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Psychiatric Sequelae of Chronic Pruritic Dermatoses

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Abstract

This comprehensive review investigates the significant psychological impact and profound psychological comorbidities found in individuals suffering from chronic pruritic dermatoses, including atopic dermatitis, chronic urticaria, and prurigo nodularis. Highlighting the complex, reciprocal relationship between pruritus and psychiatric conditions such as depression, anxiety, and sleep disturbances, this paper elucidates the comprehensive impact of dermatological disorders on the skin in addition to the far-reaching effects on an individual's psychological well-being. By evaluating the efficacy of integrated psychodermatological interventions, including cognitive behavioral therapy, mindfulness practices, pharmacological treatments, and innovative telepsychiatry and digital health solutions, this review aims to lay the foundation for a more holistic approach to treatment of concurrent dermatological and psychiatric conditions. Future research endeavors should delve deeper into the mechanistic foundation of the pruritus-psychiatry interface, the refinement of tailored treatment strategies, and the evaluation of long-term patient outcomes. In doing so, this review seeks to contribute to the optimization of patient care and well-being, underscoring the pivotal role of addressing both dermatological and psychological needs in achieving comprehensive health outcomes.

Keywords

Psychodermatology, Chronic Pruritic Dermatoses, Psychological Comorbidities, Integrated Interventions, Pruritus-Psychiatry Interface

1. Introduction

Pruritus is a common dermatological manifestation of many acute and chronic diseases. It is commonly defined as a sensation that instigates the want to scratch. Common dermatologic causes of chronic pruritus, which is described as an itch lasting six weeks or longer that is often refractory to treatment, include atopic dermatitis (AD), psoriasis, chronic urticaria (CU), and prurigo nodularis (PN) [1] [2]. These chronic pruritic dermatoses are typically self-exacerbating via the constant itch-scratch cycle, whereas the scratching of a pruritic lesion leads to the creation of secondary skin lesions and instigation of further pruritus [3] [4]. Chronic pruritic dermatoses instigate the itch-scratch cycle by triggering a cascade of physiological responses. Initially, the presence of inflammatory mediators and nerve fibers in the skin leads to the sensation of itch. This sensation prompts the individual to scratch, which provides temporary relief by stimulating the release of neurotransmitters like serotonin. However, scratching further damages the skin barrier and exacerbates inflammation, leading to the release of more pruritogenic substances and perpetuating the cycle. Over time, this cycle can result in worsening skin damage, chronic inflammation, and heightened sensations of itchiness, creating a self-perpetuating loop that can be challenging to break without targeted intervention.

Individuals experiencing chronic pruritus may have a significant psychological burden and may experience feelings such as hopelessness from this relentless disease process and adjustment disorder from difficulty coping with the diagnosis of a chronically pruritic condition [3]. Generalized psychological stress, depression, and/or anxiety may arise from experiences ranging from treatment failures to noticeable lesions on the skin [5]. In addition, sleep and quality of life are often diminished due to these pruritic conditions and mood is often subsequently affected [2]. Overall, there are many psychosocial implications for individuals with chronic pruritic dermatoses, thus psychodermatologic interventions are crucial for these patients. Psychodermatological interventions involve integrating psychological and dermatological approaches to address the interplay between mental health factors and skin conditions, aiming to improve both the psychological well-being and dermatological outcomes of patients. Patients with chronic pruritus must be monitored closely by a dermatologist for signs of psychiatric changes. Due to the effects on quality of life, a multidisciplinary approach should be applied in order to treat both dermatologic and psychiatric symptomatology.

2. Discussion

2.1. Psychological Burden and Psychiatric Comorbidities

Approximately 20% of the population has experienced chronic pruritus; when looking at patients diagnosed with a skin dermatosis such as AD, the prevalence of chronic pruritus is closer to 100% [1]. It has also been documented as a frequent complaint of the elderly population and during pregnancy [1]. In children,

chronic pruritus secondary to skin pathology is highly associated with AD. Affecting over one fifth of the population, pruritus is a common symptom that leads patients to seek dermatologic care. Pruritic dermatoses are frequently diagnosed and managed in outpatient dermatology clinics.

