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REVIEW

Sleep disorders in dermatology – a comprehensive review

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Summary
Sleep is a normal physiological process that accounts for approximately one third of a person's life. Disruption of the normal sleep cycle, which maintains physiological homeostasis, can lead to pathology. It is not known whether sleep disturbance causes skin disease or skin disease causes sleep impairment, but a bidirectional influence is suspected. We have compiled the data from published articles on "sleep disorders in dermatology" in PubMed Central from July 2010 to July 2022 (with the option "full text available") and provide an overview of sleep disorders associated with dermatological conditions and certain drugs used in dermatology as well as sleep disturbances for which some drugs used can cause itch or dermatological issues. Atopic dermatitis, eczema and psoriasis have been shown to be exacerbated by sleep problems and vice versa. Sleep deprivation, night-time pruritus and disrupted sleep cycles are often used to assess treatment response and quality of life in these conditions. Some medications used primarily for dermatological conditions have also been associated with alterations in the sleep-wake cycle. Addressing patients sleep disorders should be an integral part of the management of dermatological conditions. More studies are needed to further investigate the influence of sleep and skin disorders.

KEYWORDS
dermatology, homeostasis, itching, quality of life, sleep disorders

INTRODUCTION

Sleep is a restorative state that is essential for many physiological processes in the body. Its impairment can lead to widespread health problems, such as cardiovascular disease, psychological disorders, and infections.[1] Sleep is further defined as the natural, easily reversible periodic state of many living things, characterized by the absence of wakefulness and the loss of awareness of one's environment, the occurrence of dreams, and changes in brain activity and physiological functions.[2] Non-REM (rapid eye movement) sleep and REM sleep are distinguished. Non-REM sleep is essential for memory consolidation,[2] while REM sleep is critical for processing sensory impressions. Skin problems associated with sleep disorders are not uncommon in clinical practice, but are sometimes ignored or overlooked. We do not discuss them at our conferences. However, we know that sleep is an important factor for us, and quality of life in dermatologic patients[3] is an important aspect to consider. Very little data and RCT (Randomized Controlled Trial)/meta-analysis are available on this aspect. The purpose of this review is to discuss the basic pathogenesis of sleep problems in skin diseases and to evaluate chronic dermatologic diseases that are known to be exacerbated by sleep disorders. Basic physiology and various dermatologic disorders related to sleep disturbance and vice versa will be discussed.

METHODS

We have included the published articles based on scientific evidence found in Pubmed Central (July 2010 to July 2022), for the term "sleep disorders in dermatology", using the

