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Systematic review article

The Overlapping Therapeutics of Sleep and Atopic Dermatitis: A Systematic Review

[1] Omna Chawla, MD, [2] Tarun Narang, MD, [3] *Naveen Kumar Kansal, MD

[1] Assistant Professor, Department of Physiology, Government Doon Medical College, Dehradun, India

[2] Associate Professor, Department of Dermatology, Venereology, and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[3] Department of Dermatology and Venereology, All India Institute of Medical Sciences, Rishikesh, India

Corresponding Author: Naveen Kumar Kansal

E-mail: kansalnaveen@gmail.com

Abstract
Atopic dermatitis (AD) is a chronic, pruritic, cutaneous inflammatory disorder that often disrupts sleep. However, limited studies guide the management of sleep problems in AD. Control of the disease is essential to improve sleep as well as the quality of life. In this brief review, after exploring the mechanisms of sleep disturbances in AD, we discuss the potential benefits and limitations of therapeutic agents available to treat AD. The selection of appropriate therapy is essential to improve sleep as well as the quality of life in AD patients.
Keywords: Atopic dermatitis; Melatonin; Pruritus; Quality of life; Sleep

Introduction

Atopic dermatitis (atopic eczema; AD) is one of the commonest pruritic skin diseases, with a chronic relapsing-remitting course. AD affects approximately 15-25% of pediatric and 1-10% of the adult population worldwide.[1] The characteristic unpleasant sensation of itch in AD is associated with an urge to rub/scratch vigorously and being more intense at night, adversely affects the quality and quantity of sleep. Sleep disruption is known to have various adverse consequences on behavior and cognitive functioning, which may include anxiety, hyperactivity, inattention, emotional problems, and metabolic syndrome. Though the significance of good sleep for the overall well-being of an individual is established, limited literature is available for a dermatologist in managing sleep troubles in their AD patients. With this brief review, we attempt to focus on sleep in the management of AD, based on current evidence, so that the disease can be improved from this point of view as well.

Mechanisms of sleep disturbance in atopic dermatitis

Sleep disturbance is found to occur in active disease as well as in remission (Figure 1). Research for understanding the sleep architecture in AD indicates that the average frequency of scratching is more in stage 1 non-rapid eye movement (NREM) sleep, compared to other

stages and the patients usually have a significantly lower percentage of deep sleep and reduced latency to rapid eye movement (REM) sleep.[2]
Several hypotheses have been proposed to explain sleep disturbance in AD and attribute that to itching/scratching, imbalance of inflammatory pathways, disturbed circadian rhythm, transepidermal water loss (TEWL), disrupted barrier function, or melatonin. Only about 15% of sleep arousals seem to be associated with itching or scratching. Disturbed sleep and arousals are present in AD patients in clinical remission as well and emphasize the significant role of the other mechanisms.[3]

Disturbance of immune function is pivotal to the pathogenesis of AD, with a shift towards the T-helper (Th)-2 response. Several cytokines are implicated in the pathogenesis of AD, including interleukin (IL)-4, IL-13, and IL-31, etc.[4] IL-4 and IL-13 downregulate the expression of integral barrier proteins, e.g., filaggrin, loricrin, and involucrin, leading to skin barrier dysfunction (with increased TEWL) and increased susceptibility to allergens and infections. Cytokines have a role in sleep regulation, and sleep deprivation may also shift the immune balance towards a Th2 response. However, the evidence has not established a relationship between sleep disturbance and inflammatory disturbance in AD.[5]
The diurnal pattern of cortisol, with its lowest blood levels and, therefore, the most downward anti-inflammatory effect at night, may also contribute to the nocturnal pruritus in AD. Skin cells themselves express circadian rhythmicity, with the 'clock genes' of skin shown to influence TEWL and skin blood flow rates. Another possible etiology for sleep disturbance in AD may be dysregulation of melatonin hormone, which has a significant role in sleep induction. It also has anti-inflammatory and immunomodulatory effects. Melatonin levels were shown to be less than normal in AD patients.[6]
Therefore, more than one mechanism is likely to cause sleep disturbances in AD and should be managed accordingly.

