

Itching at night: A review on reducing nocturnal pruritus in children

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Abstract

The most common causes of chronic nocturnal itching in children are atopic dermatitis and psoriasis, with lichen simplex chronicus and prurigo nodularis contributing to lesser degrees. Despite the prevalence of nocturnal itching, its pathophysiology remains poorly understood. The most troubling consequence of itching at night is poor quality of sleep. Poor sleep quality in children with nocturnal itching has been linked to adverse neurocognitive, behavioral, and physiologic outcomes, including poor performance in school, attention deficit hyperactivity disorder, short stature, hypertension, obesity, and impaired immune function. There is no consensus on the best management of nocturnal itching in children. We conducted a review of the literature evaluating the efficacy of various treatment options for children with chronic nocturnal pruritus. Our review found three recently conducted randomized controlled trials and one case report demonstrating the efficacy of topical corticosteroids, oral melatonin, and clonidine in reducing nocturnal itching or improving sleep quality in children with nocturnal pruritus. Future research is needed to elucidate the pathophysiology of nocturnal itching to best develop targeted, effective treatment strategies.

KEYWORDS

children, itch, management, night, nocturnal, pediatric, pruritus, therapy, treatment

1 | INTRODUCTION

Nocturnal pruritus is defined as an uncomfortable sensation occurring during sleep that scratching relieves.¹ Scratching can occur during any stage of sleep but most commonly occurs during stages I and II of nonrapid eye movement sleep.^{2,3} In children, dermatologic rather than systemic conditions typically caused nocturnal itching. The two most common causes of chronic nocturnal pruritus in children are atopic dermatitis (AD) and psoriasis, with prurigo nodularis and lichen simplex chronicus contributing to lesser degrees.^{4,5}

In addition to affecting quality of life, nocturnal pruritus and subsequent scratching is of serious concern to physicians because it can interfere with quality and duration of sleep.⁶ Sleep disturbance has been shown to occur in 60%-83% of children with AD, 69% with

psoriasis, 52.8% with prurigo nodularis, and many with lichen simplex chronicus.^{4,7,8} Studies have shown that children with nocturnal itching secondary to AD have significantly longer sleep onset latency, greater sleep fragmentation, poorer sleep efficacy, and greater difficulty waking up for school in the morning.^{9,10} Similarly, patients with nocturnal itching secondary to psoriasis are more likely to have difficulty falling asleep, frequent nighttime awakenings, and shorter overall sleep duration than their healthy peers.^{5,7}

Sleep disturbance caused by nocturnal itching harms neurocognitive function and has been associated with behavioral problems such as attention deficit hyperactivity disorder and poor performance in school.^{6,11} Studies have also linked impaired sleep secondary to nocturnal itching to short stature, obesity, hypertension, and altered immune function.^{4,12} Thus, it is critically important to recognize,

understand, and treat these symptoms in children. There is no consensus on how to best manage nocturnal pruritus in children. Here in, we review the pathophysiology of nocturnal itching and summarize available treatment options for decreasing nocturnal itching and improving sleep quality in children with chronic nocturnal pruritus.

2 | PATHOPHYSIOLOGY

Despite the prevalence of nocturnal pruritus in children, its pathophysiology is poorly understood. Disturbances to children's central and peripheral circadian rhythms are believed to cause (in part) nighttime exacerbations of itching. A study by Schwarz and colleagues found that the natural rhythmic secretion of melatonin is low or absent in most patients with nocturnal itching secondary to AD, suggesting circadian misalignment.¹³ There is undoubtedly a psychological component to nocturnal pruritus as well. Patients with chronic itching tend to have higher levels of stress and depression, which are both associated with difficulty sleeping.^{14,15} It is likely that poor sleep hygiene also plays a role. A summary of all components proposed in previous studies to be implicated in the pathophysiology of nocturnal itching is shown in Figure 1.^{4,6}

3 | MANAGEMENT

In general, treatment of nocturnal itching in children should be directed at the underlying cause. Conservative, nonpharmacologic measures can be used in conjunction with topical and systemic treatments. Studies evaluating the effectiveness of various therapies in reducing nocturnal itch and improving sleep quality in children are sparse, but many of the same treatments used to treat chronic pruritus in children are also likely to improve nocturnal itching.

