁵³ Low sebum production at night and high transepidermal water loss in the evening could contribute to nocturnal itching in patients with AD.^{54,55} Cortisol levels are lowest in the evening after sleep onset and could also contribute to increased pruritus at night.⁵⁴ However, studies directly investigating the relationship between cortisol levels or diurnal skin physiology and sleep disturbance in patients with AD are lacking and need further evaluation.

Melatonin is a hormone essential for regulating sleep and the circadian rhythm. It is mainly secreted by the pineal gland but also by other tissues, such as the skin, lymphocytes, and mast cells.⁵⁶ Melatonin has effects on sleep, immunomodulation, and antioxidant ability, and therefore it was suggested that it might play some role in patients with AD.⁵⁷ Schwarz et al⁵⁸ reported that the circadian melatonin rhythm was diminished in patients with AD. Our group found that nocturnal melatonin secretion was greater in patients with AD compared with that in control subjects and that in patients with AD, higher nocturnal melatonin levels were associated with better sleep efficiency, less sleep fragmentation, and milder disease.¹⁵ In a randomized, double-blind, placebo-controlled trial, our group found that 3 mg of oral melatonin before bedtime for 4 weeks in children with AD improved sleep onset latency by 21.4 minutes compared with placebo (95% CI,

–38.6 to –4.2; $P = .02$). AD disease severity was also improved after melatonin, decreasing the SCORAD score by 9.1 compared with that after placebo (95% CI, –13.7 to –4.6; $P < .001$). The improvement in SCORAD score was not correlated with the change in sleep onset latency.⁵⁹ This supports that in addition to sleep-promoting effects, other properties of melatonin, such as immunomodulation or antioxidation, could play a role in modulating AD.

There are few studies that examine the relationship between environmental factors and sleep disturbance in patients with AD. Our group found that serum allergen-specific IgE levels to dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) were correlated with sleep disturbance in children with AD, including decreased sleep efficiency, higher percentage of time awake during sleep, and more sleep fragmentation.¹⁵ Allergic sensitization and exposure to dust mite during sleep could also contribute to sleep disturbances in patients with AD. Roles of other allergens and the sleeping environment need further study.

Studies have shown that even when AD is in clinical remission, sleep disturbances, such as sleep fragmentation and frequent arousals, can persist.²² It is possible that patients with AD acquire poor sleep habits because of their sleep disturbance during flare-ups, leading to behavior-related sleep problems that persist even without clinically evident disease. Cosleeping with parents is common in children with AD. Cosleeping has been found to be a predictor of nighttime waking in healthy children,⁶⁰ and it is unclear whether it could also contribute to further sleep disturbance in children with AD. Because of the skin condition, parents might also acquire a more permissive attitude toward the child's bedtime schedule or if the child has bedtime resistance, increasing the risk of behavioral insomnia.

- Acquired sleep habits (cosleeping, behavioral insomnia)
- Environmental factors (allergens)
- Melatonin dysregulation
- Nocturnal pruritus due to circadian rhythm of the skin
- Cytokine dysregulation (IL-4, IFN- γ , IL-6, IL-31)
- Disease flare with itch and scratching