Chronic pruritus has been found to be strongly associated with depression, anxiety, suicidality, and sleep disturbance [6]-[8]. The prevalence of comorbid psychiatric diagnoses may be greatly underdiagnosed as patients may not explicitly share their hardships in dealing with their disease [9]. A retrospective chart review by Golpanian *et al.* (2020) showed that 10.9% of patients with chronic pruritus were found to have a comorbid psychiatric diagnosis, the most common being anxiety and depression [9]. Patients presenting with increased stress due to their condition should be referred to a mental health specialist for thorough management alongside dermatologic care [2].

As pruritus becomes more difficult to manage, psychiatric symptoms may worsen in severity. While psychiatric symptoms can be a result of chronic pruritus, many other psychiatric diagnoses can lead to symptoms of pruritus [3]. This bidirectional relationship leads to clinical questioning of which condition presents initially. The interplay of psychiatric symptomology in chronic pruritic dermatoses seems to be a result of the initial dermatologic condition. The relationship between chronic pruritus and psychiatric symptoms demonstrates the need for concomitant psychiatric and dermatologic care. Psychiatric comorbidities are treatable, and a multidisciplinary approach is most beneficial to patients suffering with the burden of their chronic pruritus.

2.2. Dermatological Conditions Associated with Chronic Pruritus

AD, commonly referred to as eczema, is a chronic inflammatory skin disease affecting children and adults worldwide, with an overall lifetime prevalence of 10% [10]. The causes of AD are multifactorial and still under investigation; research has demonstrated an association between environmental influences, genetics, immune system dysregulation, skin barrier disruption, psychological factors, and medications for the development and severity of AD [11] [12]. There is strong evidence demonstrating increased risk for developing and severity of AD with mutations in the filaggrin gene, which encodes a major structural protein in the epidermis contributing to the skin barrier [11] [12]. AD is characterized by increased levels of inflammatory cells in the skin including eosinophils, mast cells, neutrophils, as well as increased IgE levels [12].

Patients with AD are at higher risk of comorbid conditions and infections such as anxiety, depression, suicidality, cardiovascular disease, food and environmental allergies, asthma, allergic rhinitis, ear infections, streptococcal pharyngitis, and urinary tract infections [10] [13]. The cutaneous manifestations of AD include scaly, pruritic, and erythematous plaques which frequently affect the flexural surfaces such as elbows, knees, neck, and wrists [12]. The most prominent symptom of AD is unremitting pruritus. Other notable reported symptoms include dryness, scaling, skin pain, and sleep disturbances [13]. Depending on

the severity of pruritus, chronic excoriation can lead to an itch-scratch cycle that greatly impacts a patient's quality of life and leads to complications such as infection, lichenification, post-inflammatory hyperpigmentation, and scar formation [10]. Therapeutic management of AD is multifaceted and includes strategies to restore skin barrier function and control inflammation through the application of emollients and topical steroids, and the use of systemic immunosuppressants in patients with more severe, unremitting symptoms. In addition to these approaches, newer treatment modalities such as biologic agents targeting specific immune pathways, phototherapy, and adjunctive therapies like wet wrap therapy and bleach baths have shown promising results in the management of atopic dermatitis.

Urticaria, commonly referred to as hives, are cutaneous lesions characterized by erythema, pruritus, and edema [14]. Chronic urticaria (CU) is defined as recurrent urticarial episodes occurring two or more times a week for at least six weeks [15] [16]. The pathogenesis of CU involves autoimmunity with immunoglobulin (Ig)-E autoantibodies directed against auto-allergens or IgG autoantibodies directed against IgE and mast cell receptors [14] [15]. Additionally, research has shown upregulation of the proinflammatory cytokines interleukin (IL)-3 and tumor necrosis factor (TNF)-alpha in the pathogenesis of urticaria [14]. Together, these pathologic alterations lead to the degranulation of mast cells and release of histamine, bradykinin, prostaglandins, leukotrienes, and other inflammatory mediators resulting in vasodilation and increased vascular permeability creating wheals and angioedema [14]. CU wheals generally form raised, round plaques lasting anywhere from 30 minutes to 24 hours and leave behind no lasting mark [16]. Patients most commonly report intense pruritus as the predominant symptom in CU with symptoms worsening at night [16]. Some patients with CU may also experience angioedema and systemic symptoms including joint pain or swelling, headache, fatigue, flushing, and GI distress [14] [16].

