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

Fatima Bawany, BA[a], **Carrie A. Northcott, PhD**[b], **Lisa A. Beck, MD**[c], **Wilfred R. Pigeon, PhD**[d]

[a]School of Medicine and Dentistry, University of Rochester Medical Center, Rochester, NY

[b]Early Clinical Development, Digital Medicine and Translational Imaging, Pfizer, Inc, Cambridge, Mass

[c]Department of Dermatology, Medicine and Pathology, University of Rochester Medical Center, Rochester, NY

[d]Department of Psychiatry, University of Rochester Medical Center, Rochester, NY

Abstract

Atopic dermatitis is one of the most common chronic inflammatory skin conditions and is associated with sleep disturbances in 47% to 80% of children and 33% to 90% of adults. Herein, we review the literature on sleep disturbances experienced by patients with atopic dermatitis, 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 atopic dermatitis research studies and in clinical practice. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

Keywords

Atopic dermatitis; Sleep; Type 2 immunity; Insomnia; Pruritus

INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin conditions and is commonly associated with sleep disturbances.[1] Although approximately 10% to 41% of children[2-4] and 7% to 48% of adults[5-7] in the general population experience sleep

Corresponding author: Wilfred R. Pigeon, PhD, University of Rochester Medical Center, 300 Crittenden Blvd, Box PSYCH, Rochester, NY 14642. Wilfred_Pigeon@urmc.rochester.edu.

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disturbances, in patients with AD, this figure climbs to 47% to 80% in children[8-17] and 33% to 90% in adults.[8,17-19] In 2019, the Federal Drug Administration's (FDA's) Patient-Focused Drug Development Initiative found that sleep was 1 of the 3 most problematic symptoms for patients with AD 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 (eg, insomnia and obstructive sleep apnea). Methods to assess sleep disturbance vary widely. Single dichotomous (eg, "Do you have trouble sleeping?") or Likert-type questions (eg, "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. In addition, some attributes of sleep can be measured objectively in the laboratory or home environment. It is unclear what method(s) is most appropriate to assess sleep disturbances in patients with AD. 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 AD

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] Children with AD 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 most, including a large longitudinal study,[33] found no significant differences in sleep duration compared with healthy controls.[25,28,29,31,34] Similarly, some studies found that younger children,[9,15] females,[35] and those of lower socioeconomic status[9] were more likely to have reduced sleep quality, whereas 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 $P < .0001$).[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 $P < .001$).[13]

Sleep disturbances can significantly impact the quality of life of children with AD, 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] In addition, 60% to 65% of parents and 63% of siblings of children with AD reported disturbed sleep.[12,14,38,45] In fact, 30% of parents coslept 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 children with AD consistently being more likely to experience difficulty falling asleep (adjusted odds ratio, 1.36; 95% CI, 1.01-1.83) and subjectively insufficient sleep (adjusted odds ratio, 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, 2 actigraphy studies demonstrated lower SE,[55] twice as many nocturnal awakenings,[55] and twice as many movements[56] 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 that in healthy controls.[55,60] Sleep disturbance was associated with more missed workdays, visits to the doctor, and poorer overall health ($P < .0001$).[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 intraindividual and interindividual 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. In addition, 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 to draw clearer conclusions.

PUTATIVE MECHANISMS OF SLEEP DISTURBANCES IN AD

We propose 3 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 (eg, 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; $P <$ .001).[31] This suggests that sleep disturbances may in part be mediated by learned behavioral patterns that persist even when the 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.[15,17,20,26,59,62] It results in scratching, which can disturb sleep. In several studies, healthy controls displayed minimal scratching during sleep, whereas patients with AD spent up to 14.3% of their sleep time scratching.[60,64,67] Scratching was associated with nocturnal awakenings, sleep fragmentation ($r = 0.5$; $P < .001$), and reduced SE ($r = -0.54$; $P < .001$).[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.[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 children with AD (n = 28) found that brain-derived neurotropic factor ($r = 0.905$; $P < .001$) and substance P ($r = 0.925$; $P < .001$) levels were associated with increased nocturnal wrist activities.[81] However, only brain-derived neurotropic factor 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-1β, IL-2, IL-6, TNF-α, and IFN-γ increase at night and promote sleep, whereas 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 patients with AD.[32,59] However, a larger study found that a lower ratio of IFN-γ/IL-4 was associated with reduced SE, whereas levels of IL-1β, 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 1 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 patients with AD with higher nocturnal melatonin had greater SE ($r = 0.4$; $P = .004$) and less fragmentation ($r = -0.34$; $P = .004$).[13]

