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Reframing Nocturnal Itch as a Distinct Psychoneurodermatologic Syndrome

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Abstract

Nocturnal itch, historically viewed as a secondary symptom of systemic or dermatologic disease, increasingly appears to represent a distinct clinical entity shaped by complex neurophysiological, circadian, and psychosocial dynamics. Growing evidence suggests that nighttime pruritus is not simply an extension of primary skin pathology but may be initiated or intensified by emotional stress, maladaptive cognitive processes, and disruption of the body's natural sleep-wake rhythms—particularly involving dysregulation of the hypothalamic-pituitary-adrenal axis and heightened sympathetic activation in the hours preceding sleep. In many patients, especially those with anxiety, depression, post-traumatic stress, or insomnia, nocturnal itch may function as a somatic channel for unprocessed psychological distress or pre-sleep hyperarousal. The temporal profile, severity, and resistance to conventional antipruritic treatments with nighttime itch often diverge significantly from those of daytime itch, pointing to distinct underlying mechanisms. Recognizing nocturnal itch as a psychoneurodermatologic syndrome would allow for a more precise diagnostic framework, including stratification based on psychosocial risk factors and neurobehavioral phenotypes. Management strategies could then move beyond topical and systemic agents to include behavioral sleep medicine, mindfulness-based cognitive therapy, trauma-informed care, and neuromodulation. Redefining nocturnal itch in this way may improve outcomes for a frequently misunderstood and profoundly distressing condition at the intersection of dermatology, psychiatry, and sleep medicine.

Keywords: *Nocturnal Itch, Pruritus, Circadian Rhythm, HPA Axis, Sleep Disturbance, Psychoneurodermatology*

Key Summary Points

- *Nocturnal itch may represent a distinct clinical syndrome rather than a secondary symptom.*
- *Psychosocial and neuroendocrine factors, including stress and circadian dysregulation, play key roles.*
- *Current treatments are insufficient when underlying psychosocial contributors are unaddressed.*

1. Introduction

Pruritus, or itch, is an unpleasant sensation that promotes the urge to scratch and can arise from a vast range of causes, including dermatologic, systemic, paraneoplastic, neuropathic, and psychogenic etiologies [1,2].

Systemic conditions associated with pruritus include chronic kidney disease, hepatobiliary disorders, rheumatologic conditions such as systemic sclerosis, and hematologic conditions like polycythemia vera [2]. Common dermatologic origins include inflammatory skin conditions such as atopic dermatitis and psoriasis, while neuropathic causes include postherpetic neuralgia, notalgia paresthetica, and brachioradial pruritus [2]. The pathophysiology of itch is complex, involving interactions between the nervous and immune systems and mediated through both histaminergic and non-

histaminergic pathways [3]. Given the diverse range of potential etiologies, pruritus presents a diagnostic and management challenge. A deeper understanding of the underlying mechanisms of itch is essential for developing targeted treatment strategies, especially considering that itch can disrupt sleep and lead to a cascade of negative health consequences and a decreased quality of life.

Chronic pruritus, defined as itch lasting six weeks or longer, may include symptoms that intensify at night. Traditionally, nocturnal itch has been considered a secondary manifestation of underlying conditions including atopic dermatitis, psoriasis, urticaria, prurigo nodularis [4], as well as infestations, insect bites, and xerosis [5]. The broad range of available treatments for pruritus – ranging from antihistamines and antidepressants to GABAergic agents, opioid receptor modulators, melatonin, and nonpharmacologic interventions like sleep hygiene [4] – often reflects the lack of a consistently effective therapy.

Despite these options, nocturnal pruritus remains difficult to manage, creating frustration for both patients and physicians. In this paper we seek to reframe nocturnal pruritus not simply as a secondary symptom, but as a distinct primary condition of its own. We explore the complex interplay between circadian rhythms, neuroendocrine dysregulation, neural sensitization, sleep arousal, and psychiatric correlations. Building on this understanding, we outline current treatment approaches and present an integrated diagnostic and therapeutic framework through a psychoneurodermatologic lens – one that acknowledges and integrates the psychological, neurological, and dermatological components of nocturnal itch.