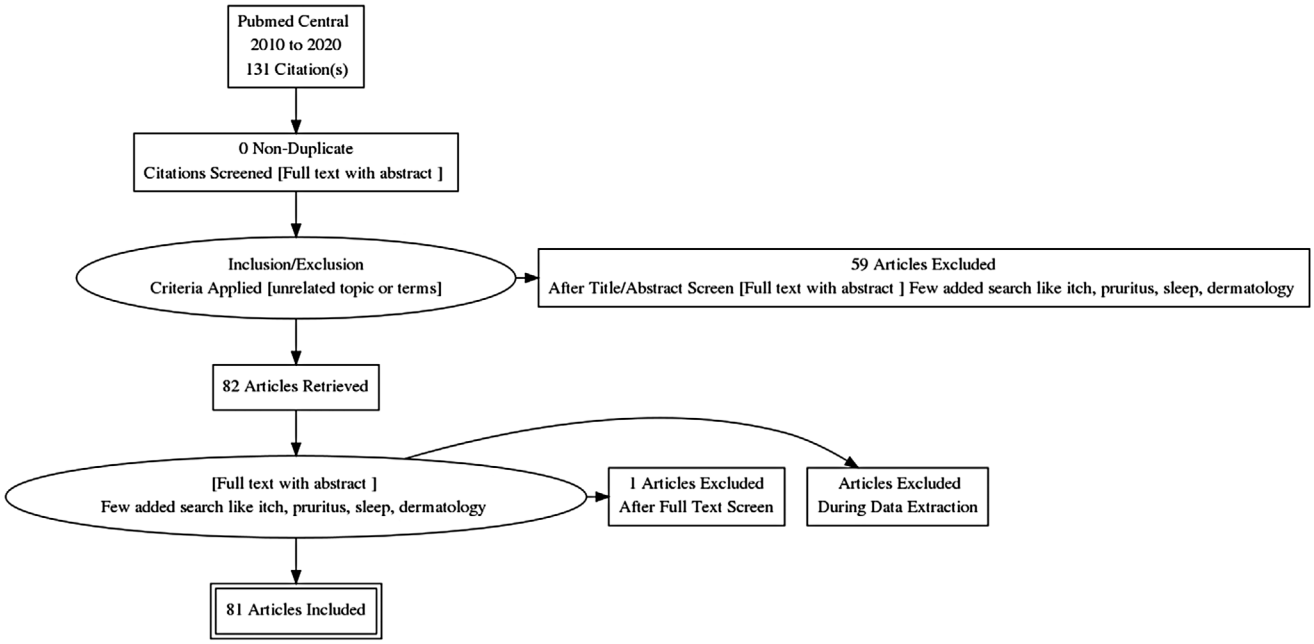

FIGURE 1 PRISMA flowchart for a method of the study.

option "sort by relevance", and provide an overview of sleep disorders associated with dermatological conditions and with certain drugs used in dermatology, or with some drugs used in sleep disorders causing itching or dermatological issues. Studies discussing topics other than sleep and skin problems, such as "skin aging," "pathogenesis or treatment of skin disorders," "sleep apnea," and "sleep in type 1 diabetes," were excluded. Out of 131 results (free full text with abstract), 59 papers were excluded because they were not directly related to the topic as mentioned or discussed some other main issues. Eleven of the publications were clinical trials (8 randomized), five were meta-analyses, 19 were reviews (6 systematic reviews) (level 1, 2 evidence), and the remainder were considered associated data (level 3, 4 evidence). These were taken into account and discussed. We searched a few terms separately to make our discussion comprehensive, such as "itch, sleep disturbances", "itch", and "hematological malignancy". Finally, 72 articles were included for review. We have partially followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and organized the data (Figure 1).

RESULTS AND DISCUSSION

This section of the study is divided into four parts:

1. Sleep disorders and dermatology – basic pathophysiology
2. Skin diseases associated with sleep disorders
3. Sleep disorders related to skin problems
4. Problems associated with dermatological and sleep disorder therapies

Sleep disorders and dermatology – basic pathophysiology

Sleep biology is a vast topic and beyond the scope of our discussion. In short, sleep and wakefulness are mediated by *(1)* circadian rhythms, *(2)* a balance between the duration of previous wakefulness and sleep, and *(3)* the hormonal and chemical milieu in the central nervous system. These factors will be briefly discussed in the following subheadings to better understand the topic.

Normal sleep-wake cycle

Two methods are mainly used to objectify and measure sleep: Polysomnography and actigraphy. Polysomnography includes a more comprehensive sleep analysis with various measurement components such as EEG (electroencephalogram), oxygen level, carbon dioxide level, ECG (electrocardiogram), snore recording, leg movements, sleep position, etc., whereas actigraphy measurements are based on motor activity.[4] A sleep cycle consists of two stages, non-REM (NREM) sleep and REM sleep. In an adult, sleep begins with NREM sleep followed by REM, each lasting about 90 minutes on average. Non-REM sleep is divided into N1, N2, and N3 in progressively deeper sleep stages. These stages occur at different frequencies throughout the night. N3, also known as "slow wave sleep" (SWS) or "deep sleep," is defined by

"delta waves," which are slow brain waves interspersed with smaller, faster waves. In this stage, there is a drop in blood pressure and temperature with relative bradypnea. There is also a lack of eye movement and reduced muscle activity. The duration of SWS corresponds to the accumulated need for sleep.[5,6] REM sleep, or the "dreaming" state, is most often achieved in the early morning hours of a normal sleep cycle. REM sleep is characterized by theta waves accompanied by rapid eye movement and an increase in muscle tone.[7] Both stages are essential for memory consolidation.

