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# Prurigo Nodularis

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## INTRODUCTION



## ORIGINAL ARTICLES

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Journal of Drugs in Dermatology

# New Horizons in Our Understanding of Prurigo Nodularis and Its Management

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Prurigo nodularis (PN) was first accurately described more than a century ago by Hyde and Montgomery as chronic itchy nodules commonly noted in symmetric distribution on extensor sites of limbs, upper back, and abdomen.[1] For decades, PN patients were among the most challenging to treat. They suffer from intractable itch that affects their sleep dominates their daily life activities and causes many psychological comorbidities such as mood disorders including anxiety, stress, and depression. In the last decade, significant advances in our understanding of the pathophysiology of PN have been achieved suggesting this condition involves mainly type 2 immune dysregulation and abnormal neural sensitization, which led to the development of new targeted treatments. In September 2022, dupilumab, an IL4R alpha inhibitor that blocks IL4, and IL 13 cytokines became the first FDA-approved medication for PN. New treatments such as Nemolizumab, an IL31R inhibitor that blocks the itchy cytokine IL31 have successfully completed phase 3 trials.[2-3] Other studies targeting type 2 cytokines and mast cells are undergoing phase 2 trials. Drugs that target the neural system using kappa opioid receptor agonists (KOR) have shown promising results.[4] In the current issue of JDD, United States (US) experts in the field of itch, prurigo nodularis and psychodermatology provide a comprehensive review of the state of the art knowledge of PN, its pathophysiology, its comorbidities, and management. Issa et al discuss the clinical pathological overview as well as psychodermatological perspectives of the disease.[5] Issa et al provide an in-depth review of recent advances in the pathophysiological aspects of this disease including transcriptomic and single cell studies that explain the role of type 2 T helper (TH2) cells in PN.[5] Moreover, Issa et al. explain that nodules and scars are developed due to upregulation of gene expression signatures of papillary fibroblasts involved in fibrosis, extracellular matrix organization, and increase in extracellular matrix protein Periostin which has shown to be highly associated with itch in PN.[6]

Another important topic that Issa et al addressed in this article is the interplay between the dermatological and the psychological aspects of PN. The severity of pruritus of PN, as well as the disfiguring skin lesions and stress, may have profound negative effects on feelings of shame and stigmatization and overall mental health.[5] Furthermore, the neural sensitization of itch in PN is also highly associated with other neural sensitization disorders of pain, such as fibromyalgia, interstitial cystitis, and irritable bowel syndrome.[7] Psychiatric conditions are significantly more prevalent in individuals with PN, for example, patients with PN have a more than six-fold chance of having body dysmorphic disorder (BDD). The authors highlight the importance of identifying those patients with neuropsychiatric comorbidities who may need more aggressive treatment and early intervention.

Kwatra et al discuss the burden of systemic comorbidities and sequelae in PN.[8] Kwatra et alanalyzed large databases of patients in the US to find an increased prevalence from age 30 and above and higher comorbidities of PN in depression, chronic kidney disease, diabetes, congestive heart failure, COPD, atopic dermatitis, and HIV.[8] All patients with PN were found to have a higher all-cause mortality. African American patients are 3.4 times more likely to have PN than White patients and have greater systemic inflammation and higher mortality rates than Whites.[10] Furthermore, patients have a higher lifetime financial burden due to multiple doctor visits.

Elmariah et al reviews the current treatments and emerging therapies for PN.[9] The authors highlight the importance of assessing pruritus intensity, and disease burden, and comorbid medical disorders. Elmariah et al emphasize that treatment goals should address first and foremost the resolution of itch followed by improvement in nodules.[9] Elmariah et al describe the exciting recent phase 3 studies of targeted treatments for Type 2 cytokines including dupilumab and nemolizumab, as well as other phase 2 studies including vixarelimab.[9,11] Elmariah et al also cover the landscape of drugs targeting the neural pathways, such as nalbuphine and non-specific drugs with nerve pain medications such as GABAergic drugs and Serotonin and norepinephrine reuptake inhibitors (SNRIs).[9]

In conclusion, PN patients are facing a new era where their disease is effectively treatable with current targeted treatments as well as new options on the horizon.

## DISCLOSURE

Gil Yosipovitch has served as an advisory board member for Abbvie, Arcutis, Escient Health, Eli Lilly, Galderma, LEO Pharma, Novartis, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals Inc., Sanofi, Vifor, GSK, and Kamari; received grants/research funding from Eli Lilly, LEO Pharma, Novartis, Pfizer, Galderma, Escient, Sanofi Regeneron, and Celldex; and as an investigator for Regeneron Pharmaceuticals Inc., and Sanofi.