2. REVIEW

2.1. Pathophysiology of Nocturnal Itch

2.1.1. Circadian Modulation of Itch

Circadian rhythms are important for regulating normal physiologic processes, including those of the skin. Nocturnal itch follows a circadian pattern, likely associated with the physiological changes that occur in the skin over a 24-hour cycle. For instance, skin barrier function decreases during the night, as evidenced by increased transepidermal water loss (TEWL), which allows pruritogens to enter the skin [4]. Studies in children with atopic dermatitis have suggested that higher TEWL is positively correlated with increased severity of pruritus, decreased quality of life, and increased disease severity [6]. Strategies aimed at preserving skin barrier function and reducing TEWL may help alleviate itch symptoms. The skin also has a role in maintaining body temperature by thermoregulation. At night, peripheral vasodilation enables the skin to dissipate heat, allowing core body temperature to decrease, a process that may increase the intensity of itch sensations [7]. Furthermore, chronic itch may alter nerve activity and disrupt sleep by affecting neurochemical signaling and activating neural pathways associated with arousal [8]. These factors that affect the skin, many of which are regulated by circadian rhythms, suggest that nocturnal itch may not be a secondary symptom but a complex, physiologically driven condition that requires further research focus.

Circadian rhythms also regulate the release of hormones – melatonin and cortisol, as well as the neurotransmitter histamine, all of which influence sleep. Melatonin, a hormone synthesized from the tryptophan-serotonin biosynthetic pathway [9], is primarily secreted by the pineal gland, and serves as a prominent regulator of the sleep-wake cycle. Melatonin secretion increases at night and is suppressed during the day in response to light exposure [9]. Erdem et al. investigated melatonin levels in adults with nocturnal itch by measuring 6-sulphatoxymelatonin in urine samples and found decreased melatonin levels compared to healthy controls ($p=0.007$) [10], suggesting that a decrease in melatonin may contribute to the pathophysiology of nocturnal itch. Exposure to light during abnormal times, such as from night shift work or artificial light sources from phones, televisions, and computers, can disrupt melatonin secretion and circadian rhythms [9]. Given this connection, it is important to ask patients experiencing nocturnal itch about their lifestyle, work schedule, sleep habits, and other factors that could contribute to circadian dysregulation or alterations in melatonin secretion.

In addition to its role in regulating the sleep-wake cycle, melatonin also has a role in the skin. Research has demonstrated that melatonin and its metabolites are present in various skin cells, including keratinocytes, melanocytes, macrophages, fibroblasts, and mast cells [11] indicating that melatonin may contribute to processes in the skin. Cutaneous melatonin production is influenced by circadian rhythms and has been shown to support skin functions, including increasing skin thickness and sebum secretion and improving skin barrier function [11], which could potentially act to offset the

physiologic process of increased TEWL at night that reduces skin barrier function. Melatonin also acts as an antioxidant in the skin by scavenging free radicals and reactive nitrogen species [11]. It exhibits anti-inflammatory properties by inhibiting the production of pro-inflammatory genes from the nuclear factor-kappa B pathway, modulating the immune system, and demonstrating anti-cancer properties [11]. The therapeutic potential of melatonin's antioxidant and anti-inflammatory effects has been explored in which varying concentrations of topical melatonin (0.5%, 2.5%, 12.5%) were applied to the skin of healthy volunteers who were then exposed to natural sunlight [12]. Participants treated with 12.5% topical melatonin had significant reduction in erythema ($p=0.001$), suggesting that melatonin may exert antioxidant and anti-inflammatory properties when applied topically at higher concentrations [12]. These findings highlight the multifaceted role of melatonin in the skin and the need for further research into its influence and therapeutic potential in nocturnal itch.

Cortisol, a hormone synthesized from cholesterol in the zona fasciculata of the adrenal cortex, is regulated by the hypothalamic-pituitary-adrenal (HPA) axis and plays an important role in regulating the body's stress response [13]. Its secretion follows a circadian rhythm, with levels waning in the evening and rising overnight to peak in the morning. It has been postulated that lower evening cortisol levels may reduce the body's anti-inflammatory effects, making the skin prone to inflammation [4]. Additionally, psychological and physiological stressors such as sleep disturbances can disrupt cortisol patterns. Zhang et al. found that individuals with chronic insomnia maintained high levels of HPA axis hormones throughout the night [14]. Similarly, a study analyzing sleep deprivation in resident physicians found that the residents had reduced morning cortisol levels ($p<0.001$), and the cortisol levels after a 26-hour shift were elevated compared to baseline levels ($p<0.001$), suggesting a dysregulation of cortisol secretion [15]. These findings propose that disrupted sleep may lead to circadian dysfunction of cortisol, which in turn could contribute to skin conditions such as nocturnal itch.