CU is more common in females with a female to male ratio of 2:1 and can occur in both children and adults [14]. However, it is more common in adults with episodes typically beginning between the third and fifth decades of life [15]. Individuals with CU have higher rates of autoimmune disorders including thyroiditis, celiac disease, rheumatoid arthritis, systemic lupus erythematosus, and Type 1 diabetes mellitus [14]. Known triggers for CU include physical stimuli, psychological stress, and medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and beta-lactams [15]. Due to the known association of comorbid autoimmune conditions, workup often involves diagnosis and treatment of an underlying cause. Nevertheless, the etiology remains unknown in anywhere from 50% - 90% of cases of CU [14] [15]. Firstline treatment of CU revolves around antihistamines, mast cell stabilizers, and short courses of steroids. Treatment modalities for chronic urticaria encompass a range of approaches aimed at alleviating symptoms and preventing recurrence. Additional treatments include leukotriene receptor antagonists, immunomodulatory therapies such as omali-

zumab, and lifestyle modifications to identify and avoid triggers. CU has been shown to negatively impact quality of life and is associated with anxiety, depression, sleep disturbance, and disruption of daily activities and thus it is essential to comprehensively treat this dermatologic condition that can manifest with psychiatric symptomatology [14].

PN is a rare disorder of the skin characterized by intense, chronic pruritus, a self-perpetuating itch-scratch cycle, and the formation of hyperkeratotic papules and nodules [17]. The literature suggests that PN is more common in adulthood with most patients presenting in the fifth and sixth decades of life [18]. The largest study to investigate demographics has shown that African Americans patients are 3.4 times more likely to have PN compared to white patients [19]. While the pathogenesis of PN is still under investigation, the overarching theory revolves around the phenomenon of neuroimmune crosstalk in which pruritogenic molecules serve as an intermediary between immune cells and sensory neurons serving to transmit sensations of itch and stimulate the release of additional itch mediators [17]. On pathohistological exam of PN lesions, there is a mixed inflammatory infiltrate in the dermis along with fibrosis, vascular remodeling, and proliferation of afferent nerves with mast cells and eosinophils in close association to peripheral nerve endings [17]. Furthermore, while the unrelenting itch-scratch cycle visibly leads to excoriation, crusting, and thickening of the skin, there is also evidence to suggest that chronic scratching may itself aggravate the disease process due to findings of increased neuropeptides and neurohyperplasia [18].

The pruritic papules and nodules of PN are hyperkeratotic, can exhibit inflammatory hyperpigmentation, vary in size and color, and are often symmetrically distributed on the extensor surfaces of the extremities and trunk in "scratchable" areas, sparing the upper central back and creating a "butterfly" sign [17] [19] [20]. In perhaps the most detailed analysis of patients with PN to date, Boozalis *et al.* (2019) found that PN is significantly associated with systemic and cardiovascular comorbidities including chronic kidney disease (CKD), chronic hepatitis C, human immunodeficiency virus (HIV), chronic obstructive pulmonary dysfunction (COPD), congestive heart failure (CHF), depression, diabetes, and AD [19]. Additionally, in a study of the association between PN and malignancy, patients with PN were found to be greater than four times more likely to have a diagnosis of malignancy compared to controls with significant associations with carcinoma of the skin, the hematopoietic system, and solid organs [21]. In a nationwide study of the disease burden of PN, Wongvibulsin *et al.* (2021) found that patients with PN have greater disease severity, itch intensity, and dramatic reductions in quality of life compared to patients with other etiologies of chronic pruritus [22]. Qualitative interviews conducted with patients with PN offered valuable insight into their lived experiences with the chronic illness as participants reported a breadth of changes in sleep, feelings, mood, relationships, social life, work, and school [23]. At this time, there is a paucity of effective therapies for PN which further contributes to the heavy disease burden

on patients with PN. Treatments typically involve both topical and systemic therapy and are generally tailored towards the patient's age, comorbidities, and the severity of disease. Common treatments include both topical and intralesional steroids, topical calcineurin inhibitors, calcipotriol ointment, antihistamines, leukotriene inhibitors, phototherapy, and immunosuppressants [18]. Novel treatments for PN, such as select topical Janus kinase (JAK) inhibitors and monoclonal antibodies targeting interleukin-31, show promise in alleviating symptoms and addressing the underlying pathophysiology of the condition.

