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PII: S2213-2198(20)31339-8

DOI: <https://doi.org/10.1016/j.jaip.2020.12.007>

Reference: JAIP 3313

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 4 November 2020

Revised Date: 25 November 2020

Accepted Date: 1 December 2020

Please cite this article as: Bawany F, Northcott CA, Beck LA, Pigeon WR, Sleep Disturbances and Atopic Dermatitis: Relationships, Methods for Assessment, and Therapies, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2020.12.007>.

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Sleep Disturbances and Atopic Dermatitis: Relationships, Methods for Assessment, and Therapies

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Funding Sources and Conflict of Interest:

FB was supported by the University of Rochester CTSA award number TL1 TR000096 from the National Center for Advancing Translational Sciences of the National Institutes of Health. **CAN** is an employee of Pfizer, Inc. and owns company stock. **LAB** is supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number U19AI117673; is a consultant for Abbvie, AI/Benevolent, Allakos, Astra-Zeneca, Galderma, Incyte, LEO Pharma, Lilly, Naos Bioderma, Novartis, Pfizer, PrincipiaBio, Regeneron, Sanofi, UCB, and Vimalan; is or has been an investigator on Abbvie, LEO Pharma, Pfizer, and Regeneron atopic dermatitis trials; and owns stock in Moderna, Gilead and Medtronic. **WRP** has consulted for Curaegis Technologies and is an employee of the U.S. Department of Veterans Affairs (VA). The content is solely the responsibility of the authors and does not necessarily represent the official views of the U.S. government, the National Institutes of Health, or the VA.

Abstract:

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin conditions and is associated with sleep disturbances in 47-80% of children and 33-90% of adults. Herein, we review the literature on sleep disturbances experienced by patients with AD, as well as the mechanisms that may underlie this. We present subjective and objective methods for measuring sleep quantity and quality and discuss strategies for management. Unfortunately, the literature on this topic remains sparse, with most studies evaluating sleep as a secondary outcome using subjective measures. The development of portable, at-home methods for more objective measures offers new opportunities to better evaluate sleep disturbances in AD research studies and in clinical practice.

Keywords: atopic dermatitis, sleep, type 2 immunity, insomnia, pruritus

Abbreviations:

AD	atopic dermatitis
aOR	adjusted odds ratio
BCG	ballistocardiography
BDNF	brain-derived neurotropic factor
CBT-I	cognitive behavioral therapy for insomnia
CI	confidence interval
CPG	clinical practice guideline
EEG	electroencephalography
EMG	electromyography
EOG	electrooculography

82		
83	FDA	Federal Drug Administration
84		
85	HR	hazard ratio
86		
87	IL	interleukin
88		
89	ISI	insomnia severity index
90		
91	JAK	Janus kinase
92		
93	nREM	non-rapid eye movement
94		
95	NRS	numerical rating scale
96		
97	OR	odds ratio
98		
99	OTC	over-the-counter
100		
101	PM	portable monitors
102		
103	PSG	polysomnography
104		
105	PRO	patient-reported outcomes
106		
107	RCT	randomized controlled trial
108		
109	RDBPCT	randomized, double-blinded, placebo-controlled trial
110		
111	SCORAD	Scoring Atopic Dermatitis
112		
113	SE	sleep efficiency
114		
115	SOL	sleep onset latency
116		
117	TSLP	thymic stromal lymphopoietin
118		
119	TST	total sleep time
120		
121	VAS	visual analog scale
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123	WASO	wake time after sleep onset
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INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin conditions and is commonly associated with sleep disturbances.¹ While approximately 10-41% of children²⁻⁴ and 7-48% of adults⁵⁻⁷ in the general population experience sleep disturbances, in AD patients, this figure climbs to 47-80% in children⁸⁻¹⁷ and 33-90% in adults.^{8, 17-19} In 2019, the Federal Drug Administration's (FDA) Patient-Focused Drug Development Initiative found that sleep was one of the three most problematic symptoms for AD patients and their families.²⁰ Impaired sleep compromises function (at work and home), mood, and interpersonal relationships. Chronic sleep disturbance can increase the risk for cardiovascular,²¹ metabolic,²² and psychiatric diseases.²³ However, objectively and efficiently quantifying AD sleep disturbance, understanding its pathophysiology, and identifying effective management strategies remain challenging.

"Sleep disturbance" is a broad term encompassing poor sleep, disrupted sleep, sleep loss, or a specific sleep disorder (e.g. insomnia, obstructive sleep apnea). Methods to assess sleep disturbance vary widely. Single dichotomous (e.g., "Do you have trouble sleeping?") or Likert-type questions (e.g., "On a scale of 1-5, what is the quality of your sleep?") are used in epidemiologic studies, or when sleep is a secondary or tertiary outcome measure. When sleep is the primary focus, numerous validated, self-reported measures of sleep, sleep quality, and sleep disorders can be deployed. Additionally, some attributes of sleep can be measured objectively in the laboratory or home environment. It is unclear what method(s) are most appropriate to assess sleep disturbances in AD patients. In this review, we summarize studies on sleep disturbance in AD, discuss possible mechanisms, critique methods for measurement, outline management strategies, and recommend areas for further study.