Unfortunately, the evidence for any of these pathways in AD is not strong. Although 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 patients with AD. 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

The “criterion” standard for objective measurement of sleep is PSG, an overnight test performed in a sleep laboratory that involves placement of more than 12 electrodes on the face/scalp, thorax, abdomen, and legs. PSG captures brain activity (electroencephalography), eye movements (electrooculography), muscle activity/activation (electromyography), and respiratory end points. The readouts are respiration metrics, limb movements, sleep stages (nonrapid eye movement stages N1, N2, and N3, and rapid eye movement), arousals from sleep, SOL, WASO, total sleep time, 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 that can be used in the home were developed. There are 4 portable monitor classes, with type I being an ambulatory PSG and types II to IV having fewer end points than PSG.

Digital wearables

Actigraphy involves typically wrist-worn devices that use an internal accelerometer to measure gross movement. The accompanying software uses the data to estimate activity and sleep/wake periods. Actigraphy is noninvasive, less expensive than PSG and portable monitors, and can be used at home. It has been shown to correlate with PSG-measured end points such as SOL, WASO, total sleep time, SE, and arousals, but it has limited ability to assess sleep stages.

Another wearable is an electroencephalography headband, with sophisticated versions having 5 electrodes, an accelerometer, pulse oximeter, and an audio component. The resulting data have 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 (ie, 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 use ballistocardiography to measure body motion generated by the

ejection of blood during the cardiac cycle. They also track thoracic movements associated with respiration. Although 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 bed partners (human and animal).

PROs and sleep diaries

PROs and sleep diaries are commonly used to assess the impact of sleep disturbances on patients' well-being. The daily sleep diary is a standard PRO with 6 to 10 items to be completed daily for 1 to 2 weeks, which provide weekly average values for SOL, WASO, total sleep time, 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 I.

The instruments and PROs/diaries briefly reviewed above and in Table I 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 in which sleep is often a secondary outcome measure, the inclusion of 1 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 as those in late-phase clinical development. The evidence on topical therapies is briefly outlined in Table II. Most studies have been conducted on adults.

Systemic immunosuppressants such as cyclosporine, methotrexate, and azathioprine are not less commonly used to treat moderate to severe AD. However, few studies have explored their effects on sleep. Uncontrolled trials of cyclosporine (1 adult, 1 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 trials of azathioprine (n = 37)[134] and methotrexate (n = 12)[133] in adults demonstrated reductions in sleep disturbance VAS scores of 30% to 50% by week 12 for azathioprine (not statistically significant) and week 24 for methotrexate ($P < .05$).

More targeted therapies have limited data with regard to sleep end points. Dupilumab, a fully humanized mAb targeting IL-4Rα, has been shown to significantly reduce pruritus within days of treatment initiation.[161] Dupilumab (300 mg biweekly) 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 (JAK) inhibitors and antibodies against IL-31Rα. Trials of JAKi have demonstrated improvements in disease severity, inflammatory biomarkers, pruritus,

and in some cases, sleep. In a phase 2 trial of baricitinib (2 mg/d; JAK1 & 2 selective), SCORAD sleep loss scores were significantly reduced ($P < .01$) after 16 weeks; phase 3 trials showed significant reductions in the Atopic Dermatitis Sleep Scale score (item no. 2) as early as 1 week into treatment ($P < .05$; 1, 2 and 4 mg/d).[162,163] Phase 3 trials of abrocitinib (100 and 200 mg/d; JAK1 selective) showed significant reductions in pruritus numerical rating scale score compared with placebo by 2 weeks ($P < .01$), but sleep was not evaluated.[164] IL-31 is a pruritogen that binds to IL-31Rα, expressed on sensory neurons and a wide range of other cell types.[165] Phase 2 trials with nemolizumab (10, 30, and 90 mg subcutaneous every 4 weeks; anti—IL-31Rα) 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 (60 mg subcutaneous every 4 weeks) observed a greater percentage of patients achieving an Insomnia Severity Index score of 7 or less after treatment.[168]

Antibodies to IL-13 (eg, tralokinumab and lebrikizumab), thymic stromal lymphopoietin (eg, 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 with placebo by week 1 ($P < .01$), while lebrikizumab and tralokinumab both resulted in improved sleep scores at week 12 ($P = .023$) and week 16 ($P < .01$), 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 is a PRO that can reliably screen for and quantify insomnia (see Table I).[104,105] Clinical practice guidelines for the management of insomnia strongly recommend that the first-line management of adult insomnia be cognitive-behavioral therapy for insomnia (CBT-I).[172-174]