4 | NONPHARMACOLOGIC APPROACHES

4.1 | Nocturnal moisturization

Topical emollients are first-line treatment for chronic pruritus, regardless of the underlying cause.¹⁶ Emollients improve barrier function, which helps prevent transepidermal water loss in children experiencing nocturnal itching.¹⁷ There are no trials evaluating the effectiveness of topical emollients in relieving nocturnal pruritus or improving quality of sleep in children, but their efficacy in treating chronic pruritus and favorable safety profile make nocturnal moisturization a safe and recommended option for children experiencing nocturnal pruritus.

4.2 | Wet wrap therapy

Wet wrap therapy (WWT) consists of applying a topical emollient under wet gauze or wet cotton pajamas at bedtime. WWT helps maintain skin hydration and suppresses inflammation. As

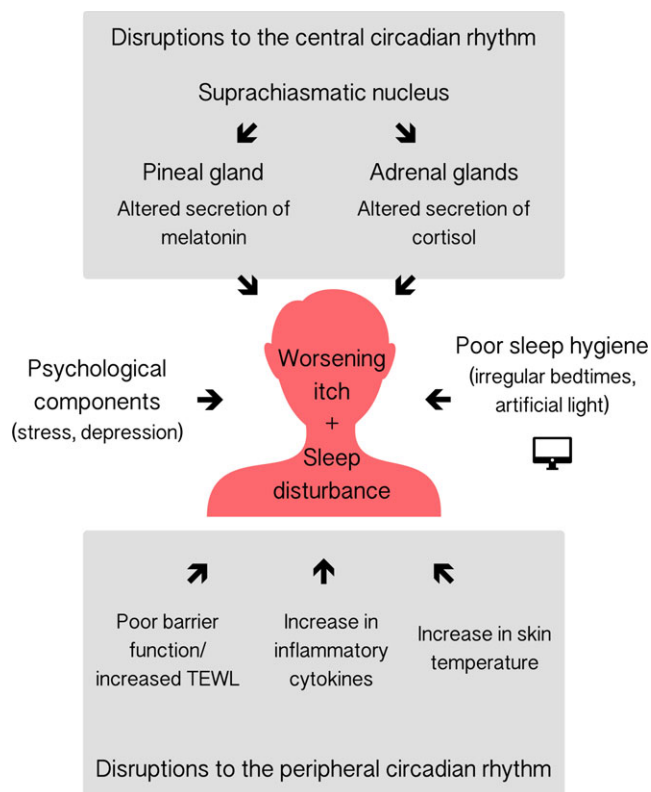


FIGURE 1 Pathophysiology of nocturnal itching in children. Under normal conditions, the suprachiasmatic nucleus regulates circadian rhythm by stimulating the pineal gland to secrete melatonin and the adrenal glands to secrete cortisol in a diurnal fashion. Melatonin then exerts a sedative, antiinflammatory, and immunomodulatory effect, which normally improves skin inflammation in addition to helping patients fall asleep. The suprachiasmatic nucleus also regulates the secretion of cortisol by the adrenal glands. Cortisol levels reach a nadir at night; it is likely that these nighttime decreases in the antiinflammatory properties of cortisol enhance systemic inflammation and contribute to nocturnal exacerbations of itching. The suprachiasmatic nucleus controls peripheral circadian rhythms, as well. Skin cells express circadian clock genes such as circadian locomotor output cycles kaput (CLOCK), which regulate physiologic parameters in the skin. These parameters include transepidermal water loss (TEWL), skin temperature, skin permeability, and surface pH. Poor skin barrier function at night, leading to greater TEWL, is believed to increase pruritic symptoms. CLOCK genes in the skin are also responsible for the diurnal secretion of inflammatory cytokines such as interleukin (IL)-6 (disrupts sleep) and IL-31 (exacerbates pruritus), leukocytes, memory T-cells, and naïve T-cells, all of which peak at night. Higher skin temperature at night secondary to neuropeptide-mediated vasodilation is also believed to contribute to nocturnal increases in itching. Psychological factors and poor sleep hygiene have been implicated in the pathophysiology of nocturnal itching as well

inflammation dermatoses improve, pruritus tends to decrease.¹⁸ WWT has the added benefit of providing a physical barrier to prevent the child from scratching, although a meta-analysis of six randomized controlled trials (RCTs) from 2016 demonstrated that the grade of evidence for WWT relieving pruritic symptoms in children with AD is low, suggesting that further studies are

needed to establish its efficacy in reducing nocturnal itching.¹⁹ Wet wrap therapy should be limited to less than 1 week at a time because of the risk of mild skin infections such as folliculitis.¹⁷

4.3 | Sleep hygiene

Blue light from electronic screens is known to suppress melatonin secretion, which is already abnormal in children with nocturnal itching secondary to AD.⁶ Improving sleep hygiene is cost effective and poses no risk to the child. Thus, consistent bedtime routines and a dark sleeping environment devoid of telephones or computer screens is one measure parents can take to improve sleep quality in children with nocturnal itching.