Sleep Disturbances in Atopic Dermatitis

Children

Most studies of sleep disturbance in AD have been conducted on children, reflecting that although prevalence ranges vary widely across studies, sleep disturbances are more common in children with AD than in adults.²⁰ AD children report difficulty falling asleep,^{13, 24} frequent and long nighttime awakenings,^{11, 24-26} difficulty waking up,^{13, 24} and excessive daytime sleepiness.^{13, 24} This has been corroborated to some degree by polysomnography (PSG) studies, which, although not uniformly consistent, have shown prolonged sleep onset latency (SOL) (time required to fall asleep),^{13, 27} more wake time after sleep onset (WASO), sleep fragmentation,²⁷⁻³¹ and lower sleep efficiency (SE) (proportion of time in bed spent asleep).^{28, 29, 32} Some studies indicate a reduction in total sleep duration,^{13, 24} but the majority, including a large longitudinal study,³³ found no significant differences in sleep duration compared to healthy controls.^{25, 28, 29, 31,} Similarly, some studies found that younger children,^{9, 15} females,³⁵ and those of lower socioeconomic status⁹ were more likely to have reduced sleep quality, while others found no such differences.^{15, 36}

Generally, as AD severity increases, the prevalence and severity of sleep disturbances also increase.^{12, 37, 38} During AD flares, sleep disturbances increased from 60 to 83%.⁹ Increased disease severity as measured by the Scoring Atopic Dermatitis (SCORAD) was associated with more bedtime resistance, nocturnal awakenings, and daytime sleepiness (all $P < 0.0001$).³⁴ Increases in SCORAD were also associated with lower SE ($r = -0.73$), increased fragmentation (r

= 0.70), longer WASO ($r = 0.62$), and increased movements during sleep ($r = 0.70$) (all $P < 0.001$).¹³

Sleep disturbances can significantly impact the quality of life of AD children, their caregivers, and other family members.^{10, 26, 39} Disturbed sleep has been associated with reduced happiness,¹² impaired performance on neurobehavioral tasks,^{40, 41} hyperactivity/inattention,^{9, 40, 42, 43} behavioral and emotional disturbances,^{9, 14, 41, 43} and stunted growth.⁴⁴ Additionally, 60-65% of parents and 63% of siblings of children with AD reported disturbed sleep.^{12, 14, 38, 45} In fact, 30% of parents co-slept with their child because of AD symptoms,¹² which exacerbated disturbances for both child and parent.⁴⁶ During disease flares, 86% of parents had disturbed sleep, losing up to 2.6 hours of sleep per night.^{47, 48} Parental sleep disturbances were maintained throughout childhood, with mothers of AD children consistently being more likely to experience difficulty falling asleep (adjusted odds ratio [aOR] 1.36, 95% CI 1.01-1.83) and subjectively insufficient sleep (aOR 1.43, 95% CI 1.24-1.66).⁴⁹ These disturbances resulted in reduced parental happiness,^{12, 46, 50} interpersonal conflicts,¹⁴ and exhaustion.^{14, 38, 46}

Adults

Studies on adults with AD are more limited. Adults reported difficulty falling asleep,^{17, 51-54} early morning awakenings,^{51, 52} and daytime fatigue.^{54, 55} Although very few objective studies have been conducted, two actigraphy studies demonstrated lower SE,⁵⁵ twice as many nocturnal awakenings,⁵⁵ and twice as many movements⁵⁶ as controls. Furthermore, increased disease severity was associated with reduced sleep quality,^{52, 54, 57, 58} increased SOL,^{17, 37, 53, 57} and reduced SE.⁵⁹ As in children, total sleep duration was similar to healthy controls.^{55, 60} Sleep

disturbance was associated with more missed workdays, visits to the doctor, and poorer overall health ($P < 0.0001$).⁶¹

Overall, most large AD studies that assess sleep use self-reports or surveys that often assess a single item drawn from a mood or quality-of-life instrument, which do not measure the complexities of sleep.⁶² Not surprisingly, self-reports do not always corroborate more objective measures of sleep.^{55, 56, 59, 63, 64} Even studies using objective measures have found conflicting results and significant intra- and inter-individual variation.⁵⁶ Notably, almost all studies conducted thus far are cross-sectional. In a chronic, relapsing and remitting disease such as AD, longitudinal studies would provide more information about how fluctuations in disease activity affect sleep. Additionally, few objective studies have been conducted on AD caregivers, partners, or other family members. Large-scale trials using objective measures of sleep quality are needed in order to draw clearer conclusions.

Putative Mechanisms of Sleep Disturbances in AD

We propose three mechanisms by which sleep disturbance and AD may be associated or even causally connected. First, as demonstrated in other chronic conditions,⁶⁵ the mere stress of having AD can precipitate acute insomnia, which becomes chronic over time. Nocturnal scratching disrupts sleep and sets the stage for cognitive and behavioral factors that reinforce insomnia as a conditioned response. When persons with insomnia are awake in bed, they may ruminate and/or worry about stressors, their pruritus, falling back asleep, and/or daytime consequences of poor sleep. They may also engage in behaviors that are counterproductive (e.g. remaining in bed while awake to maximize sleep opportunity, staying in bed past typical rise

times, and taking naps), which reduce nocturnal sleep drive and disrupt circadian rhythm. Insomnia can persist even when the co-occurring condition has resolved.⁶⁶ One study found that children with AD in remission (n=14) still had more arousals from sleep per hour than healthy controls (n=9) (24.1+/-8.1 vs. 15.4+/-6.2; $P < 0.001$).³¹ This suggests that sleep disturbances may in part be mediated by learned behavioral patterns that persist even when skin is clear.

