

## REVIEW ARTICLE

# Nocturnal Itch: Why Do We Itch At Night?

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**Pruritus is exacerbated at night in many systemic and dermatological diseases, resulting in reports of significantly diminished quality of life and sleep disturbances. At present, the underlying mechanisms responsible for night-time itching are not well understood. Nocturnal pruritus may be related to the circadian rhythm of itch mediators and possibly the disruption of such patterns. Diurnal changes in skin physiology, such as temperature and barrier function, may also play a role. Currently, the paucity of specific treatment options for nocturnal pruritus is alarming and needs to be addressed by future research. This review describes the scale of the problem associated with nocturnal pruritus, the impact it has on patients, possible underlying mechanisms and, lastly, treatment options. Key words: nocturnal pruritus; nocturnal itch; circadian rhythms; skin physiology; treatment; mechanisms.**

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Itch is exacerbated at night in many systemic and dermatological diseases (1). The purpose of this review is to outline the scale of the problem associated with nocturnal pruritus, the impact it has on patients, possible underlying mechanisms and treatment options.

Up to 65% of patients with inflammatory skin conditions including psoriasis (2), atopic dermatitis (3) and chronic idiopathic urticaria (4) have reported increased itching at night. Cutaneous diseases such as lichen simplex chronicus (5) and scabies (6) are also characterized by nocturnal pruritus. Furthermore, patients with systemic diseases including chronic renal failure (7) and hematopoietic disorders (8) have also reported an exacerbation of itch at night. The disruption of sleep patterns caused by nocturnal pruritus is a significant problem. Children with atopic dermatitis spent a mean of 46 min less time motionless or sleeping than controls, as measured using accelerometers in their own homes (9). In addition, it has been shown that adult patients with atopic dermatitis slept less, awoke twice as often, and spent more time awake during these waking episodes,

resulting in lower overall sleep efficiency compared with controls (10). This reduction in the amount and quality of sleep has a well-documented deleterious effect on human performance, contributing to irritability, daytime somnolence, impaired functioning and psychological problems (11, 12).

Several studies have investigated the relationship between nocturnal pruritus and the different stages of sleep. Aoki et al. (13) demonstrated that severely itchy patients spent little time in deep non-rapid eye movement (non-REM) sleep (stages 3 and 4) and found that scratching episodes occurred during all sleep stages, although the frequency was higher in stage 1 non-REM sleep. Other studies have shown that in patients with itchy skin diseases, especially atopic dermatitis, pruritus is more common in stages 1, 2 and REM than in deep non-REM sleep (14, 15).

Pruritus not only disturbs sleep, but also contributes to depression, agitation, changes in eating habits, and difficulty concentrating. Reduced sexual desire and sexual function is also reported amongst many patients with itch (2–4). Another major concern is that pruritus leads to increased cutaneous inflammation, which causes further itching and scratching, known as the itch-scratch cycle (16). Many times, patients are unaware of the extent to which they are scratching during the night and thus further contributing to skin inflammation. It is clearly evident that nocturnal pruritus has a significant impact upon both sleep and quality of life.

## POSSIBLE UNDERLYING MECHANISMS (Table I)

The underlying mechanisms responsible for nocturnal pruritus are unclear. One possible explanation may be related to the circadian rhythms related to skin temperature and trans-epidermal water loss (TEWL). It has been shown that TEWL is significantly increased during the night and is minimal during the morning (17). The higher TEWL in the evening suggests that the epidermal barrier function is not optimal at this time, possibly facilitating the entry of irritants and itch-causing agents. In addition, it has recently been shown that TEWL is associated with itch intensity in patients with atopic dermatitis (18) and that damage to the stratum corneum with acetone/ether and water elicits a scratching response in murine models (19). The reported increase in skin temperature during the

night may provide another plausible explanation for the nocturnal exacerbation of pruritus (17). Itch has been reported to be aggravated by ambient heat (2) and it has been suggested that heat can increase itch sensation by its effect on nerve endings (20).