Circadian rhythm

The circadian rhythm is a process that takes place over 24 hours a day to perform vital tasks. The sleep-wake cycle is part of the circadian rhythm. Each person's circadian rhythm harmonizes with a master clock in the brain, located in the suprachiasmatic nucleus.[8] It is influenced by various environmental factors, such as light. A normal circadian rhythm leads to consistent and restorative sleep, while an altered circadian rhythm leads to insomnia and other sleep disorders.[9,10]

Sleep hormones

Melatonin is a hormone that regulates the timing of the central biological clock. Melatonin is normally secreted in the absence of light. Melatonin levels rise in the evening. A decrease in melatonin results in disruption of sleep onset and/or sleep duration.[11] Growth hormone-releasing hormone (GHRH) also affects sleep. It stimulates GH and induces slow-wave sleep (SWS), but it inhibits cortisol. Corticotrophin-releasing hormone (CRH) has opposite effects and reduces SWS.[12] An alteration in the GHRH:CRH ratio leads to sleep endocrine disorders. Other hormones such as galanin and neuropeptide Y promote sleep, and vasoactive intestinal polypeptide moderates the REM-non-REM cycle. Somatostatin interferes with sleep in the elderly.

Thermoregulation and sleep

Body temperature also varies with the circadian rhythm. The "core" of the body is almost constant in maintaining a fixed body temperature, while the periphery changes its temperature. The skin of distal sites such as the hands, feet, and face maintains temperature by heat loss or heat retention by conducting heat through a cutaneous AV shunt. In healthy individuals, sleepiness increases along with an increase in the distal to peripheral gradient (DPG), meaning that the periphery becomes warmer. These findings have been supported by a study that showed that the use of a thermal blanket and an increase in hand and foot temperature led to an earlier onset of sleep.[13] The skin, therefore, already has an impact on the sleep cycle. Some inflammatory conditions, such as psoriasis, make it difficult for the body to dissipate heat and thus fall asleep.[14]

Sleep and immune function

Sleep and circadian rhythms modulate immune function. Studies show that undifferentiated naïve T cells and levels of pro-inflammatory cytokines are highest during early nocturnal sleep, whereas cytotoxic NK cells and anti-inflammatory cytokines peak in the early morning (Figure 2).

Even a modest amount of sleep loss has been associated with a 72% reduction in natural killer (NK) cell activity: *(1)* Sleep mediates the extravasation of T cells and probably their reallocation to lymph nodes. *(2)* Sleep promotes the interplay between antigen-presenting cells and helper T cells. *(3)* Adequate sleep also plays a role in the formation of immunologic memory.[15]

Studies show that sleep loss can affect different parts of the immune system, which can lead to the development of a wide variety of disorders. A modest amount of sleep loss (restricting sleep to 4 hours for one night) led to the generation of inflammatory cytokines and predisposed to infections. The release of inflammatory cytokines due to reduced sleep causes damage to the skin barrier function. This leads to the assumption that infections, as well as dermatologic diseases like non-healing ulcers, psoriasis, and eczema, are aggravated under these conditions.[16–18]

Physiological component

Chronic insomnia, loss of sleep three nights a week for at least 3 months, as defined by DSM-5,[19] is the most common sleep disorder with a prevalence of 10%–20% and is defined by difficulty in falling asleep, staying asleep, or waking up too early.[18] In a cross-sectional study of adults, insomnia was found in as many as 33% of the population.[20]

Several external and internal factors can cause or worsen insomnia. Among others, psychological distress is a strong influencing factor. Psychological problems, such as depression or anxiety, lead to flare-ups of various dermatological conditions, such as psoriasis, urticaria, and eczema. It must be discussed that insomnia may not only be a consequence of this exacerbation, but also a cause.[21,22]

Skin diseases associated with sleep disorders

Atopic dermatitis

Atopic dermatitis (AD) is a common chronic inflammatory skin condition. It is associated with sleep disturbance in approximately 47% to 80% of children and 33% to 90%