Second, a commonly held belief is that pruritus disrupts sleep.⁶² Pruritus is a key driver of impaired quality of life and commonly worsens at night.^{15, 20, 26, 17, 59, 62} It results in scratching, which can disturb sleep. In several studies, while healthy controls displayed minimal scratching during sleep, patients with AD spent up to 14.3% of their sleep time scratching.^{60, 64, 67} Scratching was associated with nocturnal awakenings, sleep fragmentation ($r = 0.5$, $P < 0.001$), and reduced SE ($r = -0.54$, $P < 0.001$).^{11, 13, 29, 67, 68} The “itch-scratch cycle” may lead to tissue damage and the release of inflammatory mediators/pruritogens, further exacerbating sleep disturbances.⁶⁹ These include: (1) eosinophil granule proteins and nerve growth factors and neuropeptides, which lead to sensory hypersensitivity;⁷⁰⁻⁷⁴ (2) circadian variations in skin blood flow, transepidermal water loss, and cortisol levels, which can promote nocturnal pruritus;⁷⁵⁻⁷⁷ and (3) cytokines overexpressed in AD lesions that may mediate pruritus, including IL-31,^{75, 78-80} IL-4, IL-13, and thymic stromal lymphopoietin (TSLP).⁸⁰ However, studies have found conflicting results or only weak correlations with pruritus, and very few have investigated the direct impact of these biomarkers on itch or scratching behaviors, and more importantly, on sleep disturbances. One study of AD children (n=28) found that brain-derived neurotrophic factor (BDNF) ($r = 0.905$, $P < 0.001$) and substance P ($r = 0.925$, $P < 0.001$) levels were associated with increased nocturnal wrist activities.⁸¹ However, only BDNF was associated with AD severity,

and neither was associated with subjective assessments of sleep loss or pruritus. Another study found that IL-31 was associated with subjective sleep loss and disease severity, but not pruritus.⁸²

A third hypothesis on sleep-AD mechanisms focuses on circadian variations in cytokines and melatonin production. Generally, cytokines such as IL-1 β , IL-2, IL-6, TNF- α , and IFN- γ increase at night and promote sleep, while cytokines such as IL-4, IL-10, and IL-13 increase after waking and promote wakefulness.^{62, 83-85} The altered expression of these cytokines in AD is thought to disrupt normal circadian patterns. Some studies found that high levels of IL-6, particularly in the morning, were associated with reduced sleep quality in AD patients.^{32, 59} However, a larger study found that a lower ratio of IFN- γ /IL-4 was associated with reduced SE, while levels of IL-1 β , IL-6 and IL-10 had no effect on sleep.¹³ Melatonin, which regulates sleep and the circadian rhythm,^{86, 87} can also have immunomodulatory, antioxidant, and cytoprotective functions.⁸⁸ In one study, only 22% of patients with AD had a normal melatonin secretion pattern, with most lacking the normal nocturnal melatonin surge.⁸⁹ A second study found that AD patients with higher nocturnal melatonin had greater SE ($r = 0.4$, $P = 0.004$) and less fragmentation ($r = -0.34$, $P = 0.004$).¹³

Unfortunately, the evidence for any of these pathways in AD is not strong. While pruritus and scratching appear to play a role, they may not account for most of the sleep disturbances the patients experience.^{31, 90} The molecular basis of sleep disturbance/homeostasis may involve a set of genes (termed “clock genes”)^{91, 92} whose role in human sleep is being investigated, albeit not yet in AD patients. Although far more studies are needed to investigate the nature of the sleep-

AD relationship before we can draw any firm conclusions, **Figure 1** is a simplified conceptual model.

Methods for Measuring and Identifying Sleep Disturbances

There are multiple methods to evaluate sleep including PSG, portable sleep monitors, actigraphy, patient-reported outcomes (PROs), and sleep diaries.

Polysomnography (PSG)

The “gold” standard for objective measurement of sleep is PSG, an overnight test performed in a sleep laboratory that involves placement of >12 electrodes on the face/scalp, thorax, abdomen, and legs. PSG captures brain activity [electroencephalography (EEG)], eye movements [electrooculography (EOG)], muscle activity/activation [electromyography (EMG)], and respiratory endpoints. The readouts are respiration metrics, limb movements, sleep stages [non-rapid eye movement (nREM) stages N1, N2, and N3, and REM], arousals from sleep, SOL, WASO, total sleep time (TST), and SE. This is a data-rich, but time- and resource-intensive test that is not widely available and can be burdensome, uncomfortable, and costly for the patient.

Portable Monitors

Because of these PSG challenges, Portable Monitors (PM) that can be performed in the home were developed. There are four PM classes, with Type I being an ambulatory PSG and Types II-IV having fewer endpoints than PSG.