Histamine is a monoamine neurotransmitter that has a variety of effects on cells of the body depending on the subtype of histamine receptor present – H1R, H2R, H3R, or H4R [16]. While it is well known for its role in allergic inflammatory responses – being released from mast cells in the skin and mediating itch [7] – histamine also functions in the immune, nervous, gastrointestinal, and integumentary systems. In the central nervous system, histamine plays a large role in promoting wakefulness and is produced by neurons in the tuberomammillary nucleus of the posterior hypothalamus, where it is packaged into vesicles and released into the synaptic cleft to bind to its receptors [17]. Additionally, histamine helps to regulate neuroinflammation and has been implicated in neurodegenerative diseases including Parkinson's disease and Alzheimer's disease by modulating glial cell function [18].

In the skin, elevated histamine levels have been observed in patients with atopic dermatitis and psoriasis. Antagonists targeting the H4 receptor may have anti-itch and anti-inflammatory effects, suggesting potential therapeutic options [19]. Further research is needed to understand the role of histamine dysregulation in nocturnal itch, both peripherally in the skin and centrally in the brain.

Given their roles in circadian regulation, alterations in melatonin, cortisol, and histamine levels may impair skin homeostasis and contribute to nocturnal itch. Chronotherapy, the administration of treatments that align with the physiologic circadian rhythms, may be a potential therapeutic option when endogenous levels are decreased during expected peak times [7]. Other potential interventions include exogenous supplementation and the use of medications that target the receptors, such as H4R antagonists to reduce cutaneous inflammation. Further research is needed to understand the circadian dynamics of these molecules in relation to nocturnal itch and to guide the development of targeted therapies.

2.1.2. Neuroendocrine Dysregulation

Sleep deprivation and chronic stress can activate neuroendocrine pathways, particularly the autonomic nervous system and the hypothalamic-pituitary-adrenal axis, leading to increased inflammation and adverse effects on the skin. The HPA axis maintains homeostasis through a negative feedback loop that regulates the release of glucocorticoids in response to stress. However, chronic stress can impair this feedback mechanism, resulting in desensitization of the HPA axis, cortisol resistance, and inflammation in the central nervous system [20]. During prolonged stress, the HPA axis and sympathetic nervous system promote the production of pro-inflammatory immune molecules including IL-1, IL-6, and TNF [20]. In

the context of itch, inflammatory cytokines include Th2 cytokines IL-4, IL-13, and IL-31, which signal through the Janus kinase pathway, a potential target for therapies [3]. Additionally, neuropeptides such as substance P and calcitonin gene-regulating protein, as well opioids, proteases, and various enzymes also contribute to itch perception and amplification [3]. Substance P, a proinflammatory neuropeptide, was found to act on Mas-related G protein-coupled receptors on sensory neurons to induce itch, presenting another potential therapeutic target for itch [21]. Collectively, neuroendocrine dysregulation – including dysregulation of the HPA axis, autonomic imbalance, and elevated pro-inflammatory cytokine and neuropeptide activity – may lower the threshold for itch and contribute to nocturnal itch.

2.1.3. Central Sensitization and Sleep Arousal

The sleep cycle is divided into non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, with NREM comprising three stages – N1, N2, and N3. In the lighter NREM stage, N1, decreased inhibition of sensory stimuli allows for increased itch perception, while in the deeper N3 stage, reduced sensory processing may allow for decreased perception of nocturnal itch [4]. The itch sensation begins at the dermal-epidermal junction, where nerve endings known as pruriceptors detect stimuli and transmit the signals through peripheral nerves to the spinal cord and brain [22]. Two pathways primarily carry these itch signals to the brain: the spinothalamic tract, which carries signals to the thalamus and then projects to other regions of the brain including the somatosensory cortex, and the spinoparabrachial tract, which projects to the parabrachial nuclei of the pons and relays the information to the amygdala and hypothalamus [22].

Understanding how sensory processing fluctuates across sleep stages and the neural pathways involved with pruritus provides further insight into the underlying mechanisms of nocturnal itch.