2.3. Integrated Psychodermatological Interventions

The integration of psychodermatological interventions has emerged as a pivotal approach in the management of chronic pruritic dermatoses, acknowledging the intricate relationship between dermatological conditions and psychological distress. Among these, cognitive behavioral therapy (CBT) has been increasingly recognized for its effectiveness in mitigating the intensity and distress associated with chronic pruritus. By addressing maladaptive thoughts and behaviors related to the itch-scratch cycle, CBT has demonstrated substantial benefits in terms of symptom relief, disease severity reduction, and enhanced quality of life [24]. Studies highlight the role of CBT in enhancing patients' coping strategies, reducing itch-related anxiety, and improving sleep disturbances commonly reported in pruritic conditions [25] [26]. A meta-analysis by Chida *et al.* (2007) further substantiates this, revealing notable decreases in itch intensity and scratching behavior in patients with AD following CBT interventions [27].

Mindfulness-based interventions (MBIs) focus on increasing awareness and acceptance of present-moment experiences, including discomfort and itching. These interventions can help patients break the itch-scratch cycle by fostering a more reflective, rather than reflexive, response to the sensation of itching, thereby decreasing the behavioral escalation of pruritic episodes. Originating from the work of Kabat-Zinn (1982) evaluating patients with chronic pain, MBIs incorporate meditation exercises, yoga, and psycho-education to address physical discomfort [28]. Intriguingly, this research was expanded into ways to explore the impact of MBIs on chronic itch, particularly in psoriasis patients, finding that those who received MBIs with light therapy experienced a faster reduction in symptoms and significant skin improvement compared to those who did not receive MBIs [29]. Furthermore, recent evidence underscores the potential of MBIs to mitigate pruritus severity, diminish levels of anxiety and depression, and enhance the overall quality of life for individuals with chronic pruritic conditions [30] [31]. Despite these encouraging outcomes, the call for further research is evident, emphasizing the need to develop standardized mindfulness practices and evaluate their long-term effectiveness. Such studies should aim to cover a broad spectrum of patient demographics and dermatological conditions characterized by chronic pruritus, paving the way for a more holistic and effective management approach to these complex conditions.

Pharmacological treatment remains fundamental in addressing the physiological aspects of chronic pruritus, offering a robust foundation for symptom management. Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs), demonstrate a pivotal role in mitigating both pruritic sensations and associated psychiatric symptoms through their serotonergic and antihistaminic properties [32]. Additionally, gabapentin and pregabalin, typically prescribed for neuropathic pain, have proven effective in managing pruritic conditions by modulating neural itch pathways [32]. The exploration of novel pharmacological agents, including interleukin (IL)-31, IL-4, IL-13, (natural killer) NK-1 receptor inhibitors, opioids, cannabinoids, Janus kinase (JAK), phosphodiesterase (PDE)-4, and transient receptor potential (TRP) channel blockers, represents a promising frontier in treatment, addressing previously unmet needs in itch pathophysiology and treatment efficacy [33]-[35]. As these pharmacological therapies evolve, a careful balance must be maintained, considering potential side effects and tailoring treatments to individual patient profiles to optimize therapeutic outcomes.

The emergence of telepsychiatry and digital health interventions has revolutionized the accessibility of psychodermatological care, especially in light of the COVID-19 pandemic's unprecedented challenges [36]. These innovative digital platforms facilitate remote delivery of CBT, mindfulness exercises, and patient education, thereby overcoming geographical and logistical barriers to care. Notably, internet-based CBT has been proven to match the efficacy of traditional, in-person therapy for a range of psychiatric and somatic disorders [37]. Furthermore, these digital solutions offer the advantage of monitoring patient symptoms and adherence to treatment in real-time, thereby tailoring a more personalized management plan for chronic conditions. A randomized clinical trial revealed that internet-delivered CBT not only significantly improved symptoms of AD but also achieved remarkable reductions in itch intensity, stress, sleep disturbances, and depression with minimal reliance on therapist resources [25]. The use of digital health technologies for psychodermatological interventions has the potential to substantially broaden the reach of effective psychological care for individuals with pruritic dermatoses. However, the variability in digital literacy and access across different demographic groups underscores the imperative for developing inclusive digital health initiatives to ensure equitable care for all.