Digital Wearables

Actigraphy are typically wrist-worn devices that use an internal accelerometer to measure gross movement. The accompanying software utilizes this data to estimate activity and sleep/wake periods. Actigraphy is non-invasive, less expensive than PSG and PMs, and can be used at home. It has been shown to correlate with PSG-measured endpoints such as SOL, WASO, TST, SE, and arousals, but has limited ability to assess sleep stages.

Another wearable is an EEG headband, with sophisticated versions having five electrodes, an accelerometer, pulse oximeter, and an audio component. The resulting data has correlated with some PSG readouts but not others (SOL and WASO). However, similar to actigraphy devices, headbands can have battery life or software issues and are positionally sensitive (i.e. can fall off during sleep). For these reasons, they may not yield consistent and useful data.

Nonwearables

These are devices placed near or under the sleeping person. Mattress-based sensors are one example, which utilize ballistocardiography (BCG) to measure body motion generated by the ejection of blood during the cardiac cycle. They also track thoracic movements associated with respiration. While mattress-sensors correlate somewhat with validated objective measures, they are confounded by a number of factors: mattress thickness, mattress size, patient weight, body movements/location, and bedpartners (human and animal).

PROs and Sleep Diaries

PROs and sleep diaries are commonly used to assess the impact of sleep disturbances on patients' wellbeing. The daily sleep diary is a standard PRO with 6-10 items to be completed daily for 1-2 weeks, which provide weekly average values for SOL, WASO, TST, and SE.⁹³ Although it is widely used to capture these measures, it typically does not correlate well with the same measures collected by PSG or actigraphy. Several variants of sleep diaries exist including a consensus sleep diary.⁹³ For an overview of other commonly used sleep PROs, see **Table 1**.

The instruments and PROs/diaries briefly reviewed above and in **Table 1** provide a range of options to use in clinical practice and/or research trials. They vary in cost, logistical challenges, burden to investigator and patient, diagnostic utility, ideal patient population, and validity. In AD clinical trials where sleep is often a secondary outcome measure, the inclusion of one or more of these measures will improve our understanding of sleep health in this population.

Methods for Management of Sleep Disturbances in AD

Treating the AD

It is unclear whether AD treatments directed at inflammation and/or pruritus will also treat sleep disturbances. Therefore, we begin by reporting sleep improvements noted from systemic therapies that are in common use, as well those in late-phase clinical development. The evidence on topical therapies is briefly outlined in **Table 2**. Most studies have been conducted on adults.

Systemic immunosuppressants such as cyclosporine, methotrexate, and azathioprine are not uncommonly used to treat moderate-severe AD. However, few studies have explored their effects on sleep. Uncontrolled trials of cyclosporine (one adult, one pediatric) showed

approximately 50% improvement in patient-reported sleep loss using a visual analog scale (VAS) after 8 weeks of treatment.^{131, 132} Similarly, small adult trials of azathioprine (n=37)¹³⁴ and methotrexate (n=12)¹³³ demonstrated reductions in sleep disturbance VAS scores of 30-50% by week 12 for azathioprine (not statistically significant) and week 24 for methotrexate ($P < 0.05$).

More targeted therapies have limited data with regards to sleep endpoints. Dupilumab, a fully humanized monoclonal antibody targeting IL-4R α , has been shown to significantly reduce pruritus within days of treatment initiation.¹⁶¹ Dupilumab (300mg bi-weekly) resulted in an improvement in SCORAD sleep loss scores by 3.3 points at 16 weeks, with 51% of subjects reporting absence of sleep disturbances.¹³⁹ Other targeted therapies with data on sleep disturbances include the Janus kinase inhibitors (JAKi) and antibodies against IL-31R α . Trials of JAKi have demonstrated improvements in disease severity, inflammatory biomarkers, pruritus, and in some cases, sleep. In a Phase 2 trial of baricitinib (2mg/day; JAK1 & 2 selective), SCORAD sleep loss scores were significantly reduced ($P < 0.01$) after 16 weeks; Phase 3 trials showed significant reductions in the Atopic Dermatitis Sleep Scale (item #2) as early as 1 week into treatment ($P < 0.05$; 1, 2 and 4 mg/day).^{162, 163} Phase 3 trials of abrocitinib (100 and 200mg/day; JAK1 selective) showed significant reductions in pruritus NRS compared to placebo by 2 weeks ($P < 0.01$), but sleep was not evaluated.¹⁶⁴ IL-31 is a pruritogen that binds to IL-31R α , expressed on sensory neurons and a wide range of other cell types.¹⁶⁵ Phase 2 trials with nemolizumab (10, 30, and 90 mg SQ every 4 weeks; anti-IL-31R α) resulted in reduced pruritus and sleep disturbance VAS by approximately 60% at 4 weeks and 90% by 52 weeks.^{166, 167} A

small, 16-week, Phase 3 trial (60mg SQ every 4 weeks) observed a greater percentage of patients achieving an Insomnia Severity Index (ISI) score ≤ 7 after treatment.¹⁶⁸

Antibodies to IL-13 (e.g. tralokinumab, lebrikizumab), TSLP (e.g. tezepelumab), and the H4 histamine receptor (ZPL-3893787) have also been investigated. IL-13 inhibitors, tezepelumab, and ZPL-3893787 improved some measures of pruritus; however, tezepelumab studies have not investigated sleep outcomes.^{142, 169, 170} ZPL-3893787 significantly improved SCORAD sleep scores compared to placebo by week 1 ($P < 0.01$), while lebrikizumab and tralokinumab both resulted in improved sleep scores at week 12 ($P = 0.023$) and week 16 ($P < 0.01$), respectively.¹⁴⁰⁻¹⁴² Overall, nearly all studies on the effects of AD therapies on sleep have investigated sleep as a secondary outcome using PROs. Incorporating more objective measures may add significant depth to current findings.

