

Managing sleep disturbances in children with atopic dermatitis

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Abstract

Atopic dermatitis is a chronic, pruritic inflammatory disease that often disrupts sleep in severely affected children, but there are limited studies to guide clinical management of these sleep problems. Disease control is crucial in improving sleep, but additional sleep aids may sometimes be helpful in decreasing scratching during the night. This review discusses the benefits and limitations of potential therapeutic agents available to manage sleep disturbances in children with atopic dermatitis.

KEYWORDS

atopic dermatitis, sleep disturbances, sleep management

1 | INTRODUCTION

Atopic dermatitis (AD) is a common chronic, pruritic inflammatory skin disease affecting approximately 15%-30% of all children.¹ The goal of treatment is to control disease, prevent continued outbreaks, and manage associated comorbidities, but because the course of the disease is often relapsing and protracted, management can be difficult.²

Disturbed sleep is reported in 47%-60% of children with AD.³⁻⁶ Chang et al showed that children with AD have significantly poorer sleep efficiency, longer sleep onset latency, greater sleep fragmentation, and less nonrapid eye movement sleep. A higher Scoring Atopic Dermatitis (SCORAD) index, a clinical tool for assessing severity of AD, is significantly associated with lower sleep efficiency and more-fragmented sleep. Worse sleep increases the likelihood that these children will scratch, which can increase the severity of skin disease.³

Sleep disturbances associated with AD negatively affect daytime functioning and could have negative effects on neurocognitive function and behavior. Sleep problems in AD may be associated with higher rates of attention deficit hyperactivity disorder (ADHD), emotional and conduct problems, and short stature.^{7,8} Lack of sleep also decreases the quality of life of patients and their families,⁴⁻⁶ which makes early identification of sleep problems important. The Brief Infant Sleep Questionnaire was developed as a screening tool to determine infant sleep patterns and has been used in infants with AD.⁹

The pathophysiology of sleep disturbances in children with AD is not completely understood. The most straightforward explanation for sleep difficulties is itching and scratching at night. The circadian

rhythm of cytokines, the immune system, skin physiology such as transcutaneous water loss and skin blood flow, low nocturnal melatonin, and environmental factors may also play a role.¹⁰

There is no consensus to guide management of sleep disturbances in individuals with AD. Disease control with skin hydration, control of inflammation, and treatment of superinfections is crucial in improving sleep in these patients, but these measures alone are not always sufficient to prevent sleep disturbances in individuals with AD. Adjunctive sleep aids may be helpful in better regulating the sleep cycle and might improve the severity of the disease by breaking the nighttime itch-scratch cycle.

This review highlights the benefits and risks of available therapeutic agents to manage sleep disturbances in children with AD. We have not included dosing in this review. We recommend further studies to determine optimal dosing, duration of treatment, efficacy in regulating sleep, and safety of these agents in AD.

2 | SLEEP AIDS

2.1 | First-generation antihistamines

First-generation antihistamines are most commonly used for sleep problems in AD.¹¹ Their sedative effects result from their ability to cross the blood-brain barrier and antagonize histamine's role in maintaining central nervous system (CNS) arousal.^{12,13} They also antagonize the inflammatory effects of histamine released from mast cells and basophils, which may have some benefit in pruritus.

Diphenhydramine and hydroxyzine are the most commonly used antihistamines for sedation.¹⁴

Tolerance is common with first-generation antihistamines. Tolerance can occur after 4-7 days if the medication is taken regularly. The sedating effect usually disappears with habitual, chronic use.^{15,16} In our experience, avoiding daily use and taking breaks from the medication has been helpful in preventing tolerance. Further studies need to be performed to evaluate whether switching from one-first-generation antihistamine to another prevents tolerance.¹²

Adverse effects of first-generation antihistamines are primarily anticholinergic and include blurred vision, dry mouth, constipation, urinary retention, tachycardia, dystonia, and confusion.¹² It is important to caution parents about overdosing. Diphenhydramine overdose can lead to anxiety, visual hallucinations, stupor, rhabdomyolysis, cardiac arrhythmia, and seizures. Fatal diphenhydramine toxicity has been reported.¹⁷ It is important to consider appropriate dosing in children because sedation can impair school performance. Antihistamines can be used intermittently to decrease sleep loss caused by pruritus, but they cannot replace topical therapies in disease management.¹⁸

Second-generation antihistamines are generally of little use in the treatment of nocturnal pruritus because of their lack of sedative properties.¹⁹

2.2 | Antidepressants

Antidepressants with sedating properties have been used to treat insomnia in children.²⁰ Doxepin, a tricyclic antidepressant that promotes sleep by blocking histamine receptors, is sometimes prescribed for nocturnal pruritus related to dermatologic disease in children and adults. It suppresses rapid eye movement (REM) and slow-wave sleep. It also has anxiolytic and antidepressant effects, which may be helpful in AD. The dose for sleep disturbances is usually lower than the antidepressant dose. Side effects include anticholinergic effects, hypotension, daytime sedation, CNS depression, and tolerance.¹² Topical doxepin is an effective therapy for AD pruritus in adults. To our knowledge, no studies of topical doxepin in children have been performed because of the risk of absorption and toxicity.