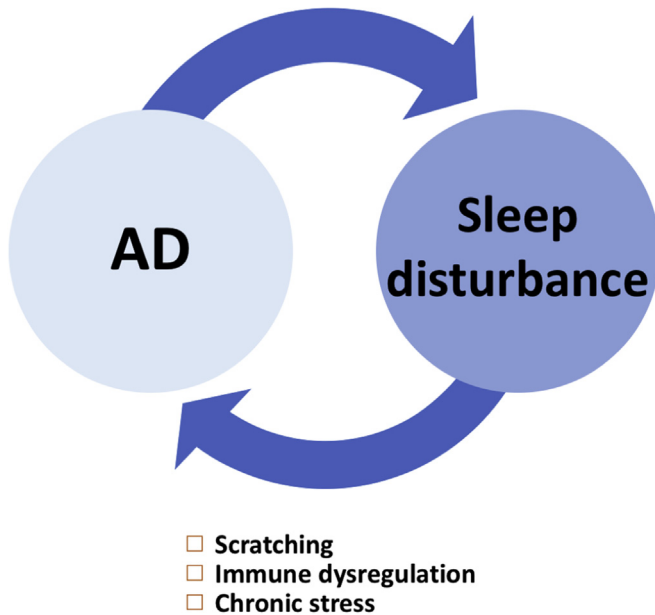


FIG 2. Bidirectional relationship between sleep disorders and AD. The mechanism of sleep disturbance in patients with AD is complex and involves multiple contributing factors. Sleep disturbance itself can also exacerbate AD, forming a vicious cycle.

DO SLEEP DISORDERS EXACERBATE AD?

Scratching leads to tissue damage and release of structural proteins, triggering an IgE response and resulting in an itch-scratch cycle that exacerbates AD.¹ Studies have found that in patients with AD, scratching occurs mainly in stage N1 sleep but is also not much suppressed during the deeper N2 and N3 sleep stages, when there is usually very little limb movement in healthy control subjects.^{15,52} Compared with daytime, it is more difficult for patients to consciously suppress their scratching at night, and frequent awakenings during the night might also increase awareness of nocturnal pruritus, leading to more scratching. Clinically, parents also often report that it is harder to prevent their child from scratching during sleep and that AD often flares up after a night of poor sleep and intense scratching. It is possible that sleep disturbance itself exacerbates the itch-scratch cycle in patients with AD.

Sleep and the circadian rhythm have complex relationships with immune function. Numerous studies have shown that sleep loss could lead to dysregulation of the immune system. Immune responses to LPS stimulation, susceptibility to infection, and vaccination vary according to the timing of stimulation and can be altered with sleep loss.^{61,62} Studies have found that IL-1 β , IL-6, and TNF- α levels are increased during acute sleep deprivation, and IL-1 β , IL-6, IL-17, and that high-sensitivity C-reactive protein levels are increased with chronic partial sleep deprivation.⁶³ In an animal model of psoriasis, those challenged with sleep deprivation had increased levels of proinflammatory cytokines,

such as IL-1 β , IL-6, and IL-12, and decreased levels of the anti-inflammatory cytokine IL-10. These cytokine levels were restored after 48 hours of sleep rebound.⁶⁴ Because of cytokine alterations, a chicken-or-egg relationship has also been suggested between sleep disorders and disease activity of inflammatory diseases, such as inflammatory bowel disease.⁶⁵

Sleep deprivation could also disturb the functional rhythm of regulatory T cells^{42,66} and could shift the T_H1/T_H2 balance toward T_H2 dominance.⁶⁷ Our group found that in children with AD, the IFN- γ /IL-4 ratio was lower in those with poor sleep efficiency.¹⁵ This is compatible with the theory that sleep loss could shift the T_H1/T_H2 balance and suggests that sleep loss itself could probably also worsen AD.

Stress has been shown to worsen proinflammatory disorders, such as AD, through mechanisms like causing a shift to predominately T_H2 cells and impairing the response to stressful stimuli by the hypothalamic-pituitary axis. Skin cells could also produce corticotropin-releasing hormone in response to stress, which can lead to local inflammatory reactions and mast cell degranulation.⁶⁸ It is possible that chronic sleep disturbances could lead to chronic stress in patients with AD, which in turn further exacerbates AD.

In summary, there are reasons to believe that sleep disturbance itself could exacerbate AD and that there is a 2-way street between sleep disorders and AD, but studies establishing clear evidence are lacking, and further studies are needed to clarify whether the sleep disturbance in patients with AD worsens the itch-scratch cycle or causes immune dysregulations or stress which result in a vicious cycle in patients with AD (Fig 2).