Treating the Sleep Disturbance Directly

The optimal management of sleep disturbance relies on accurate identification of the specific disturbance. Assuming that sleep disorders such as sleep apnea, restless legs syndrome, parasomnias, and a circadian rhythm disorder have been ruled out, the sleep disturbance that is most commonly associated with AD is insomnia.¹⁷¹ The Insomnia Severity Index (ISI) is a PRO which can reliably screen for and quantify insomnia (see **Table 1**).^{104, 105} Clinical practice guidelines (CPG) for the management of insomnia strongly recommend that the first-line management of adult insomnia is cognitive-behavioral therapy for insomnia (CBT-I).¹⁷²⁻¹⁷⁴ CBT-I is a multi-component intervention with established efficacy and durability in adolescents and adults.^{175, 176-178} This approach is effective in reducing not only insomnia, but also mood and

anxiety symptoms.¹⁷⁹ Typically, it is delivered in 6-8 weekly psychotherapy sessions, although
briefer formats have been shown to be effective.^{180, 181} Detailed descriptions of CBT-I are
available elsewhere, but its three core components are sleep restriction therapy, stimulus control
therapy, and sleep-specific cognitive therapy, which are supplemented by sleep psychoeducation
and sleep hygiene.^{171, 182} Notably, sleep hygiene is a very small part of CBT-I and the least
effective behavioral intervention.¹⁸³ When feasible, the full complement of CBT-I components
should be employed, which can also be accomplished via digital platforms.¹⁸⁴

No other non-pharmacologic treatment options for insomnia (e.g., hypnosis, biofeedback,
acupuncture, meditation and relaxation) have been consistently effective, and none are as
effective as CBT-I or sedative-hypnotic medications. The same can be said for over the counter
(OTC) formulations and supplements. OTC sedating antihistamines have limited data supporting
their effectiveness for insomnia. Some studies support the use of diphenhydramine, but a recent
task force recommended against its use for insomnia.¹⁸⁵ Supplementation with melatonin is an
established treatment for circadian rhythm disturbances¹⁸⁶ such as delayed sleep phase
disorder.¹⁸⁷ Evidence for its effectiveness in treating insomnia, however, is mixed and this,
coupled with wide variations in dose and expedients in OTC formulations, and concerns about
long-term safety, should limit its use.^{144, 188}

Several options exist for the pharmacologic treatment of insomnia (in adults) if the first-line
treatment (CBT-I) is ineffective or unavailable. These were reviewed in the 2017 CPG from the
American Academy of Sleep Medicine.¹⁸⁵ None of the agents warranted a “strong” evidence
rating, but many were rated “weak” (as opposed to not enough evidence to evaluate). Eight were
recommended for the treatment of sleep onset and/or sleep maintenance insomnia and were

FDA-approved for insomnia. These include two benzodiazepines (triazolam and temazepam), three non-benzodiazepine receptor agonists (zolpidem, zaleplon, and eszopiclone), the orexin antagonist suvorexant, the melatonin agonist ramelteon, and low-dose (3mg-6mg) doxepin, the tricyclic antidepressant with antihistaminergic properties. Notably, six agents had enough evidence to recommend against their use: the herbal supplement valerian, the amino-acid supplement tryptophan, exogenous melatonin, the antihistamine diphenhydramine, the GABA-reuptake inhibitor tiagabine, and the serotonin antagonist reuptake inhibitor trazodone. None of these six agents has an FDA indication for insomnia; yet, trazodone is one of the most widely prescribed agents for insomnia despite ongoing safety concerns (e.g., morning sedation, falls, suicide attempts).¹⁸⁹

It is striking that very few insomnia or ‘sleep disturbance’ intervention trials have been conducted in patients with AD. Among these, a small (n=73), well-designed, cross-over trial comparing melatonin to placebo in AD children with sleep disturbance found modest improvements on SOL, but no other sleep outcomes.¹⁴³ One RCT evaluating the antihistamine chlorpheniramine found no difference from placebo in relieving nocturnal AD symptoms.¹⁵⁰ A small trial (N=10) of the benzodiazepine, nitrazepam reduced the frequency, but increased the duration, of scratching.¹⁵¹ A RCT (n=24) of progressive muscle relaxation found no difference on a single item 0-10 for “loss of sleep” compared to controls,¹⁵⁵ and one sham-controlled RCT of acupuncture (n=30) showed positive effects on a visual analog scale of insomnia, although the participants in the sham condition had much higher baseline insomnia that was not controlled for in analyses.¹⁵⁹ Remarkably, no trials of CBT-I or of medications with FDA indications for insomnia have been conducted in AD populations.