Trazodone, a serotonin receptor antagonist that promotes sleep by blocking histamine receptors,²⁰ is commonly prescribed for insomnia in children with mood, anxiety, and neurodevelopmental disorders.^{21,22} Information on its use in children is limited. There are no reports or studies of its use in pediatric AD.

2.3 | Alpha agonists

Alpha-2 agonists are commonly prescribed for insomnia in individuals with ADHD.²¹ Clonidine is the most commonly used alpha-2 agonist for insomnia in individuals with ADHD. It acts as an agonist on alpha-2-adrenoreceptors on the brainstem to decrease sleep latency.¹² There has been only one case report of the use of clonidine for AD-induced nocturnal pruritus.²³

Because clonidine is an antihypertensive medication, blood pressure should be monitored. Rapid discontinuation after regular use may lead to hypertension.¹² Clonidine causes REM suppression, so discontinuation can lead to REM rebound.²⁴ It may also cause anticholinergic side effects. Because of its narrow therapeutic index, parents should be cautioned about overdose, which can lead to cardiotoxicity and death.²¹

2.4 | Melatonin

Melatonin is a physiologic hormone that the pineal gland secretes in a circadian rhythm to regulate sleep.²⁵ There is a physiologic increase in melatonin secretion 1 to 2 hours before bedtime; it is thought that melatonin may be the final trigger for inducing sleep.²⁰

Oral melatonin supplementation has been used to manage insomnia and jet lag in children.²⁶ Child and adolescent psychiatrists commonly recommend it for sleep disturbances.²¹ It improves sleep by shortening sleep-onset latency, but it has not been shown to increase total sleep time or efficiency.²⁷

Melatonin also has antiinflammatory, antioxidant, and immunomodulatory effects.²⁸⁻³⁰ Chang et al found that children with AD have lower nocturnal melatonin secretion, which may contribute to sleep disturbance and greater severity of AD.³ A recent study showed that use of oral melatonin supplementation in children with AD decreased sleep-onset latency and AD severity.²⁷

Melatonin has minimal side effects, which makes it a good option to use in children with AD-related sleep disturbances. It does not have addictive properties, and no withdrawal occurs from discontinuation. The most commonly reported side effects included drowsiness, nausea, and headaches.³¹

The National Sleep Foundation has warned against the use of melatonin in patients with immunity disorders because of possible proinflammatory properties. The safety of melatonin use in individuals with asthma is conflicting, and the current recommendation is to avoid routine use in individuals with bronchial asthma.³⁰

Melatonin is often sold as an herbal supplement. Parents should be informed that the Food and Drug Administration does not regulate it. Further studies are needed to determine optimal dosing and duration of treatment.¹²

2.5 | Benzodiazepines

Pediatricians sometimes use benzodiazepines, which act on gamma-aminobutyric acid-A (GABA) receptors to reduce sleep latency and increase total sleep time, for insomnia.³² Clinicians may choose benzodiazepines for patients with AD for their anxiolytic properties, in addition to their sedating effects.¹²

Ebata et al³³ investigated the effect of nitrazepam on nocturnal scratching in 10 adults with AD and concluded that 10 mg of nitrazepam was not effective in reducing total duration of nocturnal scratching in individuals with AD, although it decreased the frequency with which bouts of nocturnal scratching occur. To our knowledge, no reports or studies have been performed evaluating

the use of benzodiazepines for sleep disturbances in children with AD.

Side effects of benzodiazepines include alteration in sleep architecture, behavioral problems, agitation, impulsivity, memory impairments, and muscle relaxation.³⁴ They should be used cautiously in patients with asthma because the muscle relaxation side effect may increase risk of respiratory compromise during sleep. Tolerance to the sedative effect is common, and there may be rebound worsening of sleep problems upon discontinuation. There is a risk of addiction with benzodiazepine use. Using longer-acting benzodiazepines may minimize the risk of addiction.¹²

2.6 | Nonbenzodiazepine benzodiazepine receptor agonists

This category of medications differs from traditional benzodiazepines because of preferential binding to GABA-A receptors containing alpha-1 subunits.³⁵ These medications are thought to be superior to traditional benzodiazepines because they preserve sleep architecture and do not result in rebound insomnia upon discontinuation.³⁶ They are used to reduce sleep latency and decrease awakenings. Examples of medications in this category are eszopiclone, zolpidem, zaleplon, and flumazenil.