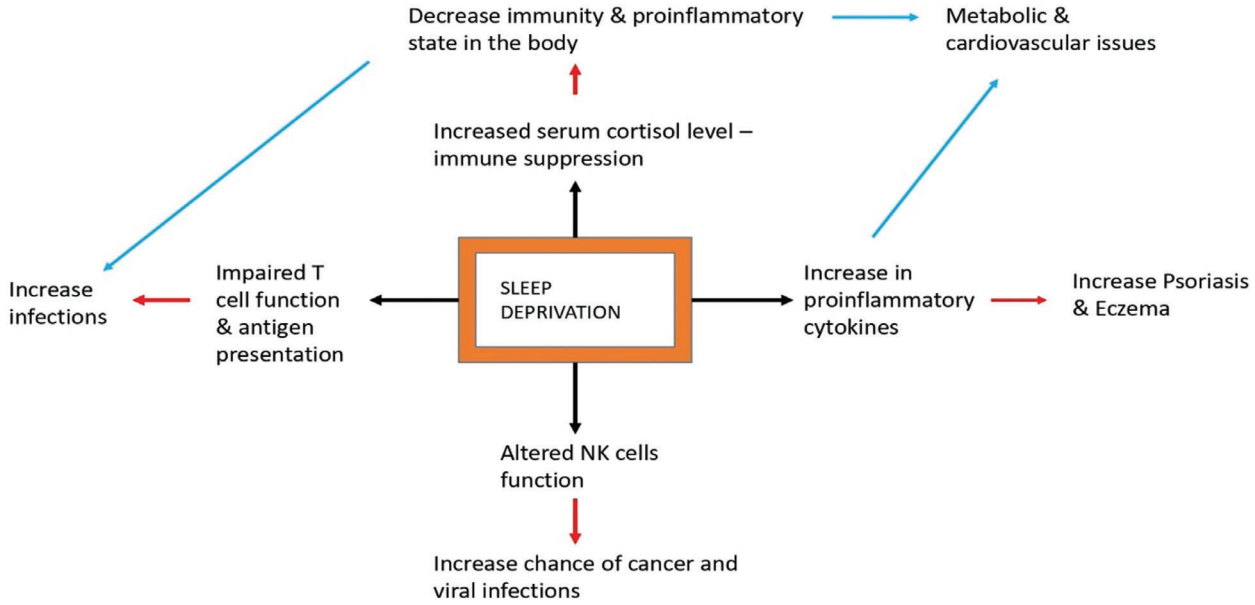

FIGURE 2 The relation between deprivation and immune function.

of adults. Again, sleep disturbance may be a symptom or cause of AD flares rather than a comorbidity. Sleep disturbances associated with AD include insomnia, with significantly more problems falling asleep and staying asleep.[22] Sleep disturbances lead to reduced quality of life in dermatologic patients,[23] more missed workdays, and an increased economic burden on individuals.[24]

Several drugs, such as cyclosporine, dupilumab, and azathioprine, resulted in substantial reductions in AD lesions and associated symptoms such as itching and sleep disturbances.[25]

Eczema: Rangel et al. and Mann et al. (unpublished) compared a group of children with atopic dermatitis over a 6-month period and showed associations of fatigue and sleep problems with the severity of eczema, as well as an association with psychological problems such as depression and anxiety disorders and physical limitations (mobility) in daily life. Children with eczema showed a significantly increased incidence of sleep problems and fatigue. [26]