Conclusions

Despite the fact that eczema has the highest disability-adjusted life years (DALY) of any skin condition worldwide, and more than 50% of AD children report sleep disturbance as one of the most bothersome symptoms, we still know very little about this AD comorbidity.¹⁹⁰ We have reviewed what is known about sleep disturbances in AD populations, provided an overview of the strengths and weaknesses of tools (both wearables and surveys) used to characterize, and in some cases, quantify sleep and/or sleep metrics, summarized several theories about pathogenesis, and reviewed traditional sleep treatments and the potential benefits of newer inflammation-directed AD therapies. Unfortunately, this exercise has highlighted the stark reality that we have much more to learn. Future studies should focus on characterizing AD-associated sleep disturbance(s), understanding their pathogenesis, identifying at-risk AD populations, defining the role that sleep disturbances play in other AD-associated comorbidities (anxiety, depression, attention-deficit disorders, social anxiety, etc.), and effectively managing it.

Figure Legend for Figure 1

The large semi-circular arrows reflect the macro level bi-directional between sleep and atopic dermatitis (AD). The large interior box reflects the putative mechanisms both driving the sleep-AD relationship and driven by current status of both sleep and AD. The individual putative mechanism boxes reflects evidence suggesting that each of these mechanisms may themselves have bidirectional relationships with each other.

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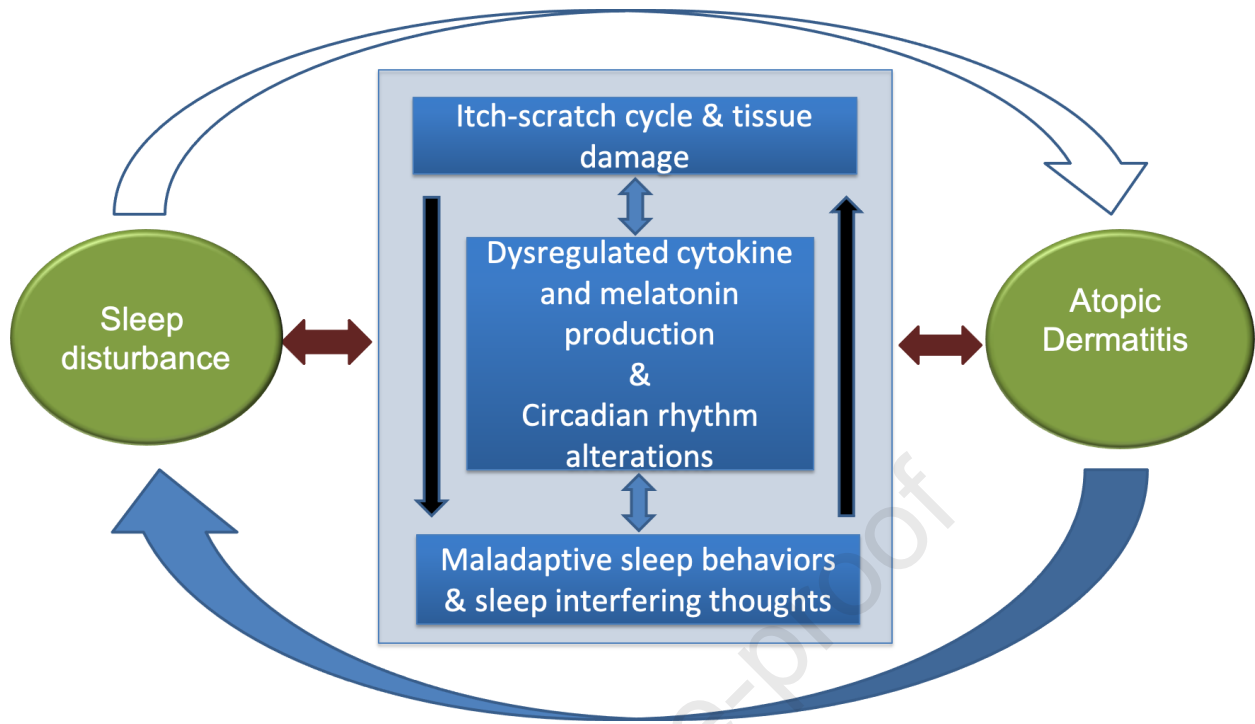


Table 1. Tools Commonly Used to Measure Sleep Disturbances.

Method	Variables measured	Advantages	Limitations
Subjective measures			
Pittsburgh Sleep Quality Index ⁹⁴	19 items answered by patient and 5 items answered by partner or caregiver regarding sleep duration and quality in the past month	Identifies specific aspects of sleep that are impaired High internal consistency Tested in a variety of disease states and countries Translated to many languages	Limited to adults May primarily reflect sleep on workdays ⁹⁵
Medical Outcomes Study (MOS) Sleep Scale ^{96, 97}	12 items answered by patient to measure 6 sleep dimensions: initiation (time to fall asleep), quantity (hours of sleep each night), maintenance, respiratory problems, perceived adequacy, and somnolence	Tested in a variety of disease states and countries Developed using a large number of patients served in primary care and specialty practice settings Covers multiple dimensions of sleep Translatable to multiple languages	Limited to adults Does not have a cutoff score Responsiveness to change/sensitivity has not been established
Children's Sleep Habits Questionnaire ⁹⁸	35 items regarding bedtime behavior, nocturnal awakenings, and sleep disorders over the past week in children 4-10 years old	High specificity and sensitivity in identifying sleep disturbances ⁹⁹ Incorporates questions regarding sleep disorders Validated in children with a wide variety of diseases Validated in	Limited to parental report, which may not be accurate Time frame limited to past week, which may not capture typical sleep habits in some circumstances