MANAGEMENT OF SLEEP DISORDERS IN PATIENTS WITH AD

Currently, there is no consensus guiding the management of sleep disorders in patients with AD, and most treatment methods are based on expert opinion.⁶⁹ Guidelines for AD have recommended that treatment of AD should focus on disease control, with sleep disturbance as one of the measures of control.⁷⁰ Clinical trials that have assessed the effect of treatment on sleep in patients with AD are also mostly trials for disease-controlling agents, which evaluated sleep as a secondary outcome. Such trials include those using topical steroids, topical tacrolimus, cyclosporine, methotrexate, azathioprine, wet wraps, light therapy, and dupilumab for AD, and they all assessed sleep quality with subjective visual analog scales.⁶⁹⁻⁷¹ From current evidence, disease severity is associated with sleep disturbance in patients with AD, and pruritus and scratching are important contributing factors. Therefore optimal disease control is crucial in managing sleep problems in patients with AD. However, with the growing knowledge of the intertwining relationship between AD and sleep disorders, we suggest that management should be focused on both disease control and sleep (Fig 3).

The most commonly used sleep aids for AD are first-generation antihistamines, which can cross the blood-brain barrier and affect histamine's role in maintaining central nervous system arousal, resulting in a sedating effect, and might also have some benefit in pruritus by antagonizing the inflammatory effects of histamine released from mast cells and basophils, although high-level evidence for reducing itch in patients with AD is lacking.^{68,72} Tolerance often occurs after 4 to 7 days of treatment, and anticholinergic side effects, such as blurred vision and dry mouth, can

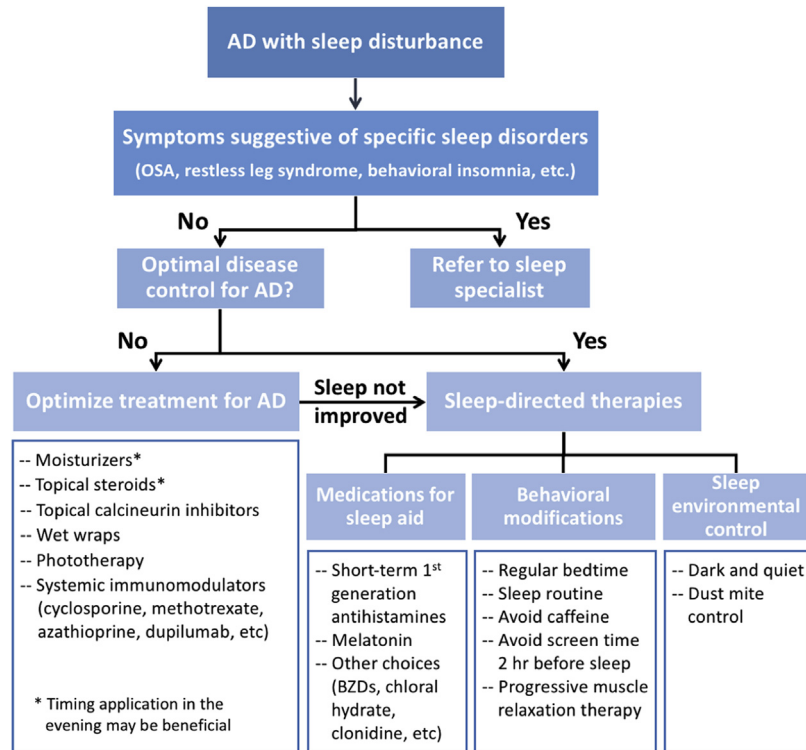


FIG 3. Proposed treatment strategy for sleep disorders in patients with AD. Patients with AD with sleep disturbance should first be screened for specific sleep disorders. Because of the intertwining relationship between sleep disorders and AD, management should be focused on both disease control and strategies to improve sleep. *BZDs*, Benzodiazepines.

occur.⁷³ Sedating antihistamines can also reduce sleep quality, decrease REM sleep, and impair daytime cognitive function and work efficiency.⁷²

Other sleep-promoting agents that have been suggested for AD, such as benzodiazepines, chloral hydrate, and clonidine, all lack supporting evidence.^{70,74} Benzodiazepines carry the risks of tolerance to sedating effects, rebound worsening of sleep on discontinuation, addiction, and memory problems.⁷⁴ Chloral hydrate use has risks of hepatotoxicity and respiratory depression.⁷⁰ Clonidine use requires blood pressure monitoring and could also have anticholinergic side effects. Clonidine could also suppress REM sleep, and rapid discontinuation could lead to REM rebound.⁶⁸

Oral melatonin supplementation has been found to improve both sleep onset latency and disease severity in children with AD in a randomized controlled trial.⁵⁹ Melatonin also has a good safety profile and might be a favorable choice for children. However, the optimal dose and duration of treatment need further study.