Approaches for management of AD and the relationship with sleep
The 'Scoring Atopic Dermatitis (SCORAD)', a validated tool to measure both AD disease extent and severity, does include subjective assessment for loss of sleep. However, a formal and comprehensive evaluation of the associated sleep problems in chronic cutaneous disorders, e.g., AD, is usually not considered in current dermatological practice. Therefore, few sleep questionnaires may be helpful in screening, e.g., Insomnia Symptom Questionnaire, Pittsburgh Sleep Quality Index, etc. AD patients with significant sleep disturbance should be promptly referred for further evaluation.[7]

Topical and behavioral therapies
The topical treatment of AD is based upon a well-organized skincare routine, with sufficient skin hydration by use of emollients and topical treatments, and attention to the triggering factors so that itch and flares may be minimized. Wet wrap therapy is helpful in AD as a physical barrier to decrease nighttime scratching. The evening applications of topical steroids and topical calcineurin inhibitors, the anti-inflammatory therapies, have been shown to improve AD as the TEWL is highest at this time, and skin blood flow rate is most affected by topical steroids. Daily massage therapy along with standard topical treatment showed improvement in one study. Massage seems to improve peripheral blood flow and relieve anxiety associated with the disease, and therefore, enhancing sleep quality in AD. These treatment approaches, along with psychological interventions, e.g., cognitive behavioral therapy (CBT), may improve sleep quality and help disease remission.[7]

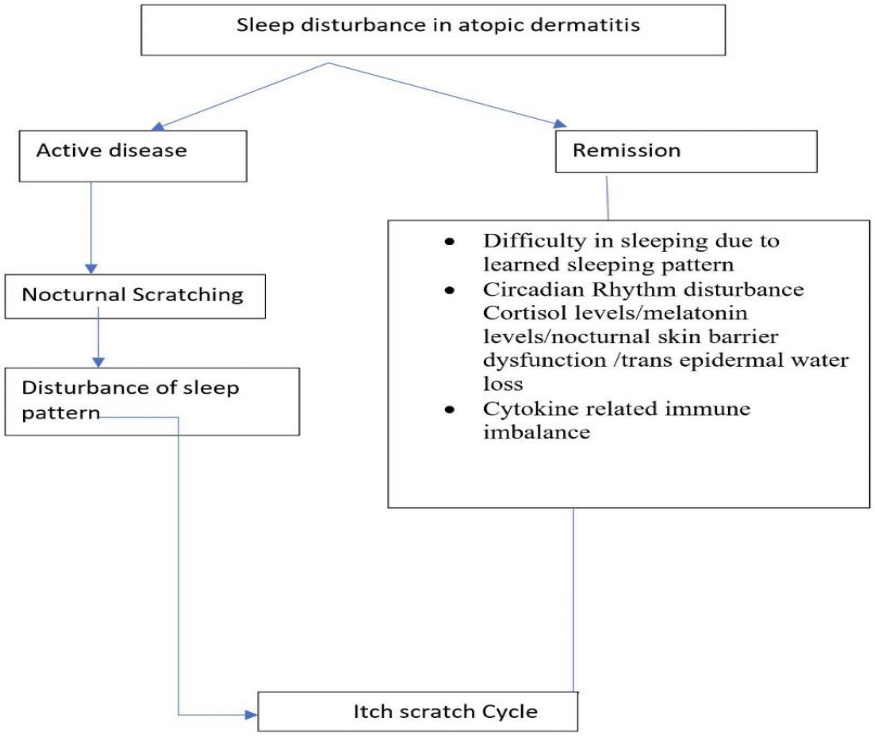

Figure 1: Relationship of sleep disturbance with atopic dermatitis during active disease and in remission.

Systemic therapy

While selecting a systemic therapeutic agent(s) in AD, sleep disturbance should be considered as an associated clinical problem. Therefore, as far as possible, the choice of medications should cause minimal interference with the sleep mechanisms.

Antihistamines have been traditionally prescribed to relieve itch by their H_1 antagonist action and sedative effects. However, antihistamines do not have much role in controlling pruritus in AD, and their use is limited to ensure sound sleep. The first-generation antihistamines like diphenhydramine and hydroxyzine, when taken at night, increase the REM sleep latency and reduce the duration of REM sleep, therefore, leading to poor sleep and residual attention impairment the following day. These paradoxical effects on sleep indicate that the use of these antihistamines should be discouraged. Second-generation antihistamines like cetirizine, olopatadine, etc., do not compromise sleep quality in AD.[8] Therefore, these newer antihistamines may be preferred in AD.

Several ***antidepressants*** have significant H_1 blocking action and sedative properties. Amongst these, low-dose tricyclic antidepressants, e.g., doxepin and trimipramine, decrease sleep latency and may be helpful in improving sleep quality.[9] Mirtazapine, a selective norepinephrine reuptake inhibitor (SNRI), also relieves itching in AD and enhances sleep quality by decreasing the number of awakenings and their duration.[7] These agents improve sleep quality as the deep slow-wave sleep time increases, with no disturbance on REM sleep. Selective serotonin reuptake inhibitors (SSRIs) like paroxetine, fluvoxamine also have antipruritic effects supposedly due to their central actions on 5-HT_3 receptors. SSRIs, however, may not be preferred in AD as they exacerbate sleep bruxism and disturb muscle tone regulation during REM sleep.[10]