Psoriasis

Due to the cutaneous symptoms of psoriasis, a direct influence on sleep is plausible. Psoriasis (PS) causes problems with the thermoregulatory function of the skin, thus interfering with sleep onset.[27] More recently, psoriasis has been considered a systemic inflammatory disorder because it can affect the musculoskeletal, cardiovascular, renal, and other systems of the body, which indirectly results in sleep problems. Both psoriatic arthritis (PsA) and PS causes increased fatigue, sleep alteration, poor quality of life, and psychological problems when compared with the general population. In a study, 62 patients with PS and 52 patients with PsA were assessed for sleep and quality of life using the Pittsburgh Sleep Quality Index (PSQI), fatigue using the fatigue subscale of the FACIT-F questionnaire, quality of life using the Health Assessment Questionnaire (HAQ), psoriasis severity using the Psoriasis Area Severity Index (PASI), and arthritis activity using the Disease Activity Score of 28 joints. The visual analog scale (VAS) was used to assess pain severity. Interestingly, they showed that more than 67% of patients with PsA and 52% with PS had sleep disturbances and felt extreme fatigue during the day.[28]

According to one study, the prevalence of obstructive sleep apnea in psoriasis patients is approximately 36% to 82%. In addition, the prevalence of restless leg syndrome is about 15% to 18 %. The prevalence of insomnia in psoriasis patients ranges from 6% to 45%.[29,30]

Chronic urticaria

Patients with chronic urticaria also experience itching and burning of the skin. Sleep disturbance due to urticaria has been reported in more than 50% of patients with chronic spontaneous urticaria (CSU). Anxiety, depression, somatization, obsessive-compulsive disorder, hostility, paranoid ideation, and psychosis have a higher prevalence in patients with chronic urticaria. In their study, He at al. analyzed a large group of patients (retrospective matched cohort including 105,892 patients with new-onset sleep disorders [SD cohort] and 105,892 randomly selected controls [control cohort]) and showed in a 10-year follow-up that patients with sleep problems are more prone to develop chronic urticaria and other comorbidities, namely atopic dermatitis, thyroid disorders, anxiety, and depression.[31]

In a pilot study, it was suggested that higher doses of second-generation antihistamines may improve sleep patterns in patients with urticaria. The level of histamine release spikes at dawn and dusk, leading to early awakening in chronic urticaria patients.[23]

Infections

Skin infestations usually lead to nocturnal pruritus. The most common infestation is scabies. Scabies mites are more active at night, which partially explains the nocturnal pruritus. The feces of *Sarcoptes scabiei*, called scabella, contain proteases that trigger a pruritic receptor called protease-activated receptor 2 (PAR-2). *Sarcoptes scabiei* releases numerous pruritic cytokines such as IL-31. Secondary infections may also cause pruritus. Post-scabies pruritus may be caused by a hypersensitivity reaction with central neural hypersensitization.[32,33]

Pruritus/itch

Pruritus often affects individuals with a range of chronic skin conditions including eczema, atopic dermatitis, psoriasis, and urticaria. The intensity of pruritus can lead to sleep disturbances, behavioral disturbances, poor quality of life, and other psychological dysfunctions such as anxiety. In a prospective study of more than 800 patients, moderate to severe pruritus in chronic disease was found to lead to disturbances in sleep quality, work productivity, depression, and anxiety when compared to normal controls.[34]

Itching in AD leads to significant sleep loss in both the affected child and the parent. A study by Chamlin et al. elegantly analyzed the co-sleeping behavior of parents in a cohort of over 300 parents of children with AD. They showed that when parents tried to sleep beside their children to protect them from scratching at night, they got insufficient sleep. Ultimately, nighttime itching affected the quality of sleep for both parent and child.[35]

Body temperature during sleep and waking, skin barrier function, and a few unknown factors are thought to control nocturnal pruritus. Thermoregulatory changes occur during the night. Core body temperature is highest in the early evening and lowest in the early morning, but different stages of sleep also dictate changes in core body temperature. During NERM sleep, the hypothalamic temperature set point is reduced, leading to increased heat dissipation through the skin via vasodilation and thereby possibly to an increase in itching. Cortisol levels decrease in the evening and are lowest at night, resulting in the lowest anti-inflammatory effect at night. Because of this cardigan pattern of the hypothalamic-pituitary-adrenal (HPA) axis inactivity at night, cutaneous inflammation in chronic skin conditions peaks, leading to itching.[36]

Skin barrier function and transepidermal water loss (TEWL) also play some roles in nocturnal itching. At night TEWL increases and this diurnal impairment makes the skin dry at nighttime leading to itching.[37]