Itch perception is also influenced by cognition. During the day, executive functions of the frontal lobe facilitate conscious decision making, which may suppress itch by diverting attention away from itch sensations [8]. At night, reduced inhibitory control from the executive frontal lobe may reduce suppression of itch-related sensations [8], thereby amplifying the itch sensations. Additionally, chronic itch may result from changes in the nervous system called neural sensitization, a condition in which the nervous system becomes hypersensitive to itch-inducing stimuli [23]. This can occur in both the peripheral nervous system (PNS) and the central nervous system (CNS). In the PNS, the nerves may become hypersensitive to pruritogens, often influenced by itch-inducing cytokines and neuropeptides including substance P, which leads to amplification of the itch sensation [23]. In the CNS, there may be over activity of the pathways that send itch signals to the brain or dysfunction in the inhibitory pathways that suppress itch sensation [23]. The cognitive modulation of itch and potential neural sensitivities in the PNS and CNS helps to explain the amplification of itch at night and the integration of the brain, nervous system, and skin in itch perception.

Sleep disturbance carries a range of negative consequences, including increased daytime sleepiness, fatigue, poor concentration, higher risk for injuries and accidents, and reduced quality of life [24]. Disrupted sleep also impacts the body at the cellular level, disrupting the body's overall homeostasis. Sleep deprivation is associated with depression, anxiety, obesity, and hypertension, and these comorbidities increase the risk for heart attack and stroke [24].

Electroencephalogram spectral analyses in patients with chronic insomnia has demonstrated increased beta band power, a neurophysiological biomarker of cortical hyperarousal, during both wakefulness and sleep, suggesting a persistent state of hyperarousal in the brain [25]. The amplification of itch at night and the adverse health effects of sleep disruption highlight the need to investigate the physiological and psychological implications of nocturnal itch.

2.2. Psychosocial and Psychiatric Correlates of Nocturnal Itch

Nocturnal itch is becoming an increasingly recognized multifactorial condition with many psychosocial and psychiatric correlates. Although further studies are needed, it is believed that nocturnal itch is relatively common among patients with depression, anxiety, and post-traumatic stress disorder (PTSD). Although the prevalence of nocturnal itch has not been well established, recent studies have found that nocturnal itch is present in nearly 90% of the chronic itch population [26]. While data specifically quantifying the prevalence of psychiatric comorbidities in patients with nocturnal itch are limited, the high prevalence overlap between nocturnal itch and generalized chronic itch suggests that similar psychiatric comorbidity patterns likely apply. Studies have

consistently demonstrated strong correlations between chronic itch and depression. One study found that 14.1% of patients with chronic itch experienced clinical depression [27]. Regarding anxiety, the rates are slightly higher. A recent prospective cross-sectional study found the prevalence of anxiety in patients with chronic itch was closer to 17% [28]. Although there is a lack of current research evaluating rates of PTSD and chronic/nocturnal itch, it is believed that, for similar reasons as anxiety and depression, the rates of chronic and nocturnal itch are higher in individuals with PTSD compared to the general population. While most studies emphasize the psychological burden caused by chronic itch, fewer have explored the bidirectional relationship, where primary psychiatric conditions may also precipitate or exacerbate itch.

2.3. Cognitive and Somatic Manifestations

In addition to the clinical overlap with various psychiatric conditions, maladaptive cognitive patterns may play a significant role in the intensification of nocturnal itch. In many patients, nocturnal itch may serve as a physical manifestation of unprocessed psychological distress or pre-sleep hyperarousal. Psychological factors such as stress, anxiety, pre-sleep worry, and catastrophizing have been linked to the exacerbation of itchiness [29]. The exacerbation of itchiness, in turn, can potentially worsen mood symptoms. Rumination, defined as a tendency for repetitive thinking on negative feelings and distressing thoughts, has been thought to lead to increased nocturnal itch. In the evening, when there is a relative lack of external stimuli, it allows for an increase in rumination due to reduced distractions. These cognitive rumination patterns can amplify the immediate relief from pruritic stimuli, therefore perpetuating a cycle of discomfort and sleeplessness. Functional itch disorders like nocturnal pruritus may serve as a somatic outlet for unprocessed psychological distress. This is reinforced by the concept that these types of itch disorders not only consist of negative features, but also positive features of anxiety, worry, and stress [30]. This phenomenon is commonly categorized as somatization, demonstrating how internal emotional states can manifest as bodily symptoms like pruritus. Due to this, the inclusion of psychological therapies could prove especially beneficial in cases resistant to antipruritic treatments.