CBT-I is a multicomponent intervention with established efficacy and durability in adolescents and adults.[175-178] This approach is effective in reducing not only insomnia but also mood and anxiety symptoms.[179] Typically, it is delivered in 6 to 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 3 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 used, which can also be accomplished via digital platforms.[184]

No other nonpharmacologic treatment options for insomnia (eg, 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 formulations and supplements. Over-the-counter 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 disturbances[186] 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 over-the-counter 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 clinical practice guideline 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 2 benzodiazepines (triazolam and temazepam), 3 non-benzodiazepine receptor agonists (zolpidem, zaleplon, and eszopiclone), the orexin antagonist suvorexant, the melatonin agonist ramelteon, and low-dose (3-6mg) doxepin, the tricyclic antidepressant with antihistaminergic properties. Notably, 6 agents had enough evidence to recommend *against* their use: the herbal supplement valerian, the amino-acid supplement tryptophan, exogenous melatonin, the antihistamine diphenhydramine, the gamma aminobutyric acid-reuptake inhibitor tiagabine, and the serotonin antagonist reuptake inhibitor trazodone. None of these 6 agents has an FDA indication for insomnia; yet, trazodone is one of the most widely prescribed agents for insomnia despite ongoing safety concerns (eg, morning sedation, falls, and 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 children with AD with sleep disturbance found modest improvements on SOL, but no other sleep outcomes.[143] One randomized controlled trial evaluating the antihistamine chlorpheniramine found no difference from placebo in relieving nocturnal AD symptoms.[150] A small trial (N = 10) of the benzodiazepine nitrazepam found that it reduced the frequency, but increased the duration, of scratching.[151] A randomized controlled trial (n = 24) of progressive muscle relaxation found no difference on a single-item 0 to 10 scale for “loss of sleep” compared with controls,[155] and 1 sham-controlled randomized controlled trial of acupuncture (n = 30) showed positive effects on a VAS 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 populations with AD.

CONCLUSIONS

Despite the fact that eczema has the highest disability-adjusted life-years of any skin condition worldwide, and more than 50% of children with AD report sleep disturbance as 1

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 populations with AD, 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 populations with AD, defining the role that sleep disturbances play in other AD-associated comorbidities (anxiety, depression, attention-deficit disorders, social anxiety, etc), and effectively managing it.

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Abbreviations used

AD	Atopic dermatitis
CBT-I	Cognitive-behavioral therapy for insomnia
FDA	Federal Drug Administration
JAK	Janus kinase
PSG	polysomnography
PRO	Patient-reported outcome
SCORAD	CORing Atopic Dermatitis
SE	Sleep efficiency
SOL	Sleep-onset latency
VAS	Visual analog scale
WASO	Wake time after sleep onset

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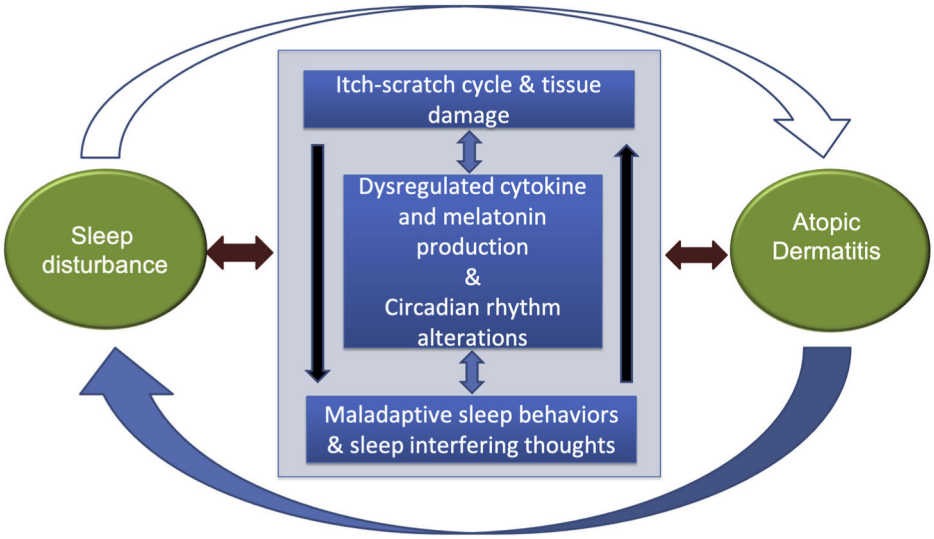

FIGURE 1.