The importance of implementing methods to improve sleep hygiene and sleep-directed behavioral therapies should be stressed for the purposes of both improving sleep and preventing acquired behavioral insomnia, which could persist after disease control. General measures for improving sleep hygiene include adhering to regular bedtimes and wake-up times, performing a relaxing bedtime routine, keeping a quiet sleeping environment, and avoiding caffeine intake.⁶⁹ Because of the effect of the circadian rhythm on AD, applying moisturizers and topical steroids in the evening could be advantageous because transepidermal water

loss is greatest and skin blood flow rate is most affected by topical steroids at this time.⁴² Use of moisturizers and topical medications could also be incorporated into the bedtime routine. Light, particularly blue light, suppresses melatonin secretion, and therefore it is important to avoid screen time 2 hours before sleep and maintain a dark sleeping environment.⁴²

Dust mite sensitization might have a role in the sleep disturbance seen in patients with AD,¹⁵ and therefore dust mite control in the sleeping environment should be encouraged. Progressive muscle relaxation therapy, which involves cycles of tensing a target muscle group for 10 seconds and then relaxing the muscle group for 20 seconds, has also been shown to be helpful in reducing pruritus, sleep loss, and anxiety in patients with AD and could be tried in older children or adults with AD.⁷⁵

If behavioral insomnia occurs, referral to a psychologist or sleep medicine specialist is suggested for behavioral modification strategies, such as extinction, graduated extinction, scheduled awakenings, bedtime fading, and response cost.⁶⁹ Mindfulness meditation has recently been used to improve insomnia in adults and adolescents,^{76,77} and it has been suggested that it could be helpful for treating psoriasis or other dermatologic diseases.⁷⁸⁻⁸⁰ Further study is needed to explore whether mindfulness meditation could improve sleep disorders in patients with AD.

Screening for specific sleep disorders that have been found to be associated with AD is also important. Frequent snoring, apneas or choking during sleep, mouth breathing, or abnormal sleeping positions, such as being propped up on pillows or sleeping with the neck hyperextended, could suggest OSA. Uncomfortable sensations in the lower extremities accompanied by an almost

irresistible urge to move the legs exacerbated by resting or lying in bed and partially relieved by movement could indicate restless leg syndrome.⁸¹ If symptoms are suggestive of specific sleep disorders, referral to a sleep specialist is recommended for further evaluation and management (Fig 3).

CONCLUSIONS

Sleep disorders are very common in patients with AD and have a wide range of effects. The relationship between sleep disorders and AD seems to be bidirectional and likely forms a vicious cycle. Instead of regarding sleep disorders as only one of the symptoms or disease severity measures for AD, we suggest viewing sleep disorders as a comorbidity of AD for which one should screen regularly, and specific treatments for sleep disorders should be incorporated into management strategies.

We acknowledge the help of Dr Chun-An Chen, Department of Pediatrics, National Taiwan University Hospital, for the illustration of the figures in this review.