2.4. Sleep Disturbance and Mental Health

There is a well-established bidirectional relationship between sleep disturbances and psychiatric health. This concept plays a central role in nocturnal itch. Disrupted sleep exacerbates mood symptoms, which, as discussed above, can heighten the sensitivity to pruritic stimuli, especially at night. Studies on sleep disturbances in individuals with chronic pruritic symptoms have been found in numerous studies of different diseases. Itch intensity has been shown to negatively correlate with sleep and quality of life in various conditions [31, 32, 33]. Although there is a lack of studies on nocturnal itch, it would seem reasonable that individuals with nocturnal itch have a similar disruption in sleep, quality of life, feelings of stigmatization, and mood symptoms. In addition to this, sleep deprivation reduces emotional coping capacity, which in turn may intensify maladaptive cognitive responses [34].

These intensified maladaptive responses can cause an increase in somatization and therefore pruritus. By addressing sleep as a component of this condition, clinicians can develop holistic treatments for nocturnal itch.

2.5. Clinical Phenotyping: Defining Subtypes of Nocturnal Itch

Given the numerous factors contributing to presentation, nocturnal itch may be best understood through a clinical phenotyping model that distinguishes it from daytime itch. Patients with nocturnal itch often report an increased severity of their symptoms in the late evening and greater interference with sleep quality and quantity [4]. Based on the discussions throughout this paper, we propose three distinct subtypes for nocturnal itch: psychogenic-dominant, circadian-disrupted, and mixed. The psychogenic subtype is characterized by nocturnal itch, predominantly influenced by psychological stress, cognitive hyperarousal, and mood symptoms as primary influences of itch.

The circadian-disrupted subtype is characterized by disrupted melatonin secretion, dysregulated cortisol rhythms, increased histamine secretion, or other biologic dysfunctions that dysregulate the hypothalamic-pituitary-adrenal axis, and in turn, circadian rhythm. The last proposed mixed subtype includes patients with psychological and biological contributors to nocturnal itch. Implementing this clinical-phenotyping framework into clinical settings may help create more effective treatments and improve patient outcomes where nocturnal itch has been historically misclassified and undertreated.

Phenotypic classification could serve as a foundation for targeted therapies and personalized care models.

2.6. Limitations of Current Treatment Approaches

Despite recent advancements in dermatologic and systemic therapies, the management of nocturnal itch still has significant limitations. One primary challenge is the insufficient recognition of nocturnal itch as a distinct clinical entity, rather than merely a secondary manifestation of underlying dermatologic or systemic conditions. Consequently, current treatment protocols tend to focus predominantly on targeting primary skin pathologies with topical corticosteroids, antihistamines, or biologic agents. This approach often fails to address the unique neuropsychological and circadian factors that underpin nocturnal pruritus, leading to suboptimal therapeutic outcomes. As a result, these agents frequently do not adequately alleviate nighttime symptoms in affected patients.

Furthermore, pharmacologic interventions often demonstrate inadequate responses in managing nocturnal itch. The central nervous system plays a crucial role in modulating this condition, yet it is frequently overlooked as a therapeutic target. Central pathways involved in nocturnal itch are modulated by brain mechanisms, especially in chronic cases where habitual scratching may develop [35]. While topical steroids and antihistamines primarily modulate peripheral inflammation and allergic responses, they do not sufficiently target neurophysiological pathways, such as dysregulation of the HPA axis or sympathetic hyperactivation. Although biologics show promise in certain dermatological conditions, they are often not designed to address the psychosocial and neurocircuitry components of nocturnal itch, resulting in persistent symptoms despite their use. Another significant limitation is the underutilization of non-pharmacologic interventions, including behavioral sleep strategies, cognitive-behavioral therapy (CBT), mindfulness-based approaches, and trauma-informed care. These modalities have demonstrated efficacy in managing related neuropsychiatric conditions and sleep disturbances, particularly in patients with comorbid anxiety, depression, or trauma-related disorders. Stress, for instance, is known to alter thermoregulation and hemodynamic balance, leading to elevated histamine levels. Depression can lower the central itch threshold by increasing endogenous opiates and disrupting the balance between μ- and κ-opioid receptor pathways [4]. Despite this, psychoneurobiological treatments remain underemphasized in clinical practice. Supporting this, a crossover trial involving children with atopic dermatitis found that melatonin (3 mg at bedtime) significantly reduced sleep-onset latency compared to placebo [36]. Additionally, habitual reversal therapy as an adjunct to corticosteroids showed significant improvements in the objective Severity Scoring of Atopic Dermatitis (SCORAD) index [37]. Improving sleep quality and addressing psychological factors contributing to nocturnal itch are essential steps toward enhancing patients' quality of life. The lack of integrated psychosocial assessment and intervention perpetuates a cycle of patient dissatisfaction and suboptimal treatment outcomes.