4.4 | Psychological interventions

Patients with chronic pruritus are known to have higher levels of anxiety and depression than their healthy peers. Relaxation techniques such as progressive muscle relaxation and habit-reversal training have been shown to relieve itching in adults with chronic pruritus,²⁰ but no studies have evaluated the effects of psychological interventions on children experiencing chronic nocturnal itching. Despite the lack of data, these methods are cost effective and safe and can easily be implemented as adjuvant therapy to other treatments.

5 | TOPICAL THERAPIES

5.1 | Topical corticosteroids

Cortisol levels tend to drop at night, which may play a role in nighttime exacerbation of pruritic symptoms.⁶ Although topical glucocorticoids exert antiinflammatory rather than antipruritic effects, they have been shown to improve sleep quality in children with nocturnal pruritus secondary to AD and in adults with nocturnal itching secondary to psoriasis.^{21–23}

5.2 | Topical calcineurin inhibitors

Topical calcineurin inhibitors (TCIs; tacrolimus ointment, pimecrolimus cream) are antiinflammatory agents recommended for children with inflammatory dermatoses or chronic scratch lesions.¹⁶ Although no studies have evaluated the efficacy of TCIs in relieving nocturnal itching or improving sleep quality, TCIs provide targeted relief of inflammation with minimal local or systemic side effects and are approved for use in children aged 2 years and older.²⁴ The American Academy of Dermatology recently published guidelines suggesting that topical calcineurin inhibitors are safe and effective for off-label use in children younger than 2 and in infants.²⁴ The most commonly reported side effects of TCIs are stinging and burning at the application site, which typically resolve after a few days of use.

6 | SYSTEMIC THERAPIES

6.1 | Antihistamines

First-generation antihistamines (chlorpheniramine, diphenhydramine, hydroxyzine, promethazine) work by antagonizing H1 receptors and are commonly used as first-line therapy for the treatment of nocturnal pruritus in children,⁴ but there is insufficient evidence to support their use as a first-line agent.¹⁶ There have been no RCTs suggesting that first-generation antihistamines lead to any significant improvement in pruritic symptoms or quality of sleep in children with nocturnal itching,²⁵ and a multicenter, double-blind, placebo-controlled study of 155 children with AD demonstrated that chlorpheniramine was no more effective than placebo in relieving nocturnal itching.²⁶ Short-term, first-generation antihistamines may be useful for their sedative properties, but they should not replace first-line topical treatments.²⁷ Tolerance can develop to antihistamines after 4–7 days, diminishing their sedative effects and limiting their long-term usefulness.²⁸ Furthermore, studies have shown that sedating antihistamines in school-age children may harm their performance in school.²⁹ With the exception of more frequent dosing during severe, acute disease flares, their use should therefore be limited to nighttime dosing. Future research is needed to determine the role of antihistamines in treating children with nocturnal itching.

6.2 | Benzodiazepines

Benzodiazepines have sedating and anxiolytic effects and are thought to improve quality of sleep in children with nocturnal pruritus by shortening the latency of sleep onset and increasing total sleep time,⁴ but no studies have directly evaluated their effectiveness in reducing nocturnal pruritus or improving the quality of sleep in children with chronic nocturnal itching. One small study in adults with AD ($n = 10$) demonstrated that benzodiazepines did not significantly decrease nocturnal itching time, suggesting that these agents may be ineffective in relieving nocturnal itching in children as well.³⁰ Adverse effects of benzodiazepines include addiction, tolerance, and rebound worsening of sleep problems if abruptly discontinued. They also carry a risk of memory problems, which make them a less favorable option in children.³¹ Furthermore, benzodiazepines may suppress nocturnal secretion of melatonin, which could further disrupt a child's natural circadian rhythm.³² They are not recommended for treatment of chronic pruritus in children.