The large semicircular arrows reflect the macro-level bidirectional between sleep and 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 reflect evidence suggesting that each of these mechanisms may themselves have bidirectional relationships with each other.

TABLE I.

Tools commonly used to measure sleep disturbances

Method	Variables measured	Advantages	Limitations
Subjective measures			
Pittsburgh Sleep Quality Index[94]	A total of 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 various disease states and countries Translated into many languages	Limited to adults May primarily reflect sleep on workdays[95]
Medical Outcomes Study Sleep Scale[96,97]	A total of 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 various 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 into 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]	A total of 35 items regarding bedtime behavior, nocturnal awakenings, and sleep disorders over the past week in children aged 4-10 y	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 longitudinal studies[99] Available in multiple languages	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
Brief Infant Sleep Questionnaire[100]	A total of 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]	A total of 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	A total of 7 items evaluating patient's assessment of his or her insomnia and its impact on daily functioning in the past 2 wk[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[106,107]	A total of 41 items related to sleep habits, sleep disturbances, and daytime sleep-related impairments in the past 7 d	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 retrospective estimates of sleep quality over the past week/month[109]	May not accurately reflect objective measures[109,110] Require daily completion Most are not formally validated[106]
Children's Dermatology Life Quality Index	A total of 10 items assessing skin symptoms and impacts on various aspects of quality of life in children aged 4-16 y in the past week	Dermatology-specific Easy to administer Translated into 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]	A total of 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

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Method	Variables measured	Advantages	Limitations
Infant's Dermatitis Quality of Life Index[10]	A 10-item questionnaire assessing infant daily activities and quality of life in children aged <4 y 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			
PSG: criterion 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 associated with body movements	Not done in the individual's natural habitat May cause skin irritation in patients with AD May require monitoring for multiple nights to 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 done 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 mattress sensors	Changes in pressure, body movements, or respiratory movements detected by sensors placed in mattresses	Correlates fairly well with validated objective measures[116-119] Can be used at home Does not require wearing a device	Limited evidence Lack of movement may be detected as sleep May be confounded by mattress thickness and size, patient weight, and bed partners
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 WASO in some studies[120]

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TABLE II.

Treatment strategies to manage sleep disturbances in patients with AD

Method	Advantages	Limitations	Quality of evidence in AD
Optimizing treatment of AS			
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 RCTs with varied control groups and results Improvements in sleep assessed through VAS of sleep loss in nearly all studies
Topical calcineurin inhibitors (eg, tacrolimus and 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 VAS Actigraphy used in 1 RCT on pimecrolimus, found no differences in sleep outcomes with treatment[128]
Topical phosphodiesterase-4 inhibitors (eg, 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 JAK inhibitors (eg, 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 (eg, cyclosporine,[131,132] methotrexate,[133]	Lead to significant improvements in AD	Side effects and toxicities limit them to short-term use	RCTs[131,132,134] and open-label study[133] showing positive effect Limited evidence on children Results on sleep are based on VASs
Anti—type 2 immunity approaches (eg, dupilumab and IL—13 targeting therapies)[135-142]	Lead to significant improvements in AD Well tolerated with minimal side effects Typically dosed once every few weeks	Require injection Few trials in pediatric patients for most therapies	Several RPCTs with large sample sizes showing positive effect Sleep outcomes based on VASs 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 patients with bronchial asthma, due to potential for exacerbating inflammation[88] May worsen autoimmune diseases[145]	One RDBPCT (n = 73) with cross-over on children with AD Sleep outcomes measured using actigraphy and PSG Only improved SOL
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 RCTs 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 patient with AD showing positive effect on reported sleep quality[153]

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Method	Advantages	Limitations	Quality of evidence in AD
Cognitive-behavioral therapy[154]	Does not require medications Minimal side effects Addresses behavioral and psychological aspects of sleep disturbances	Limited evidence in AD	Small uncontrolled study (n = 10) showing no effect[154]
Biofeedback (eg, 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 VAS evaluating sleep loss
Sleep hygiene (eg, 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 RCTs on sleep quality in AD Sleep outcomes based on VASs 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 VAS of insomni[159] A second RCT underway using EEG to evaluate sleep[160]

EEG, Electroencephalography; *RCT*, randomized controlled trial; *RDBPCT*, randomized, double-blind, placebo-controlled trial; *RPCT*, randomized placebo-controlled trial.

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