Treatment gaps often lead to patient frustration. Many individuals with nocturnal itch report persistent sleep disturbances, daytime fatigue, mood disturbances, and social withdrawal, all of which significantly diminish quality of life. Nocturnal itch is frequently associated with physiological stress, which can further exacerbate symptoms [35]. The failure of conventional therapies to provide comprehensive relief fosters feelings of helplessness and may reduce treatment adherence. Recognizing nocturnal itch as a psychoneurodermatologic syndrome is crucial for developing more effective, personalized management strategies that encompass both dermatological and psychosocial domains.

2.7. Proposed Diagnostic and Therapeutic Framework

Though the precise pathophysiology of nocturnal itch (NI) remains multifaceted and ambiguous, clinicians and their patients are unequivocally aware of its deleterious effects on one’s quality of life (QoL). Indeed, patients with NI are more likely to suffer from anxiety, depression, suicidal ideation, insomnia, and impaired productivity. Unfortunately, this exhausting presentation is often bi-directional, as the severity of NI positively correlates with stress, which further exacerbates itch [38]. Because attention to itch is influenced by such psychological factors, it is imperative we reassess clinical criteria and screening tools. Currently, the clinical manifestations of NI are measured using the visual analogue scale (VAS), numerical rating scale (NRS), and subjective questionnaires [39].

Though useful in assessing and treating visible excoriations, these guidelines are often

unidimensional, and therefore do not fully capture the importance of the aforementioned psychological factors. Given that the degree of depression has been shown to correlate with the severity of pruritus [40], integrated treatment plans from dermatologists, psychiatrists, and sleep specialists would be exceptionally useful in combating this condition.

Usage of more wholistic screening tools such as the Pittsburgh Sleep Quality Index (PSQI) questionnaire, Insomnia Severity Index (ISI), Generalized Anxiety Disorder (GAD)-7 Scale, and the Patient Health Questionnaire (PHQ)-9 can significantly aid in the diagnosis and management of NI. The PSQI and ISI assess self-reported sleep quality and effects of sleep disturbance on QoL, respectively [41]. Patient responses are tallied numerically, with higher scores indicating more severe or distressing symptoms. Similarly, the GAD-7 and PHQ-9 are self-reported questionnaires that assess the severity of anxiety and depression. While these measures can be used for a myriad of sleep and psychological disorders, they are especially insightful for the assessment of NI when used in conjunction. When examining the relationship between pruritus and psychological wellbeing, individuals with daily pruritus had over 3-fold risk of GAD, even with GAD scores in the moderate range [42]. These findings indicate the pivotal role sleep quality plays in our mental and emotional wellbeing, and strongly signals the need for more psychological diagnosing criteria. In a study examining the link between stress and atopic dermatitis, results suggested that depression was a predictor of pruritus, as symptoms proved to be more severe in this patient population [43]. To halt disease progression and treat patients effectively, clinicians should strongly consider treating underlying psychological disorders alongside their dermatological manifestations.

Randomized controlled trials specifically evaluating therapies for nocturnal itch are currently lacking. However, an integrated treatment model that targets the multifactorial contributors to nighttime pruritus may offer more effective relief. Systemic agents remain the mainstay of treatment, with first-generation antihistamines such as hydroxyzine and diphenhydramine commonly used due to their ability to cross the blood-brain barrier and cause drowsiness, thereby improving sleep continuity [4]. Hydroxyzine may be particularly beneficial, as it not only causes sedation but also blocks serotonin receptors to reduce anxiety, a common contributor to sleep disturbance [4]. Other systemic agents shown to alleviate nocturnal itch include gamma-aminobutyric acid (GABA) agonists such as gabapentin and pregabalin, which are also helpful due to their sedative properties [8]. Mirtazapine is another agent frequently recommended as first-line therapy for nocturnal itch given its sedative and anxiolytic effects, and it may be used synergistically with GABA agonists [8]. Other antidepressants such as doxepin, amitriptyline, and paroxetine have also shown efficacy for nocturnal itch [4]. Therapies used for chronic pruritus can also improve nocturnal itch. For example, biologic agents have been shown to reduce nighttime pruritus in patients with inflammatory conditions such as psoriasis and atopic dermatitis [4].