2.4. Efficacy and Challenges of Integrated Interventions

Integrated interventions are essential to the treatment and management of chronic pruritic dermatoses and the psychological manifestations that can arise. Steinhoff *et al.* (2012) describes topical treatments, systemic treatments, phototherapy, and psychological intervention as common initial therapies for chronic pruritic dermatoses [38]. Topical treatments are available in the form of emollients, menthol, capsaicin, anesthetics, anti-inflammatory agents, antihistamines,

and tricyclic antidepressants [38]. Systemic treatments include antihistamines, opioid receptor modulators, and neuromodulators [38]. Various UV therapies including ultraviolet (UV)-A, UV-A1, broad-band UV-B, narrow-band UV-B, and psoralen UV demonstrate reduced nerve fiber activity in the epidermis, making this a viable therapy if the chronic pruritus stems from an inflammatory etiology [38]. Current psychological interventions focus on body relaxation, eliminating scratching behavior, and use of cognitive behavioral therapy to reduce the anxiety and depression that may both cause and be caused by pruritus [38].

In recent years, pharmacologic interventions have begun to utilize autoimmune therapies in chronic dermatologic pathologies. Nakashima *et al.* (2022) researched the use of select topical Janus kinase (JAK)-inhibitors including delgocitinib, ruxolitinib, and tofacitinib, and oral JAK-inhibitors including baricitinib, abrocitinib, and upadacitinib in the treatment of chronic AD [39]. According to phase III clinical trials, both topical and oral JAK inhibitors demonstrated significant improvement in pruritus and other skin symptoms through inhibition of abnormal immune activation of T-helper (Th)-2, Th-17, and Th-22 cytokines in the JAK-signal transducer and activator of transcription (STAT) pathway, a pathway that plays a large role in intracellular signaling for cytokines [39]. Another pharmacologic intervention under recent clinical trials is nemolizumab, a monoclonal antibody that targets IL-31, which leads to a greater reduction in pruritus and a decreased severity of skin lesions [40].

Nonpharmacologic interventions are crucial in management of chronic pruritic dermatoses to prevent associated morbidity, including sleep disturbances and suicidal ideations that have presented in both the adult and pediatric populations. The methods of these interventions include changing patient perception of pruritus and altering the itch signaling pathway through the use of meditation, acupuncture, psychotherapy, cryotherapy, and wearing clothing created with bioactive materials to provide anti-itch and anti-inflammatory properties [41]. However, there are several barriers to the use of both pharmacologic and nonpharmacologic interventions in management of chronic pruritic dermatoses. Major barriers to the use of JAK inhibitors can include high medication cost, individual patient variability in drug efficacy, limited research data, and limited approval of both research and use of biologics in the United States. Nonpharmacologic treatment modalities barriers can include potential high treatment cost and lack of both patient and provider knowledge of nonpharmacologic options.

2.5. Future Directions

Future research in psychodermatology should prioritize investigating specific patient demographics and disease severities that present unique challenges in management and treatment outcomes. Targeted studies focusing on vulnerable populations such as children, the elderly, and pregnant individuals can provide valuable insights into the distinct psychological and dermatological needs of these groups. For instance, exploring the prevalence and impact of chronic pru-

ritic dermatoses in pediatric patients with comorbid conditions like atopic dermatitis can inform tailored interventions to improve disease management and quality of life in this demographic. Similarly, investigating the psychological burden and treatment efficacy in pregnant individuals with chronic pruritic dermatoses can shed light on the challenges of managing these conditions during pregnancy and postpartum periods, offering guidance for optimal care delivery and maternal well-being.

Moreover, future research endeavors should analyze the differential effects of disease severity on psychological comorbidities and treatment outcomes. While the association between chronic pruritus and psychiatric symptoms is well-established, understanding how disease severity influences the prevalence and severity of these psychological comorbidities is essential for developing targeted interventions. Longitudinal studies tracking changes in psychiatric symptoms in relation to fluctuations in disease activity and severity can help to further identify the dynamic interplay between dermatological and psychological factors over time. Furthermore, exploring the impact of disease severity on treatment response and adherence can inform personalized treatment approaches tailored to the needs of patients with varying disease severities, ultimately optimizing therapeutic outcomes and patient satisfaction.