Pruritus and pain have a complex interaction, which is only beginning to be elucidated. A reduction in pain can induce itch, while a painful stimuli can reduce it. Furthermore, different opioid receptors have varying effects upon pruritus. Both  $\mu$ -opioid receptor agonists and  $\kappa$ -opioid receptor antagonists can induce itch while, unsurprisingly,  $\mu$ -receptor antagonists and  $\kappa$ -receptor agonists can reduce it (21). In addition, it has been shown that patients with atopic dermatitis have a significantly increased concentration of serum  $\beta$ -endorphin compared with controls (22) and that there is a significant down-regulation of  $\mu$ -opioid receptor expression in the epidermis of such patients (23). Interestingly,  $\beta$ -endorphin has also been reported to be associated with both itch intensity and disease severity in atopic dermatitis patients (18). All of these observations are of relevance given the well-documented circadian rhythm of pain (24). Although the exact pattern of pain perception varies with different disease processes, both human and animal data show that there is a clear circadian rhythm to plasma and brain concentrations of  $\beta$ -endorphin and enkephalins, with peak values always occurring during the activity period (24). One hypothesis accounting for nocturnal pruritus involves a dysfunction of the circadian rhythm releasing different opioids, with peaks occurring during evening hours as opposed to the morning. Interestingly, a dysfunction in the diurnal secretion of melatonin, the principle hormone regulating circadian rhythm, has already been reported in patients with atopic dermatitis (25).

One of the most important circadian rhythms in the human body involves the hypothalamus-pituitary axis. Corticosteroid levels are normally at a trough in the evening, meaning the anti-inflammatory effects of this hormone are at a minimum during this time, possibly allowing for an exacerbation of inflammatory skin diseases. Another important circadian rhythm involves the autonomic nervous system (ANS), where parasympathetic tone is increased during the night and sympathetic tone in the morning (26). This circadian

rhythm in ANS function has been suggested to play a role in nocturnal asthma (27) and thus may also have a role to play in pruritic exacerbations of atopic dermatitis during the night given the vast overlap between these two disease processes.

Other plausible explanations for nocturnal pruritus may be related to the disruption of the cytokine and prostaglandin (PG) circadian patterns. Interleukin (IL)-2, IL-8 and IL-31 have all been shown to induce itch, while interferon (INF)- $\gamma$  demonstrated a beneficial effect (28). It has been shown that there is a nocturnal increase in secretion of IL-2 in healthy volunteers, possibly making more susceptible individuals prone to itch (29). With regards to PGs, a diurnal change in secretion from rat diaphyseal bone has been reported (30). Except for prostacyclin, elevated secretion of  $\text{PGD}_2$ ,  $\text{PGE}_2$  and thromboxane  $\text{B}_2$  occurred during the evening and night hours. Of note, the painful bone conditions of osteoid osteoma (31) and osteolytic metastatic cancer (32) have also shown elevations in PG levels. In addition, it has been suggested that  $\text{PGD}_2$  and  $\text{PGE}_2$  accelerate the recovery process of cutaneous barrier disruption caused by mechanical scratching, via specific prostanoid DP1, EP3 and EP4 receptors (33). We postulate that the circadian rhythm of PG is disrupted in patients with exacerbations of itch at night.

Nocturnal pruritus may also have a psychological component. Exacerbations of pain have been attributed to the lack of external stimuli (34) and boredom (35), both of which are normally increased during the evening hours and before going to sleep. This explanation could also possibly account for the increase in itch experienced at night. Furthermore, the lack of distraction at night allows for increased ruminations and anxiety, which in turns leads to mental stress. Both mental stress and depression have been demonstrated to enhance pruritus perception (36).