		longitudinal studies ⁹⁹ Available in multiple languages	
Brief Infant Sleep Questionnaire ¹⁰⁰	13 items regarding initiation and maintenance of sleep in infants in the past week	Sensitive and specific tool to identify sleep problems ⁹⁹ Correlated with actigraphy ¹⁰⁰ Translated into several languages	Proxy reporting of infant sleep by parents may be inaccurate
Epworth Sleepiness Scale ¹⁰¹	8 items regarding present-day daytime sleepiness	Correlated with PSG to some degree ¹⁰² Easy to administer Useful in screening for sleep disorders ¹⁰¹	Limited to daytime sleepiness, which may be affected by other factors Does not investigate specific disturbances during sleep May have limited validity between individuals ¹⁰³
Insomnia Severity Index (ISI)	7 items evaluating patient's assessment of his or her insomnia and its impact on daily functioning in the past 2 weeks ¹⁰⁴	Sensitive, validated screening tool to identify patients with insomnia and assess treatment response ¹⁰⁵ Brief, easy to administer	Use is limited to assessing insomnia, rather than specific parameters of sleep quality
Patient Reported Outcomes Information System (PROMIS) ^{106, 107}	41 items related to sleep habits, sleep disturbances, and daytime sleep-related impairments in the past 7 days	Validated in adults with AD ¹⁹ Used internationally ¹⁰⁸ Easy to administer	Inconsistent results in adolescents ¹⁰⁸
Sleep diaries ⁹³	Variable (typically logs of daily sleep duration and disturbances)	Cost-effective May be more accurate than	May not accurately reflect objective measures ^{109, 110}

		retrospective estimates of sleep quality over the past week/month ¹⁰⁹	Require daily completion Most are not formally validated ¹⁰⁶
Children's Dermatology Life Quality Index	10 items assessing skin symptoms and impacts on various aspects of quality of life in children 4-16 years old in the past week	Dermatology-specific Easy to administer Translated to many languages High internal consistency ¹¹¹ Self-reported	May not correlate well with other quality-of-life measures ¹¹² Only 1 item regarding sleep
Dermatitis Family Impact ¹⁴	10 items assessing impacts of child's disease on caregiver's daily activities and quality of life	AD-specific One of the few tools assessing caregiver sleep Easy to administer High internal consistency ¹¹¹	May be impacted by parental health and comorbidities Only 1 item assessing sleep
Infant's Dermatitis Quality of Life Index ¹⁰	10 item questionnaire assessing infant daily activities and quality-of-life in children < 4 years old in the past week	AD-specific Easy to administer Shows test-retest reliability ¹¹¹	Weak reliability and content validity ¹¹³ Only 2 items addressing sleep
Objective measures			
Polysomnography (PSG): gold standard	Brain function, heart rate, eye movements, muscle movements, and respiratory parameters	Multiple biophysiological variables measured Can aid in diagnosing sleep disorders, including disordered breathing Can detect disturbances that are	Not done in the individual's natural habitat May cause skin irritation in patients with AD May require monitoring for multiple nights to

		not associated with body movements	capture some disturbances Costly
Actigraphy	Limb acceleration (activity count in a certain amount of time)	Can be completed at home Less invasive than PSG Correlates well with PSG ¹³	Limited to measuring movements (unable to accurately measure sleep fragmentation or respiratory parameters) Correlation with PSG may depend on population studied and make of actigraphy device Quiet wakefulness may be measured as sleep Value of readouts is dependent on the software algorithm used to analyze the data
Video Monitoring/Observation	Visualized movements or other disturbances during sleep	Allows for direct visualization of sleeping and waking ¹¹⁴ Can be performed at home Allows for differentiation between scratching behaviors and other movements ^{64, 115}	May not capture brief nocturnal awakenings not associated with movements May not capture disordered breathing May not be as accurate in timings of events Rating and coding video is labor-intensive and can present rater variability
Biomotion Sensors and	Changes in pressure,	Correlates fairly well	Limited evidence

Mattress Sensors	body movements, or respiratory movements detected by sensors placed in mattresses	with validated objective measures ¹¹⁶⁻¹¹⁹ Can be performed at home Does not require wearing a device	Lack of movement may be detected as sleep May be confounded by mattress thickness and size, patient weight, and bedpartners
Headband Electroencephalograms	Stages of sleep detected through brain electrical patterns	Can be performed at home Agrees fairly well with other objective measures ¹²⁰⁻¹²²	Limited evidence Does not always stay on throughout the night ¹²⁰ Was not able to accurately measure sleep onset latency and wake time after sleep onset in some studies ¹²⁰

Table 2. Treatment strategies to manage sleep disturbances in atopic dermatitis patients.