Topical agents can provide additional benefits. Bedtime application of topical corticosteroids can help control inflammatory flares and has been shown to reduce nocturnal pruritus and associated sleep disturbance in inflammatory dermatoses [4]. In addition, topical anesthetics including capsaicin, pramoxine, and lidocaine-prilocaine mixtures have shown benefit in chronic pruritus and neuropathic itch by reducing levels of the pruritogen substance P [44]. Overall, various topical and systemic pharmacologic agents can be used to manage nocturnal itch, though they warrant additional study.

Pharmacologic agents may be insufficient to address nocturnal itch, particularly when sleep disruption is a prominent feature. Behavioral sleep medicine interventions offer an accessible adjunct that can be readily integrated into patient care. Sleep hygiene practices, such as maintaining a dark sleep environment and minimizing blue light exposure before bed are recommended to support uninterrupted sleep [4].

Bathing routines should also be adjusted, as warm showers or baths before bedtime for as little as ten minutes have been shown to improve sleep [45]. In addition, applying emollients to damp skin at bedtime can improve epidermal barrier function and may help reduce nocturnal itch, similar to their role in managing chronic pruritus [4]. Screening for insomnia is also important, as patients with comorbid insomnia may benefit from cognitive-behavioral therapy for insomnia (CBT-I), a structured approach that includes sleep restriction, stimulus control, and cognitive restructuring [46]. While melatonin is used for circadian rhythm disturbances, evidence for its effectiveness in treating insomnia is mixed, and its use should generally be limited

[46]. In contrast, CBT-I techniques may be valuable in addressing sleep habits that contribute to nighttime wakefulness and scratching.

Addressing the mental health and trauma history of patients with nocturnal itch is another crucial part of an integrated treatment model. Cognitive behavioral therapy, which combines habit reversal training, arousal reduction, and cognitive techniques, has demonstrated efficacy in managing chronic itch [47]. These strategies work by targeting the psychological and behavioral patterns that perpetuate the itch-scratch cycle, and they may be adapted to treat the nighttime exacerbations in nocturnal itch. In addition, relaxation-based trainings such as progressive muscle relaxation and mindfulness based stress reduction, which emphasizes nonjudgemental, present-moment awareness, have also been shown to help reduce symptoms and improve quality of life in chronic itch conditions [47]. These interventions may help modulate the stress response, which can be heightened at night and contribute to itch exacerbation. An important contributor to stress is trauma, and nearly 90% of United States adults report exposure to traumatic events [48].

Given this, a trauma-informed care approach is essential, encouraging clinicians to consider the impacts of past trauma while creating a safe, collaborative, and empowering clinical environment [49]. For patients with co-morbid PTSD, trauma-focused psychotherapy may be especially important to address autonomic arousal states that may contribute to nocturnal itch. Furthermore, to address broader psychosocial stressors, family constellation seminars offer a structured space for patients to explore and reframe social stressors [38]. This innovative method has shown promising results in patients with chronic pruritus and may offer additional benefit in those with nocturnal symptoms. Overall, collaboration between dermatologists and mental health professionals is essential to effectively address nocturnal itch.

Adjunctive strategies should also be considered as part of a comprehensive approach to nocturnal itch. Emerging research is exploring noninvasive brain stimulation to modulate itch processing in the central nervous system. For example, transcranial magnetic stimulation (TMS) applied over the somatosensory cortex was found to significantly reduce itch intensity in healthy volunteers [50], suggesting the excitability of itch pathways in the brain can be altered externally. While still experimental, neuromodulation holds promise for patients with refractory itch who do not respond to other treatments. Narrowband ultraviolet B phototherapy is another adjunctive option with demonstrated benefit in patients with chronic pruritus [4]. Additionally, blue light therapy has shown potential in small studies, improving both itch severity and sleep quality in patients with atopic dermatitis [51]. Although additional research is needed, these findings suggest potential new avenues for treatment.

3. Limitations And Future Directions

Despite the growing recognition of nocturnal itch as a potential psychoneurodermatologic syndrome, significant limitations persist within the current body of literature. A primary limitation is the absence of standardized diagnostic criteria that can reliably distinguish nocturnal itch as an independent condition from chronic pruritus or skin disorders that worsen at night. Most existing studies have been conducted within disease-specific contexts, particularly atopic dermatitis and psoriasis, constraining external validity. The prevalence of nocturnal itch as an independent clinical phenomenon remains unknown, and its associated psychosocial burden has not been adequately quantified in population-based cohorts. Future research should prioritize the development of a validated diagnostic framework that incorporates objective assessments of circadian dysregulation, neuropsychiatric comorbidities, and sleep quality metrics.