## TREATMENT OPTIONS (Table II)

Although there are several types of remedies available – both over-the-counter and prescription – that may relieve non-specific pruritus, the paucity of treatments for nocturnal itch is astonishing. Specific treatment options are clearly needed given the profound impact nocturnal

Table I. Summary of possible mechanisms for nocturnal pruritus

Decreased epidermal barrier function
Increased skin temperature
Normal circadian rhythms
• Corticosteroids
• Autonomic nervous system
Disruption of circadian rhythms
• Opioids
• Cytokines
• Prostaglandin
Lack of external stimuli and distraction

Table II. Summary of treatment options for nocturnal pruritus

Emollients and moisturizers
Emollients and moisturizers with low pH
Topical calcineurin inhibitors
Topical corticosteroids
Sedating antihistamines
Mirtazapine
Butorphanol
Melatonin
Bright light therapy

pruritus has upon sleep and quality of life. Oral antihistamines have traditionally been the cornerstone of pruritus treatment. Although sedating antihistamines may have a role in treating nocturnal itch through their soporific effects, there is little objective evidence that non-sedating antihistamines relieve itch (16, 37, 38). Sleeping pills are also sometimes prescribed in order to reduce nocturnal pruritus, but there have been few studies investigating their efficacy. Interestingly, Ebata et al. (39) investigated the effects of one of the most widely used benzodiazepines, nitrazepam, on nocturnal scratching. Although direct observation revealed no change in the total time scratching, patients taking nitrazepam reported improved sleep and decreased scratching.

Mirtazapine has been shown to reduce nocturnal itch in patients with chronic pruritus (40). This antidepressant acts as an antagonist at noradrenergic  $\alpha_2$ -receptors and 5-HT<sub>2</sub> and 5-HT<sub>3</sub> serotonin receptors, increasing central noradrenergic and serotonergic neurotransmission. It also has a sedative effect through its H1-antihistamine properties. Which of these mechanisms mediates the anti-pruritic properties of mirtazapine is still unclear, but it has been suggested that the  $\alpha_2$ -adrenergic antagonism acts centrally to reduce pruritus (40). Given the possible role of opioids in nocturnal pruritus, butorphanol may also have a beneficial therapeutic effect. This  $\kappa$ -opioid receptor agonist and  $\mu$ -receptor antagonist has already been shown to be effective in the treatment of chronic intractable itch (41). The fact this drug also has sedative properties makes it potentially very useful in the treatment of nocturnal pruritus and a large prospective study would be of great interest.

Given that TEWL is associated with itch intensity in patients with atopic dermatitis and that it increases at night, moisturizers and emollients may have a central role to play in treating nocturnal pruritus. These products not only moisturize the skin, but also produce an occlusive film that limits water evaporation. Moisturizers with a low pH may be especially useful in optimizing the skin barrier function through their maintenance of the normal acidic pH of the skin surface (16). In addition, low pH moisturizers may be of further benefit through their reduction of tryptase activity, which is known to activate proteinase-activated receptor-2 (PAR-2) in skin nerve fibers (42). The topical calcineurin inhibitors, tacrolimus and pimecrolimus, also have a possible role in treating nocturnal pruritus. Tacrolimus has been shown to relieve the pruritus of atopic dermatitis, although it has no direct anti-pruritic action (43). Furthermore, treatment with pimecrolimus cream demonstrated skin improvement that correlated with improved sleep in children with atopic dermatitis (44).

As mentioned above, nocturnal itch may be related to the circadian rhythm of mediators and the possible disruption of such patterns. The suprachiasmatic nucleus, located in the hypothalamus just above the optic chiasm,

makes up the human pacemaker known as the circadian or biological clock (45). It receives essential peripheral input from both light and melatonin (46). As a result, bright light and melatonin have been used separately and together in the treatment of circadian rhythm disorders such as advanced and delayed sleep phase syndromes, jet lag, shift-work and seasonal affective disorder (47). Bright light therapy and melatonin may thus have a role to play in the treatment of nocturnal pruritus. Indeed, bright light therapy directed towards the eyes has been successfully used to treat the severe itch of cholestasis (48). In addition, controlled-release melatonin has been shown to improve sleep quality in the elderly (49).

## CONCLUSION

In summary, nocturnal pruritus is a significant problem in many systemic and cutaneous diseases. It clearly has a profound impact upon sleep and quality of life, and is often overlooked by many clinicians. At present, the underlying mechanisms responsible for these exacerbations of pruritus at night are unclear. We propose that nocturnal itch is related to the circadian rhythm of various possible mediators as well as skin temperature and barrier function. The paucity of specific treatment options is also of concern and there is a huge need for this area to be addressed in the future.

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