In addition to demographic and disease-specific investigations, future research should prioritize evaluating the effectiveness and feasibility of integrated psychodermatological interventions in real-world clinical settings. While cognitive behavioral therapy (CBT), mindfulness-based interventions (MBIs), pharmacological treatments, and digital health solutions show promise in improving patient outcomes, rigorous studies assessing their efficacy, cost-effectiveness, and scalability are warranted. Comparative effectiveness research comparing different intervention modalities and their combinations can guide clinicians in selecting the most appropriate treatment approaches based on individual patient characteristics and preferences. Moreover, exploring the long-term sustainability and patient-reported outcomes of integrated interventions can provide valuable evidence for their integration into routine clinical practice, fostering a holistic and patient-centered approach to the management of chronic pruritic dermatoses and associated psychiatric comorbidities.

The treatment of psychodermatologic conditions requires a multidisciplinary team and must focus on the needs of the patient and their individual goals. The bidirectional nature of psychological and dermatologic conditions may make it difficult to determine the inciting condition, thus the patient history and interview has an important role in differentiating and determining the individual needs of the patient [42]. The use of standard therapies is effective in many dermatologic conditions but may not address rare or advanced conditions. Tailored treatment approaches are becoming essential in the treatment of psycho-dermatologic conditions. Precision medicine further allows clinicians to tailor treatment approaches while considering the genetic, environmental, and psychosocial factors that are unique to each individual as they apply to treatment

[43]. The use of precision medicine therapies are informed by the patient's molecular disturbances resulting in improved patient outcomes when compared to standard therapies. Currently, precision medicine is being investigated as it relates to dermatologic oncology and its use for other dermatologic conditions is in development as the biomarkers associated with heterogeneous conditions, such as AD, are identified [44] [45]. Precision medicine is growing within the field of psychopharmacology, which could have important implications in the pharmacologic treatment of psychodermatologic conditions.

Genetics also have an important role in determining the metabolism, safety, and efficacy of psychiatric drugs. The metabolism of the major classes of psychiatric drugs is determined by genomic variety in absorption, distribution, metabolism, and accretion genes including certain cytochrome P450 genes, human leukocyte antigen (HLA)-A, and HLA-B [46]. Pharmacologic interventions are important in the treatment of psychiatric comorbidities; thus, genomic sequencing can help determine the most effective therapeutic interventions for patients, furthering the ability to practice precision medicine. Genetic variations have been identified that are associated with both dermatologic and psychiatric conditions. However, more research is needed to determine the potential role of genetics in the interface between dermatologic and psychiatric conditions and the potential for precision medicine in the field of psychodermatology. Future research endeavors investigating the intersection of psychiatric conditions and pruritic dermatoses should embrace innovative treatment modalities. Despite the growing interest in psychodermatologic treatment, there remains a paucity of longitudinal data evaluating efficacy and patient-reported outcomes, necessitating comprehensive investigations into long-term follow-up and therapeutic outcomes.

3. Conclusion

This comprehensive review provides a meticulous examination of the intricate interplay between pruritic dermatoses and the concomitant psychological conditions they engender. It underscores the indispensability of adopting a multidisciplinary approach in managing dermatologic disorders alongside their psychiatric comorbidities, thereby advocating for a holistic treatment paradigm that addresses the complex biopsychosocial dimensions of these conditions. While traditional pharmacologic interventions, Mind-Body Interventions (MBIs), and Cognitive Behavioral Therapy (CBT) have demonstrated efficacy in mitigating symptoms, the emerging integration of precision medicine heralds a new frontier in patient-centered care. By leveraging advancements in genomic profiling, biomarker identification, and personalized treatment algorithms, precision medicine holds promise in tailoring therapeutic strategies to the unique biological and psychosocial profiles of individuals afflicted with pruritic dermatoses and accompanying psychiatric disorders. Consequently, further research endeavors focusing on the refinement and validation of precision medicine approaches stand poised to discover novel insights and long-term treatment outcomes, the-

reby paving the way for enhanced therapeutic modalities and improved quality of life for patients navigating pruritic dermatoses and psychiatric comorbidities.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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