Method	Advantages	Limitations	Quality of evidence in AD
Optimizing treatment of atopic dermatitis			
Topical Corticosteroids ¹²³⁻¹²⁷	Easy to use, with minimal side effects Well-tolerated in adults and children	Must be applied regularly (often daily) Chronic use may thin skin	Nine RCT's with varied control groups and results Improvements in sleep assessed through visual analog scale of sleep loss in nearly all studies
Topical Calcineurin Inhibitors (e.g. tacrolimus, pimecrolimus) ^{126, 128}	Easy to use, with minimal side effects	Must be applied regularly (often daily) Can cause burning/stinging on application	Most studies assessed sleep on a visual analog scale Actigraphy used in one RCT on pimecrolimus, found no differences in sleep outcomes with

			treatment ¹²⁸
Topical Phosphodiesterase-4 Inhibitors (e.g. crisaborole)	Easy to use, with minimal side effects	Must be applied regularly (often daily) Typically not sufficient for severe cases Can cause burning/stinging on application	Improved sleep of children and caregivers in Phase 3 trials ¹²⁹ Data largely based on single item assessing sleep in quality-of-life questionnaires
Topical Janus kinase (JAK) Inhibitors (e.g. ruxolitinib)	Easy to use, with minimal side effects	No trials in children	Phase 3 trials showed improvements in patient-reported perceptions of sleep quality, sleep depth and restoration associated with sleep (PROMIS Short Form-Sleep Disturbance (8b) questionnaire) Phase 2 trials showed improved pruritus and quality of life, but sleep was not specifically discussed ¹³⁰
Systemic Immunosuppressants used off-label for AD (e.g. cyclosporine, ¹³¹ methotrexate, ¹³² azathioprine) ¹³⁴	Lead to significant improvements in AD	Side effects and toxicities limit them to short-term use	Randomized controlled trials ^{131, 132, 134} and open-label study ¹³³ showing positive effect Limited evidence on children Results on sleep are based on visual analog scales
Anti-Type 2 Immunity Approaches (e.g. Dupilumab, IL-13 targeting therapies)	Leads to significant improvements in AD Well-tolerated with minimal side effects	Requires injection Few trials in pediatric patients for most therapies	Several RPCTs with large sample sizes showing positive effect

¹³⁵⁻¹⁴²	Typically dosed once every few weeks		Sleep outcomes based on visual analog scales of sleep loss
Sleep aids			
Melatonin ¹⁴³	Minimal side effects, and little potential for addiction or withdrawal ¹⁴⁴ May improve disease severity ¹⁴³	Not recommended for bronchial asthma patients, due to potential for exacerbating inflammation ⁸⁸ May worsen autoimmune diseases ¹⁴⁵	One RDBPCT (n = 73) with crossover on children with AD Sleep outcomes measured using actigraphy and PSG Only improved sleep onset latency
First-Generation Antihistamines	Can reduce inflammatory effects of mast cells ¹⁴⁶	May develop tolerance ¹⁴⁷ Anticholinergic side effects ¹⁴⁸ Excessive sedation may impede daytime performance	No RCT's or high-level evidence on sleep quality in AD ¹⁴⁹ RCT on nocturnal itch/scratch showed similar efficacy to placebo ¹⁵⁰
Benzodiazepines ¹⁵¹	Can also be effective for concurrent parasomnias ¹⁴⁵	Side effect profile: behavioral problems, daytime sleepiness, muscle relaxation (especially problematic in asthma) ¹⁵² Potential for addiction, tolerance, and withdrawal Rebound insomnia on discontinuation ¹⁴⁵	RDBPCT with small sample size (n = 10 adults) Reduced frequency but increased duration of scratching No RCT on children
Alpha-Receptor Agonists	Can also be effective for treating comorbid ADHD ¹⁴⁵	Adrenergic side effects ¹⁴⁵ Potential for overdose given narrow therapeutic index ¹⁴⁵	Case report in pediatric AD patient showing positive effect on reported sleep quality ¹⁵³
Cognitive Behavioral Therapy (CBT) ¹⁵⁴	Does not require medications	Limited evidence in AD	Small uncontrolled study (n = 10) showing no effect ¹⁵⁴

	Minimal side effects Addresses behavioral and psychological aspects of sleep disturbances		
Biofeedback (e.g. progressive muscle relaxation) ¹⁵⁵	Does not require medications Minimal side effects Addresses behavioral and psychological aspects of sleep disturbances	Limited evidence in AD	RCT with small sample size (n = 25) showing positive effect Sleep outcomes assessed using visual analog scale evaluating sleep loss
Sleep Hygiene (e.g. blue light therapy, altering bedtime routines) ^{156, 157}	Does not require medications Minimal side effects Addresses behavioral aspects of sleep disturbances	Limited evidence in AD	No RCT's on sleep quality in AD Sleep outcomes based on visual analog scales or global assessment of "sleepiness" ¹⁵⁷
Acupuncture	May address psychological aspects of sleep disturbances May relieve pruritus ¹⁵⁸	Limited evidence	Sham RCT (n = 30) showed positive effects on visual analog scale of insomnia ¹⁵⁹ A second RCT underway using EEG to evaluate sleep ¹⁶⁰