REFERENCES

- Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358:1483-94.
- Leung DY, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. *J Allergy Clin Immunol* 2014;134:769-79.
- Camfferman D, Kennedy JD, Gold M, Martin AJ, Lushington K. Eczema and sleep and its relationship to daytime functioning in children. *Sleep Med Rev* 2010;14:359-69.
- Ricci G, Bendandi B, Bellini F, Patrizi A, Masi M. Atopic dermatitis: quality of life of young Italian children and their families and correlation with severity score. *Pediatr Allergy Immunol* 2007;18:245-9.
- Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract* 2006;60:984-92.
- Nantes B. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology* 1993;186:23-31.
- Hon KL, Lam MC, Leung TF, Chow CM, Wong E, Leung AK. Assessing itch in children with atopic dermatitis treated with tacrolimus: objective versus subjective assessment. *Adv Ther* 2007;24:23-8.
- Leo HL, Bender BG, Leung SB, Tran ZV, Leung DY. Effect of pimecrolimus cream 1% on skin condition and sleep disturbance in children with atopic dermatitis. *J Allergy Clin Immunol* 2004;114:691-3.
- Simpson EL, Gadkari A, Worm M, Soong W, Blauvelt A, Eckert L, et al. Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): a phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). *J Am Acad Dermatol* 2016;75:506-15.
- Bartlett LB, Westbroek R, White JE. Sleep patterns in children with atopic eczema. *Acta Derm Venereol* 1997;77:446-8.
- Chamlin SL, Mattson CL, Frieden IJ, Williams ML, Mancini AJ, Cella D, et al. The price of pruritus: sleep disturbance and cosleeping in atopic dermatitis. *Arch Pediatr Adolesc Med* 2005;159:745-50.
- Hon KL, Leung TF, Wong KY, Chow CM, Chuh A, Ng PC. Does age or gender influence quality of life in children with atopic dermatitis? *Clin Exp Dermatol* 2008;33:705-9.
- Reid P, Lewis-Jones MS. Sleep difficulties and their management in preschoolers with atopic eczema. *Clin Exp Dermatol* 1995;20:38-41.
- Dogan DG, Canaloglu SK, Kivilcim M, Kum YE, Topal E, Catal F. Sleep patterns of young children with newly diagnosed atopic dermatitis. *Postepy Dermatol Alergol* 2017;34:143-7.
- Chang YS, Chou YT, Lee JH, Lee PL, Dai YS, Sun C, et al. Atopic dermatitis, melatonin, and sleep disturbance. *Pediatrics* 2014;134:e397-405.
- Jeon C, Yan D, Nakamura M, Sekhon S, Bhutani T, Berger T, et al. Frequency and management of sleep disturbance in adults with atopic dermatitis: a systematic review. *Dermatol Ther (Heidelb)* 2017;7:349-64.
- Lewis-Jones MS, Finlay AY, Dykes PJ. The Infants' Dermatitis Quality of Life Index. *Br J Dermatol* 2001;144:104-10.
- Urrutia-Pereira M, Sole D, Rosario NA, Neto HJC, Acosta V, Almendarez CF, et al. Sleep-related disorders in Latin-American children with atopic dermatitis: a case control study. *Allergol Immunopathol (Madr)* 2017;45:276-82.
- Camfferman D, Kennedy JD, Gold M, Martin AJ, Winwood P, Lushington K. Eczema, sleep, and behavior in children. *J Clin Sleep Med* 2010;6:581-8.
- Silverberg JI, Garg NK, Paller AS, Fishbein AB, Zee PC. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. *J Invest Dermatol* 2015;135:56-66.
- Dahl RE, Bernhisel-Broadbent J, Scanlon-Holdford S, Sampson HA, Lupo M. Sleep disturbances in children with atopic dermatitis. *Arch Pediatr Adolesc Med* 1995;149:856-60.
- Reuveni H, Chapnick G, Tal A, Tarasiuk A. Sleep fragmentation in children with atopic dermatitis. *Arch Pediatr Adolesc Med* 1999;153:249-53.
- Monti JM, Vignale R, Monti D. Sleep and nighttime pruritus in children with atopic dermatitis. *Sleep* 1989;12:309-14.