Increased nocturnal levels of 2 prostaglandins, PGD2 and PGE2, are involved in the repair of skin barrier damage caused by scratching. It is hypothesized that disruption of the PG-CoA rhythm in chronic skin disease leads to nocturnal pruritus.[28] Several cytokines are also elevated at night and may contribute to nocturnal pruritus; IL2, IL8, and IL31 can increase itch severity, and IL2 levels increase at night. IL2 secretion is also associated with decreased cortisol production at night.[38]

Injection of morphine, a μ (mu)-opioid receptor agonist, induces itching, whereas μ and κ (kappa)-opioid receptor antagonists reduces itching. Dysregulation in the pattern of release of different opioids may be associated with nocturnal pruritus.[33]

Melatonin, a hormone from the pineal gland, maintains the sleep-wake cycle and secretes in a pulsatile manner known as the circadian rhythm. One study found that children with AD have a significant drop in melatonin levels at night, leading to sleep deprivation and pruritus.[39]

Pruritus can be a symptom of many serious diseases such as hematologic malignancies. Leukemia, lymphoma, multiple myeloma, and polycythemia may cause paraneoplastic pruritus. In Hodgkin's lymphoma, 30% of patients may have nocturnal itching, which may be very severe and symptomatic; it may precede the disease by 6 months to 1 year. Itching is one of the proposed B symptoms in Hodgkin's lymphoma, and it could be an important clue to diagnose the disease. Mycosis fungoides causes severe pruritus in the late stage and is an indicator of severity and prognosis.[40,41]

Sleep disturbance is common in cholestatic pruritus and is associated with a significant decrease in quality of life. Pruritus may occur in up to 30% of patients with liver disease and cholestasis. Nighttime itching, mainly on the hands and feet and in areas irritated by clothes, and sometimes generalized itching, is the feature of hepatic pruritus. Bilirubin metabolites, bile salts, and bile acids are thought to be the cause, although the exact mechanism is still unknown.[42]

Prurigo nodularis is a condition that might lead to severe paroxysmal itching at night. Sleep disturbances along with behavioral changes are common in this condition. It may also be associated with other conditions such as chronic kidney disease, hematologic malignancies, diabetes, and sleep disorders that contribute to poor quality of life.[43]

Sleep disorders related to skin problems

Obstructive sleep apnea (OSA)

The prevalence of obstructive sleep apnea is approximately 2% in females and 4% in males. The high prevalence of OSA is attributed to the high body mass index. There is a high prevalence of OSA in psoriasis, probably due to the high prevalence of obesity in these patients. The intermittent

hypoxemia seen in OSA patients causes a proinflammatory state, which in turn exacerbates many inflammatory dermatoses. A Taiwanese study showed that patients with obstructive sleep apnea (OSA) also have a higher risk of AD.[44]

One patient with severe obstructive sleep apnea developed post-inflammatory hyperpigmentation and lichenification of the forehead due to constant rubbing of the forehead against a wall while trying to sleep.[45]

Narcolepsy

Narcolepsy is a sleep disorder of central origin. Narcolepsy is usually associated with excessive sleep propensity during the daytime. Patients with narcolepsy have altered daytime skin temperature and a distal-proximal gradient (DPG) in skin temperature that is greater than normal.[46] In one study, an association was found between alopecia areata and narcolepsy.[31] One case was reported of an association between type 1 narcolepsy and atopic dermatitis.[47] In addition, people with cutaneous morbidities may be difficult to treat because of the altered sleep-wake cycle.