6.3 | Melatonin

Melatonin is a hormone that is essential for regulating sleep and the circadian rhythm. Low melatonin levels are known to be correlated with disease severity and degree of sleep disturbance in children with nocturnal itching secondary to AD.³³ To our knowledge, only one study in the literature has demonstrated the effectiveness of

exogenous melatonin in improving sleep quality in children with nocturnal itching. That RCT found that 3 mg of oral melatonin administered before bedtime over the course of 4 weeks resulted in a sleep onset latency that was 21.4 minutes shorter than in those given placebo,³³ although that study demonstrated only sedative and not antipruritic properties of melatonin, and a sample size of only 24 patients in the treatment group limited it. Furthermore, multiple studies have found melatonin to be pro-inflammatory in patients with nocturnal asthma, and thus its use in individuals with AD is controversial.^{34,35} Future research is needed to determine the optimal dose, if any, and duration of melatonin treatment for children with nocturnal pruritus.

6.4 | Antidepressants

6.4.1 | Mirtazapine

Mirtazapine is an atypical antidepressant that works by antagonizing noradrenergic, serotonergic, and histaminergic receptors. At low doses (below the threshold for antidepressant activity), mirtazapine has demonstrated efficacy in relieving nocturnal itching in adults,^{36,37} but no studies have evaluated its effectiveness in reducing nocturnal itching in children. Thus, research is needed to determine the effectiveness and optimal dosing regimens for children with nocturnal itching. Mirtazapine has a better safety profile than other antidepressants. Weight gain is the most common side effect.

6.4.2 | Doxepin

Doxepin is a tricyclic antidepressant with antihistaminergic properties. At low doses (below the threshold for antidepressant activity), doxepin exerts sedative effects by antagonizing the H1 receptor, which helps improve sleep quality.⁴ Although one small study ($n = 12$) demonstrated that tricyclic antidepressants improve sleep onset latency in adults with AD, no improvement in pruritus was observed.³⁸ Furthermore, no studies have examined the effects of doxepin on nocturnal pruritus or sleep quality in children. Thus, further research is needed to determine the efficacy and dosing regimens of doxepin for children with nocturnal itching. Adverse reactions to doxepin include anticholinergic effects, such as blurred vision and dizziness.

6.4.3 | GABAergics

GABAergics (gabapentin and pregabalin) are structural analogs of gamma-aminobutyric acid (GABA) that improve sleep quality through their sedative properties. They have been shown to reduce pruritus secondary to neural hypersensitization, which is commonly seen in patients with AD,¹⁵ but no studies have evaluated their effectiveness in relieving nocturnal itching or improving sleep quality in children with nocturnal pruritus. Side effects of gabapentinoids include fatigue, dizziness, blurred vision, and weight gain.¹⁶

6.4.4 | Clonidine

Clonidine is an alpha 2 adrenergic agonist primarily used to treat hypertension.³⁹ Similar to antihistamines, clonidine is believed to improve sleep quality through its sedative properties. There has been one case report describing significant improvement in pruritic symptoms and sleep quality in a 6-year-old boy with severe AD after treatment with oral clonidine 0.005 mg/kg and oral trimeprazine 0.17 mg/kg nightly.³⁹ Common side effects of clonidine include hypotension, bradycardia, tachycardia, and sedation.

7 | DISCUSSION

Our review found four studies evaluating various treatments for nocturnal itching in children that found significant improvement in nocturnal itching or sleep quality (Table 1). All four studies examined only children with AD. We could not find any studies evaluating treatments to improve nocturnal pruritus or sleep quality in children with psoriasis, prurigo nodularis, or lichen simplex chronicus, despite the fact that children with all of these conditions experience nocturnal itching. The main reason for this was that most studies evaluating the effects of therapies on chronic pruritus failed to record nocturnal itching or sleep quality as an outcome measure.

In general, we suggest that physicians treating children with nocturnal pruritus use conservative, nonpharmacologic approaches in conjunction with topical therapies. Systemic treatments can be added in a step-wise approach. A therapeutic ladder for the treatment of nocturnal itch in children is shown in Figure 2. The efficacy of exogenous melatonin has recently been demonstrated in improving the quality of sleep in patients with nocturnal pruritus and is generally well tolerated with few side effects. In addition, although sedating antihistamines are often used clinically for the treatment of nocturnal pruritus, there is insufficient evidence to support their use as a first-line agent in children with chronic itching.²⁷ Clinicians should bear in mind that the behavior of children varies at different ages, so management should be targeted to the child's stage of development.