- Hon KL, Leung TF, Ma KC, Li AM, Wong Y, Yin JA, et al. Resting energy expenditure, oxygen consumption and carbon dioxide production during sleep in children with atopic dermatitis. *J Dermatolog Treat* 2005;16:22-5.
- Stores G, Burrows A, Crawford C. Physiological sleep disturbance in children with atopic dermatitis: a case control study. *Pediatr Dermatol* 1998;15:264-8.
- Benjamin K, Waterston K, Russell M, Schofield O, Diffey B, Rees JL. The development of an objective method for measuring scratch in children with atopic dermatitis suitable for clinical use. *J Am Acad Dermatol* 2004;50:33-40.
- Hon KL, Lam MC, Leung TF, Kam WY, Lee KC, Li MC, et al. Nocturnal wrist movements are correlated with objective clinical scores and plasma chemokine levels in children with atopic dermatitis. *Br J Dermatol* 2006;154:629-35.
- Chng SY, Goh DY, Wang XS, Tan TN, Ong NB. Snoring and atopic disease: a strong association. *Pediatr Pulmonol* 2004;38:210-6.
- Tien KJ, Chou CW, Lee SY, Yeh NC, Yang CY, Yen FC, et al. Obstructive sleep apnea and the risk of atopic dermatitis: a population-based case control study. *PLoS One* 2014;9:e89656.
- Hu JM, Lin CS, Chen SJ, Chen CY, Lin CL, Kao CH. Association between obstructive sleep apnea and atopic dermatitis in children: a nationwide, population-based cohort study. *Pediatr Allergy Immunol* 2018;29:260-6.
- Gupta MA, Simpson FC, Vujcic B, Gupta AK. Obstructive sleep apnea and dermatologic disorders. *Clin Dermatol* 2017;35:319-27.
- Cicek D, Halisdemir N, Dertoglu SB, Berilgen MS, Ozel S, Colak C. Increased frequency of restless legs syndrome in atopic dermatitis. *Clin Exp Dermatol* 2012;37:469-76.
- Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol* 2006;155:145-51.
- Meltzer LJ, Moore M. Sleep disruptions in parents of children and adolescents with chronic illnesses: prevalence, causes, and consequences. *J Pediatr Psychol* 2008;33:279-91.
- Moore K, David TJ, Murray CS, Child F, Arkwright PD. Effect of childhood eczema and asthma on parental sleep and well-being: a prospective comparative study. *Br J Dermatol* 2006;154:514-8.
- Lawson V, Lewis-Jones MS, Finlay AY, Reid P, Owens RG. The family impact of childhood atopic dermatitis: the Dermatitis Family Impact Questionnaire. *Br J Dermatol* 1998;138:107-13.
- Sadeh A, Gruber R, Raviv A. Sleep, neurobehavioral functioning, and behavior problems in school-age children. *Child Dev* 2002;73:405-17.
- Touchette E, Petit D, Seguin JR, Boivin M, Tremblay RE, Montplaisir JY. Associations between sleep duration patterns and behavioral/cognitive functioning at school entry. *Sleep* 2007;30:1213-9.
- Schmitt J, Chen CM, Apfelbacher C, Romanos M, Lehmann I, Herbarth O, et al. Infant eczema, infant sleeping problems, and mental health at 10 years of age: the prospective birth cohort study LISApus. *Allergy* 2011;66:404-11.
- Silverberg JI, Paller AS. Association between eczema and stature in 9 US population-based studies. *JAMA Dermatol* 2015;151:401-9.
- Romanos M, Gerlach M, Warnke A, Schmitt J. Association of attention-deficit/hyperactivity disorder and atopic eczema modified by sleep disturbance in a large population-based sample. *J Epidemiol Community Health* 2010;64:269-73.
- Chang YS, Chiang BL. Mechanism of sleep disturbance in children with atopic dermatitis and the role of the circadian rhythm and melatonin. *Int J Mol Sci* 2016;17:462.
- Yamaguchi J, Aihara M, Kobayashi Y, Kambara T, Ikezawa Z. Quantitative analysis of nerve growth factor (NGF) in the atopic dermatitis and psoriasis horny layer and effect of treatment on NGF in atopic dermatitis. *J Dermatol Sci* 2009;53:48-54.
- Misery L. Atopic dermatitis and the nervous system. *Clin Rev Allergy Immunol* 2011;41:259-66.