In parallel, large-scale epidemiologic studies employing such criteria are warranted to define prevalence, demographic variability, and prognostic implications. Establishing nocturnal itch as a distinct nosologic entity through standardized classification would enable more accurate case identification, enhance clinical trial enrollment, and facilitate its inclusion in dermatologic and psychiatric diagnostic manuals.

Mechanistic understanding of nocturnal itch is similarly underdeveloped, particularly in relation to the neuroendocrine and central neural processes hypothesized to drive its pathophysiology. While preliminary data implicate alterations in melatonin secretion, HPA axis dysregulation, and heightened sympathetic tone, few studies have directly assessed these variables in nocturnal itch cohorts using objective biomarkers. Rigorous translational investigations employing salivary or plasma

hormone assays (e.g., cortisol, melatonin, histamine) across circadian phases are necessary to characterize the temporal dynamics of these pathways. Functional neuroimaging studies, such as resting-state fMRI or positron emission tomography (PET), may help delineate the neural circuitry implicated in itch perception, cognitive-emotional regulation, and pre-sleep hyperarousal.

Furthermore, the roles of central sensitization and cortical excitability that are well-described in chronic pain syndromes remain speculative in itch and should be evaluated using electrophysiological measures (e.g., EEG spectral analysis) and autonomic biomarkers (e.g., heart rate variability). The development of animal models replicating nocturnal-specific pruritic phenotypes under stress or circadian disruption could offer an invaluable platform for mechanistic exploration and preclinical therapeutic screening.

From a therapeutic standpoint, the current literature lacks (RCT) that specifically address the multidimensional nature of nocturnal itch. Existing pharmacologic interventions primarily target cutaneous inflammation or peripheral itch mediators and often fail to address the central, circadian, and psychosocial components that may underlie treatment resistance. Future RCTs should be designed around an integrative treatment model that combines systemic pharmacotherapy with behavioral, psychological, and chronotherapeutic interventions. Trials should incorporate clinical phenotyping, such as stratification into psychogenic-dominant, circadian-disrupted, or mixed subtypes to better personalize treatment regimens and assess differential response rates. In addition, trials should employ comprehensive outcome measures that extend beyond itch intensity to include validated instruments for sleep quality, functional impairment, mood symptoms, and cognitive-affective processing.

Investigating the efficacy of interventions such as cognitive behavioral therapy for insomnia (CBT-I), trauma-informed psychotherapy, neuromodulation (e.g., transcranial magnetic stimulation), and targeted circadian interventions (e.g., timed melatonin, blue light therapy) in trials has the potential to enhance management. A concerted effort to address these research gaps will be instrumental in legitimizing nocturnal itch as a discrete clinical syndrome and improving care for affected patients.

4. Conclusion

Recognizing nocturnal itch as a distinct clinical syndrome requires the development of comprehensive diagnostic criteria that reflect its multifaceted biological, psychological, and circadian underpinnings. The lack of standardized definitions has contributed to diagnostic inconsistency, limited epidemiologic characterization, and misclassification within broader pruritic conditions. Ambiguity surrounding the diagnosis hampers effective clinical management and complicates research efforts by introducing variability into study populations and obscuring response patterns to targeted interventions. Diagnostic algorithms should incorporate both subjective and objective elements, including validated assessments of sleep quality, psychological distress, and biomarkers of circadian disruption such as melatonin, cortisol, and histamine levels. Instruments like the Pittsburgh Sleep Quality Index, Insomnia Severity Index, Generalized Anxiety Disorder Scale, and Patient Health Questionnaire can capture key psychosocial domains, while structured evaluation of symptom timing and intensity can clarify the temporal distinctiveness of nocturnal itch. Delineating neurobehavioral phenotypes such as psychogenic dominant, circadian disrupted, and combined presentations would support the development of personalized therapeutic approaches. Recognizing nocturnal itch as a distinct clinical entity would enable a more nuanced understanding of its multifactorial pathophysiology and facilitate the implementation of tailored, evidence-based care that addresses both the biological and psychosocial dimensions of the condition.

Authorship

All the named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the reliability of this work cited, and have given their approval for this version to be published.

Author Contribution

Kelly Frasier conceived the literature review concept, developed the manuscript outline, and created the abstract. Sarah Beach coordinated author assignments and established project timelines. Sarah Beach, Travis Jackson, Kelly Frasier, Kaylahn Jones, Jacquelyn Berman and

Shivani Ambardekar were all involved in literature search, manuscript writing, and editing.

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