There are limited studies on the use of nonbenzodiazepine benzodiazepine receptor agonists in children, in whom their use is off-label. There are no studies or reports evaluating the use of these medications for sleep disturbances in adults or children with AD.

Side effects include sleepwalking, drowsiness, ataxia, dizziness, confusion, slurred speech, and CNS depression.³⁷ No fatalities have been reported with overdose.

2.7 | Chloral hydrate

Chloral hydrate acts on GABA receptors to cause sedation, but its use has become limited because of the risk of hepatotoxicity and respiratory depression. Chloral hydrate should be used for sleep disturbances in children with great care and is generally not recommended. If starting this medication, the recommendation is to admit the patient for one night and administer the medication under hospital observation before using it in an outpatient setting.¹²

2.8 | Disease-controlling therapies

Managing the severity of AD may secondarily improve sleep. Topical moisturizers (emollients, occlusive agents, humectants) can help treat xerosis and decrease symptoms of AD. They should be applied after bathing. Wet wraps can also reduce AD severity by occluding the topical treatments to help enhance penetration and reduce transepidermal water loss. Topical corticosteroids and calcineurin inhibitors are antiinflammatory therapies that have also been shown to improve AD.³⁸ Phototherapy can be considered as a second-line option for patients who have failed topical therapies and can be used as a maintenance therapy in patients with chronic disease.

Systemic immunomodulators can be used in patients who require additional treatments to control their disease, including methotrexate, cyclosporine, azathioprine, and mycophenolate mofetil.¹⁸ Of these systemic agents, methotrexate has not been well studied in children with AD. A relatively new human monoclonal antibody, dupilumab, was found to improve disease severity in adults with moderate to severe AD,³⁹ and studies are being performed to evaluate its use in children.

Several studies of various disease-controlling agents have reported sleep as a secondary outcome. All of them used a visual analogue scale (VAS) to assess subjective sleep disturbance and sleep loss that ranged from 0 (none) to 10 (worst ever). SCORing AD (SCORAD) includes a separate subjective sleep-reported item that uses a VAS from 0 (no sleep loss) to 10 (worst sleep loss). The Patient-Oriented Eczema Measure (POEM) also measures how the symptoms of AD affect sleep.⁴⁰ Harper et al studied short-term and 1-year continuous cyclosporine treatment in 40 children (3-16 years old) with severe AD and found that both treatment groups had improved sleep. Patients experienced significant improvements in sleep from baseline to 8 weeks, 12 weeks, and 1 year of follow-up. There was no significant difference in sleep between the two treatment arms.⁴¹ In a study evaluating the safety and efficacy of methotrexate, the dose of methotrexate was escalated 2.5 mg each week (starting dose 10 mg) until patients responded to treatment or the dosage could not be increased because of toxicity. In 12 adults (mean age 37) with moderate to severe AD, there was significant improvement in sleep.⁴² Berth-Jones et al performed a randomized, placebo-controlled crossover trial studying the effects of azathioprine in 37 adults (aged 17-73) with AD. Intention-to-treat analysis showed that treatment with azathioprine (2.5 mg/kg per day) significantly decreased sleep disturbance from baseline to the end of treatment (12 weeks).⁴³

More recently, a phase IIb randomized, placebo-controlled trial of dupilumab in 380 adults with AD found that those treated at various doses (200 mg every 2 weeks, 300 mg every 2 weeks, 300 mg every week) had significantly better sleep according to the SCORAD and POEM sleep measures than those receiving placebo. This improvement began 1 week after beginning treatment on the SCORAD and 2 weeks after beginning treatment on the POEM and was maintained during follow-up. Patients treated with dupilumab 100 mg every 4 weeks did not have significantly greater improvements in sleep on the SCORAD and POEM than those receiving placebo.⁴⁴ Further research is needed to determine whether methotrexate, azathioprine, and dupilumab are effective in improving sleep for children with AD.