45. Foster EL, Simpson EL, Fredrikson LJ, Lee JJ, Lee NA, Fryer AD, et al. Eosinophils increase neuron branching in human and murine skin and in vitro. *PLoS One* 2011;6:e22029.
46. Hon KL, Lam MC, Wong KY, Leung TF, Ng PC. Pathophysiology of nocturnal scratching in childhood atopic dermatitis: the role of brain-derived neurotrophic factor and substance P. *Br J Dermatol* 2007;157:922-5.
47. Geiger SS, Fagundes CT, Siegel RM. Chrono-immunology: progress and challenges in understanding links between the circadian and immune systems. *Immunology* 2015;146:349-58.
48. Opp MR. Cytokines and sleep. *Sleep Med Rev* 2005;9:355-64.
49. Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol* 2017;139(suppl):S65-76.
50. Trier AM, Kim BS. Cytokine modulation of atopic itch. *Curr Opin Immunol* 2018;54:7-12.
51. Lin YT, Shau WY, Wang LF, Yang YH, Hwang YW, Tsai MJ, et al. Comparison of serum specific IgE antibodies to staphylococcal enterotoxins between atopic children with and without atopic dermatitis. *Allergy* 2000;55:641-6.
52. Bender BG, Ballard R, Canono B, Murphy JR, Leung DY. Disease severity, scratching, and sleep quality in patients with atopic dermatitis. *J Am Acad Dermatol* 2008;58:415-20.
53. Yosipovitch G, Sackett-Lundeen L, Goon A, Yiong Huak C, Leok Goh C, Haus E. Circadian and ultradian (12 h) variations of skin blood flow and barrier function in non-irritated and irritated skin-effect of topical corticosteroids. *J Invest Dermatol* 2004;122:824-9.
54. Vaughn AR, Clark AK, Sivamani RK, Shi VY. Circadian rhythm in atopic dermatitis-Pathophysiology and implications for chronotherapy. *Pediatr Dermatol* 2018;35:152-7.
55. Yen CH, Dai YS, Yang YH, Wang LC, Lee JH, Chiang BL. Linoleic acid metabolite levels and transepidermal water loss in children with atopic dermatitis. *Ann Allergy Asthma Immunol* 2008;100:66-73.
56. Acuña-Castroviejo D, Escames G, Venegas C, Díaz-Casado ME, Lima-Cabello E, López LC, et al. Extrapeineal melatonin: sources, regulation, and potential functions. *Cell Mol Life Sci* 2014;71:2997-3025.
57. Marseglia L, D'Angelo G, Manti S, Salpietro C, Arrigo T, Barberi I, et al. Melatonin and atopy: role in atopic dermatitis and asthma. *Int J Mol Sci* 2014;15:13482-93.
58. Schwarz W, Birau N, Hornstein OP, Heubeck B, Schonberger A, Meyer C, et al. Alterations of melatonin secretion in atopic eczema. *Acta Derm Venereol* 1988;68:224-9.
59. Chang YS, Lin MH, Lee JH, Lee PL, Dai YS, Chu KH, et al. Melatonin supplementation for children with atopic dermatitis and sleep disturbance: a randomized clinical trial. *JAMA Pediatr* 2016;170:35-42.
60. Sadeh A, Mindell JA, Luedtke K, Wiegand B. Sleep and sleep ecology in the first 3 years: a web-based study. *J Sleep Res* 2009;18:60-73.
61. Besedovsky L, Lange T, Born J. Sleep and immune function. *Pflugers Arch* 2012;463:121-37.
62. Lange T, Dimitrov S, Born J. Effects of sleep and circadian rhythm on the human immune system. *Ann N Y Acad Sci* 2010;1193:48-59.
63. Mullington JM, Simpson NS, Meier-Ewert HK, Haack M. Sleep loss and inflammation. *Best Pract Res Clin Endocrinol Metab* 2010;24:775-84.
64. Hirotsu C, Rydlewski M, Araujo MS, Tufik S, Andersen ML. Sleep loss and cytokines levels in an experimental model of psoriasis. *PLoS One* 2012;7:e51183.