Benzodiazepines act on γ-aminobutyric acid (GABA) receptors and are sometimes used in AD for their anxiolytic and sedating effects. However, a study examining the effects of nitrazepam in adult AD patients found that the number of scratching episodes was reduced, but the duration of individual episodes was increased. Therefore, the actual time of scratching remained the same.[11]

Melatonin, a neurohormone, and circadian rhythm regulator, has significant roles in sleep onset, duration, and quality; it also has immunomodulatory properties. The plasma melatonin levels are found to be generally lower in AD.[6] However, the therapeutic use of melatonin may not be recommended due to the immunomodulatory effects, which have the potential to worsen AD.[12]

***Biologics*.** Dupilumab acts by inhibiting IL-4 and IL-13 receptors and improves the disease by suppressing mRNA expression of Th2 inflammation. Dupilumab possibly decreases TEWL. However, it does not increase stratum corneum hydration in AD. Dupilumab leads to significant improvement in sleep quality in AD compared to the placebo.[13] As sleep deprivation is known to elevate levels of inflammatory cytokines, improving sleep quality in AD is likely to improve the disease.[14]

Conclusion

Current evidence indicates the co-occurrence of sleep disturbance and AD, therefore improving sleep has a significant role in improving the quality of life of AD patients. The selection of appropriate therapy for the purpose may be difficult in a busy clinical practice. However, attempts should be made to choose a medication with minimum interference with sleep. To conclude, this area remains relatively unexplored in therapeutics in AD and needs further research.

References

1. Buggiani G, Ricceri F, Lotti T. Atopic dermatitis. *Dermatol Ther*. 2008;21(2):96-100. doi:10.1111/j.1529-8019.2008.00176.x
2. Monti JM, Vignale R, Monti D. Sleep and nighttime pruritus in children with atopic dermatitis. *Sleep*. 1989;12(4):309-314. doi:10.1093/sleep/12.4.309
3. Ramirez FD, Chen S, Langan SM, et al. Association of Atopic Dermatitis With Sleep Quality in Children. *JAMA Pediatr*. 2019;173(5):e190025. doi:10.1001/jamapediatrics.2019.0025
4. De la O-Escamilla NO, Sidbury R. Atopic Dermatitis: Update on Pathogenesis and Therapy. *Pediatr Ann*. 2020;49(3):e140-e146. doi:10.3928/19382359-20200217-01
5. Krueger JM. The role of cytokines in sleep regulation. *Curr Pharm Des*. 2008;14(32):3408-3416. doi:10.2174/138161208786549281
6. Alexander H, Patton T, Jabbar-Lopez ZK, Manca A, Flohr C. Novel systemic therapies in atopic dermatitis: what do we need to fulfil the promise of a treatment revolution? *F1000Research*. 2019;8. doi:10.12688/f1000research.17039.1
7. Mostaghimi, L. (2019). Sleep and skin. In: França K., Lotti T. eds. Advances in Integrative Dermatology. Hoboken, NJ: Wiley Blackwell: 361-366.
8. Yamanaka K, Motomura E, Noro Y, et al. Olopatadine, a non-sedating H1 antihistamine, decreases the nocturnal scratching without affecting sleep quality in atopic dermatitis. *Exp Dermatol*. 2015;24(3):227-229. doi:10.1111/exd.12630
9. Wichniak A, Wierzbicka A, Walęcka M, Jernajczyk W. Effects of Antidepressants on Sleep. *Curr Psychiatry Rep*. 2017;19(9):63. doi:10.1007/s11920-017-0816-4

10. Ständer S, Böckenholt B, Schürmeyer-Horst F, et al. Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof-of-concept study. *Acta Derm Venereol*. 2009;89(1):45-51. doi:10.2340/00015555-0553
11. Ebata T, Izumi H, Aizawa H, Kamide R, Niimura M. Effects of nitrazepam on nocturnal scratching in adults with atopic dermatitis: a double-blind placebo-controlled crossover study. *Br J Dermatol*. 1998;138(4):631-634. doi:10.1046/j.1365-2133.1998.02174.x
12. Srinivasan V, Maestroni GJM, Cardinali DP, Esquifino AI, Perumal SRP, Miller SC. Melatonin, immune function and aging. *Immun Ageing A*. 2005;2:17. doi:10.1186/1742-4933-2-17
13. Beck LA, Silverberg JI, Simpson EL, et al. Dupilumab significantly improves sleep outcomes in adult patients with atopic dermatitis: results from five randomized clinical trials. *J Eur Acad Dermatol Venereol JEADV*. 2021;35(2):e130-e133. doi:10.1111/jdv.16865
14. Mullington JM, Simpson NS, Meier-Ewert HK, Haack M. Sleep loss and inflammation. *Best Pract Res Clin Endocrinol Metab*. 2010;24(5):775-784. doi:10.1016/ j.beem.2010.08.014