Wet wraps and light therapy have been shown to be effective in improving sleep outcomes as well. In a small study of six patients, including three children, wet wraps, using emollients and dressings soaked in chlorhexidine, were applied for 3 days. Patients experienced improvements in disease severity and sleep on the SCORAD.⁴⁵ Blue light therapy using a full-body irradiation device was studied in 36 adults with severe AD. Patients were treated with five consecutive irradiation treatments (28.9 J/cm²). Each side of the

body was treated for 24 minutes during each treatment session. The sessions decreased disease severity and significantly decreased subjective sleeplessness when assessed 3 and 6 months after treatment initiation.⁴⁶ To our knowledge, blue light therapy has not been studied in children with AD.

2.9 | Behavioral therapies

Behavioral modification strategies may aid in decreasing sleep disturbance. Several strategies have been found to be effective in changing poor sleep habits: extinction (unmodified and graduated), scheduled awakenings, bedtime fading with response cost, positive routines, and patient education. Unmodified extinction or (the "cry it out" method) involves parents putting their child to bed at his or her scheduled bedtime and then disregarding crying, tantrums, or requests until the child's scheduled wake-up time. Graduated extinction is similar but involves ignoring crying for set time frames and gradually increasing these time limits. To perform scheduled awakenings, parents note the times that their child spontaneously awakens in the middle of the night and awaken the child 15-30 minutes before his or her usual spontaneous awakening. Upon awakening the child, parents will respond as they would to a spontaneous awakening (e.g., rocking their child to sleep). Parents gradually increase the time between these scheduled awakenings. Bedtime fading involves setting a consistent sleep schedule (bed time and wake time). Once the child is able to fall asleep quickly, the bedtime is advanced earlier by 15-30 minutes each night until the original predetermined bedtime is met. Response cost involves making the child get out of bed when he or she is having trouble falling asleep and delaying bedtime to improve sleep latency. Parents can also create a positive bedtime routine that allows the child to play quietly before going to bed.⁴⁷ Referral to a psychologist or sleep medicine physician may be necessary for instruction and guidance in learning these techniques.

In general, individuals with AD can practice good sleep hygiene by following a predictable sleep schedule (same bedtime each night and using bedtime fading as described above if necessary), performing a relaxing bedtime routine, minimizing screen time with telephones and television before bed, and avoiding caffeine use before bed.^{48,49} The bedtime routine should be consistent each night, last approximately 30 minutes, and consist of two to three activities. A chart can be used to ensure consistency.⁴⁸ Although telephone use should be minimized before bed, there are downloadable applications for smart phones (e.g. Relax Melodies, Sleep Pillow Sounds, Sleep Well Hypnosis, and Sleepo) that can provide calming sounds to aid in sleep onset.

Gloves or socks can be worn to prevent scratching in the middle of the night. Cold, wet cloths may also help in managing disruptions during the night and can be kept in the bedroom along with moisturizer.

Other useful techniques, including progressive muscle relaxation (PMR) therapy, have been tried. PMR has mental and physical aspects. Patients are taught to tense a target muscle group for 10 seconds and

then relax the muscle group for 20 seconds. In a small study of 25 individuals with AD aged 12-40, patients were randomized to receive PMR and conventional treatment or conventional treatment only. The PMR treatment group was instructed to perform PMR therapy (specifically modified for patients with AD) twice a day for 1 month. PMR therapy significantly reduced patients' subjective pruritus and loss of sleep (measured using a horizontal VAS from 0 to 10).⁵⁰

Although psychological and educational interventions may improve quality of life, more research is needed to demonstrate conclusive evidence for these therapies.⁵¹

3 | CONCLUSION

Although the negative effects of sleep disturbances in AD have been well established, there are limited studies illustrating which medications are safe and effective in improving sleep in individuals with AD. This review highlights the benefits and risks of sedative medications that can be used in individuals with AD.

At our institution, we first try to optimize disease-controlling therapies to improve sleep in AD. We teach patients and parents about behavioral techniques to improve sleep and emphasize the effect that behavioral modification can have on sleep. If these methods alone are not sufficient, we frequently prescribe first-generation antihistamines to be used in age-appropriate dosing, with intermittent usage if possible. If a patient develops tolerance to a first-generation antihistamine, we favor switching to a different one. We often alternate between first-generation antihistamines to prevent tolerance. If patients do not respond to first-generation antihistamines, we recommend the use of melatonin before bedtime. We advise parents that the Food and Drug Administration has not approved melatonin and that its use is considered off-label. We prescribe antidepressants such as doxepin in refractory cases. Duration of treatment depends on the individual.

We do not have any experience using alpha agonists, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonists, or chloral hydrate for sleep disturbances in individuals with AD.

We recommend further studies to evaluate which medication works best to decrease sleep-onset latency, increase sleep efficiency, decrease awakenings, and increase total sleep time while avoiding the risks of tolerance, addiction, rebound effects, and daytime sedation.¹²

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