65. Parekh PJ, Oldfield IV EC, Challapallisri V, Ware JC, Johnson DA. Sleep disorders and inflammatory disease activity: chicken or the egg? *Am J Gastroenterol* 2015;110:484-8.
66. Bollinger T, Bollinger A, Skrum L, Dimitrov S, Lange T, Solbach W. Sleep-dependent activity of T cells and regulatory T cells. *Clin Exp Immunol* 2009;155:231-8.
67. Sakami S, Ishikawa T, Kawakami N, Haratani T, Fukui A, Kobayashi F, et al. Coemergence of insomnia and a shift in the Th1/Th2 balance toward Th2 dominance. *Neuroimmunomodulation* 2002;10:337-43.
68. Barilla S, Felix K, Jorizzo JL. Stressors in Atopic Dermatitis. In: Fortson EA, Feldman SR, Strowd LC, editors. Management of atopic dermatitis: methods and challenges. Berlin: Springer International Publishing; 2017. pp. 71-7.
69. Patel D, Levoska M, Shwayder T. Managing sleep disturbances in children with atopic dermatitis. *Pediatr Dermatol* 2018;35:428-33.
70. Fishbein AB, Vitaterna O, Haugh IM, Bavishi AA, Zee PC, Turek FW, et al. Nocturnal eczema: Review of sleep and circadian rhythms in children with atopic dermatitis and future research directions. *J Allergy Clin Immunol* 2015;136:1170-7.
71. Doss N, Kamoun MR, Dubertret L, Cambazard F, Remitz A, Lahfa M, et al. Efficacy of tacrolimus 0.03% ointment as second-line treatment for children with moderate-to-severe atopic dermatitis: evidence from a randomized, double-blind non-inferiority trial vs. fluticasone 0.005% ointment. *Pediatr Allergy Immunol* 2010;21:321-9.
72. He A, Feldman SR, Fleischer AB Jr. An assessment of the use of antihistamines in the management of atopic dermatitis. *J Am Acad Dermatol* 2018;79:92-6.
73. Richardson GS, Roehrs TA, Rosenthal L, Koshorek G, Roth T. Tolerance to daytime sedative effects of H1 antihistamines. *J Clin Psychopharmacol* 2002;22:511-5.
74. Kelsay K. Management of sleep disturbance associated with atopic dermatitis. *J Allergy Clin Immunol* 2006;118:198-201.
75. Bae BG, Oh SH, Park CO, Noh S, Noh JY, Kim KR, et al. Progressive muscle relaxation therapy for atopic dermatitis: objective assessment of efficacy. *Acta Derm Venereol* 2012;92:57-61.
76. Gong H, Ni CX, Liu YZ, Zhang Y, Su WJ, Lian YJ, et al. Mindfulness meditation for insomnia: A meta-analysis of randomized controlled trials. *J Psychosom Res* 2016;89:1-6.
77. Blake M, Waloszek JM, Schwartz O, Raniti M, Simmons JG, Blake L, et al. The SENSE study: Post intervention effects of a randomized controlled trial of a cognitive-behavioral and mindfulness-based group sleep improvement intervention among at-risk adolescents. *J Consult Clin Psychol* 2016;84:1039-51.
78. Franca K, Lotti T. Mindfulness within psychological interventions for the treatment of dermatologic diseases. *Dermatol Ther* 2017;30.
79. Montgomery K, Norman P, Messenger AG, Thompson AR. The importance of mindfulness in psychosocial distress and quality of life in dermatology patients. *Br J Dermatol* 2016;175:930-6.
80. Talbot W, Duffy N. Complementary and alternative medicine for psoriasis: what the dermatologist needs to know. *Am J Clin Dermatol* 2015;16:147-65.
81. Mindell JA, Owens JA. *A Clinical Guide to Pediatric Sleep*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2010.