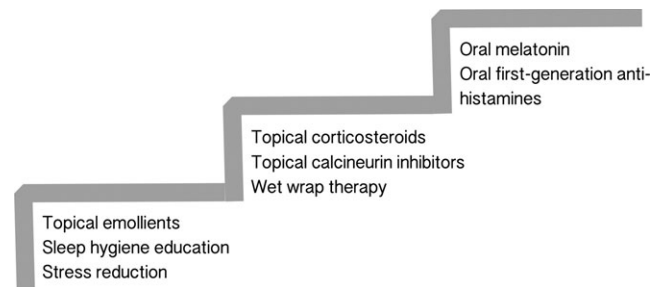
Our review found that psychological interventions and low-dose antidepressants such as mirtazapine and doxepin appear to be effective in relieving nocturnal itching in adults, but their efficacy has not been evaluated in children. Thus, future research is needed to evaluate their usefulness and optimal dosing regimens in children with nocturnal pruritus. Furthermore, several preliminary studies have described the use of biologic agents to relieve atopic pruritus, including the monoclonal antibody dupilumab, H4R antagonists, antibodies against the interleukin-31 receptors, and phosphodiesterase 4 inhibitors. These agents warrant further research but are promising options in the management of chronic itching.⁴⁰

Understanding and treating nocturnal itching in children is essential for preventing adverse behavioral, neurocognitive, and physiologic outcomes. Future studies evaluating chronic itching secondary to AD, psoriasis, prurigo nodularis, or lichen simplex chronicus should

TABLE 1 Therapies that have demonstrated efficacy in reducing nocturnal itching or improving sleep quality in children with nocturnal pruritus

Type of therapy	Grade of evidence ^a	Condition	Study design	N	Age range, years	Treatment	Duration of treatment	Relief of symptoms	Reference
Topical	A	AD	Five-center, investigator-blinded, randomized trial	121	1–18	Fluticasone (Cutivate) cream	28 d	Statistically significant improvement in pruritus and improved sleep habits at 14 and 28 d	Sugarman, Parish, 2009 ²¹
Topical	A	AD	Double-blinded, noninferiority study	239	2–15	Fluticasone 0.005% ointment applied twice daily	3 wk	92% of patients experienced better sleep quality; median pruritus scores improved by 91.5%	Doss, et al. 2010 ²²
Systemic	A	AD	Randomized, double blind, placebo-controlled trial	73	1–18	3 mg/d oral melatonin before bedtime	4 wk	Sleep onset latency 21.4 min shorter than with placebo	Chang, et al. 2016 ³³
Oral	C	AD	Case report	1	6	0.005 mg/kg oral clonidine and 0.17 mg/kg oral triepazine before bedtime	1.5 y	Patient “was calmer, scratched less, and slept more peacefully”	Genois, et al. 2014 ³⁹

AD, atopic dermatitis.

^aGrade of evidence is based on Oxford Centre for Evidence-based Medicine levels of evidence.**FIGURE 2** Therapeutic ladder for treatment of nocturnal itching in children. In general, physicians should begin with conservative, nonpharmacologic approaches in conjunction with topical therapies. Systemic treatments can be added in a step-wise approach. We suggest beginning with sleep hygiene education, topical emollients, and stress reduction, in addition to topical corticosteroids, topical calcineurin inhibitors, or wet wrap therapy. Oral melatonin and oral first-generation antihistamines are reserved for treating impaired sleep in children with nocturnal itching that is refractory to first-line therapies

assess sleep patterns as a crucial parameter of disease control. The two most common objective methods of measuring sleep disturbances in patients with nocturnal itching are actigraphy and laboratory-based polysomnography. Actigraphy is the preferred method of assessing sleep quality in children; it involves using a small, wrist-worn device to monitor sleep-wake patterns and record nocturnal awakenings caused by scratching.^{4,6} Actigraphy can be used in a child's home environment, is easy to use, and is relatively cost effective. Future studies should also work toward elucidating the pathophysiology of nocturnal pruritus to develop more effective targeted therapies for children.

CONFLICT OF INTEREST

Dr. Kwatra is an advisory board member for Menlo therapeutics.

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