Parasomnias

A study reported an increased incidence of self-reported parasomnias in patients with vitiligo.[48] Sleep-related scratching may occur as a primary parasomnia of any known etiology. This may be due to altered sleep-related physiological changes in the stratum corneum that increase pruritus susceptibility or an altered inflammatory profile.[49]

Problems associated with dermatological and sleep disorders therapies

Corticosteroids

Melatonin plays a central role in the sleep cycle.[8] The release of melatonin promotes sleep onset and maintenance. Corticosteroids cause a decrease in serum melatonin with a marked alteration in circadian secretion. Steroids also inhibit brain uptake of tryptophan, an amino acid that serves as a precursor for melatonin.[50,51]

Retinoids

Isotretinoin, a drug widely used in dermatology, has been found to cause sleep disturbances. In a study evaluating the US *FDA Adverse Event Reporting System* (FAERS), data indicate a significantly higher incidence of sleep apnea with isotretinoin compared to all other drugs; here, the increased incidence was mainly in patients using isotretinoin for acne and needs to be evaluated with structured studies.[52,53]

Anti-histamines

First-generation antihistamines such as diphenhydramine are available over-the-counter (OTC) in most countries, and H2 antihistamines are widely used for dyspepsia. First-generation antihistamines are often used by physicians to induce sleep in patients with nocturnal, sleep-disrupting pruritus, but regular use in individuals with insomnia is not recommended.[54] Bizarre dreams and sleep loss have been reported with full-dose ranitidine, which resolved with discontinuation.[55]

Classical H1 antihistamines increase the latency of REM sleep at night, and the residual effects are manifested as daytime drowsiness. This affects working memory, vigilance, and sensorimotor performance.[56]

Sedatives causing itch and skin rash

Benzodiazepines such as chlordiazepoxide, diazepam, and midazolam have been used as sedative-hypnotics since the 1960s. Although they are safe and have a long history of use, they can also cause anaphylaxis or anaphylactic reactions. Severe itching, redness of the skin, hives, bronchospasm, and even death can occur. This hypersensitivity reaction is common with chlordiazepoxide, followed by diazepam and flurazepam through a common metabolite desethyldiazepam. Midazolam shows no cross-reactivity with diazepam, suggesting a separate pathway of sensitization.[57]

Ways to manage sleep in dermatology

Managing the itching associated with chronic skin conditions leads to good nighttime sleep. There are several known methods to reduce pruritus at night:

- Keep cool at night, as an increase in temperature may increase pruritus.[58] Choose soothing and clean bedding. Patients with a known allergy to dust mites should use special encasement materials for their sheets, as dust mites can cause pruritus and disrupt sleep. Clean, soft linens made of breathable fabrics are a good choice for people with eczema.[59]
- Keep your nails clean and trimmed. Dirty and long nails can aggravate inflammation in people who accidentally scratch at night.[60]
- Making a habit of applying moisturizer before bed can be beneficial, as hydrated skin is less prone to itching and can lead to an undisturbed night's sleep.[61]

- Use relaxation techniques such as listening to soothing music and doing breathing exercises before bed.[62]
- Adhering to a structured sleep-wake cycle maintains a circadian rhythm that prevents inflammatory flares. Eating junk food, caffeine, alcohol, or smoking before bed disrupts sleep. Reducing screen time or using the screen in night mode (which blocks blue light) can help improve sleep.[63]
- Better control of chronic skin disease leads to improved sleep quality and duration.

Historically, sedating antihistamines have been used to treat insomnia and pruritus in atopic dermatitis; however, a review by Herman and Vender was inconclusive.[64] Another large landmark study concluded that classic trials of sedating antihistamines are flawed and there is no evidence to support the role of sedating antihistamines in AD.[65]

CONCLUSIONS

Sleep accounts for approximately one-third of a person's life. Skin diseases that cause sleep loss may be transient, long-term and/or recurrent and may lead to psychological complications. Treating the underlying skin condition can help treat the sleep disorder and vice versa. After understanding the detrimental effects of sleep disturbance, clinicians need to consider sleep disturbance as an important comorbidity of skin disease and treat it accordingly to improve the quality of life of dermatologic patients. Sleep quality and duration can be measured for quality of life in chronic skin diseases. Maintaining a proper sleep cycle may help patients have better behavioral control during the day. The dermatologist should also focus on taking a specific history when evaluating a patient with chronic skin conditions, and therapy should be directed toward managing nighttime sleep quality.

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CONFLICT OF INTEREST

None.

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