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ORIGINAL ARTICLE

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# Prurigo Nodularis: Current Clinicopathologic Overview and Psychodermatological Perspectives

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## ABSTRACT

Prurigo nodularis (PN) is a quintessential neurocutaneous condition characterized by neural sensitization and intractable itch leading to intense scratching. This causes the formation of nodules with epidermal thickening and further release of pro-inflammatory mediators that recruit immune cells and increase dermal nerve proliferation and hypertrophy perpetuating the itch-scratch cycle. Those with PN have a significant quality-of-life (QoL) burden due to itch, anxiety, and sleep disturbance. In addition, PN exhibits psychiatric comorbidities that affect mental wellbeing such as depression, mood disorders, and substance abuse. This paper serves as an overview of the clinicopathologic aspects of PN, the burden of PN on QoL, and the psychodermatological aspects of the disease state.

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## INTRODUCTION

Prurigo nodularis (PN) is a neurocutaneous pruritic disorder that disproportionately affects black individuals.[1] Recent advances in research technologies have allowed for granular elucidation of the pathogenesis of the disease. There exists an interplay between the skin, immune, and nervous systems. Here we discuss the current understanding of the clinicopathologic and epidemiological features of PN, cutaneous and non-cutaneous co-morbidities, as well as the psychodermatologic aspects of the disease.

### Definition and Clinicopathologic Features of PN

Also known synonymously as chronic nodular prurigo (CNPG), PN is a subtype of chronic prurigo with an extensive global burden on quality of life (QoL).[2] According to the European Academy of Dermatology and Venereology Task Force for Pruritus, chronic prurigo is defined as "a distinct disease defined by the presence of chronic pruritus (>6 weeks) and multiple localized or generalized pruriginous lesions."[3] It is thought that PN commences with neural sensitization with subsequent development of the itch-scratch cycle.[3] Continued itch results in multiple hyperkeratotic papules and nodules that are typically distributed symmetrically along the extensor surfaces of the extremities.[4-6] Oftentimes lesions can be found on the upper and lower back, sparing the central back due to an inability of the patient to reach those areas to scratch; this finding is known as the "butterfly sign."[7] The PN lesions themselves may also be severely pruritic, leading to the continuation of the itch-scratch cycle. Depending on skin type, PN lesions may appear as red-pink in patients who are White and violaceous papules/nodules in patients with skin of color. On histology, PN lesions demonstrate epidermal hyperplasia, hypergranulosis, spongiosis, compact hyperkeratosis, as well as vertically arranged collagen fibers with an increased number of fibroblasts.[8] Compared to matched healthy skin, lesional PN skin also exhibits greater inflammatory cells including lymphocytes, neutrophils, mast cells, and eosinophils.[9]

**Epidemiology of PN**

PN is classified as a rare disease by the National Institutes of Health Genetic and Rare Diseases Information Center (GARD)[10] and the National Organization for Rare Diseases (NORD).[11] In the US, the prevalence of PN is estimated to range from 36.7 to 43.9 per 10,000 individuals.[12,13] In Europe, rates of between 0.65 to 11.1 per 10,000 individuals have been cited.[14-16] The estimated prevalence of PN in the United Kingdom is 3.27 per 10,000 individuals, and prevalence increases with age.[17]

The mean age of patients with PN at incident diagnosis is ~60 years, which has been reported in numerous studies.[17-19] African American patients are approximately 3 times more likely to have PN than White patients.[20,21] There is also a gender predilection for PN with females more commonly affected than males.[17,19,22] Estrogen is known to modulate the immune response and has been shown to enhance the production of T helper 2 (Th2) cytokines such as interleukin (IL)-4, IL-5, and IL-13.[23] The immunomodulatory function of estrogen may explain the greater burden of pruritus in females in general.[24]

Most common comorbidities associated with PN include atopic dermatitis (AD) and psychiatric diagnoses such as anxiety and depression.[17,25,26] Other comorbidities include chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, human immunodeficiency virus (HIV), and type 2 diabetes.[27] With respect to chronic kidney disease, circulating plasma angiotensinogen levels were dysregulated only in Black patients with PN.[28] Black patients with PN also had stronger associations with end-stage renal disease and faster progression of their renal disease compared to White patients with PN. Higher all-cause mortality was also observed in Black patients with PN and not in Asian patients with PN.[29] Compared to the general population, patients with PN are more likely to be hospitalized, have longer inpatient stays, and experience a high infectious disease burden, which corresponds to higher healthcare utilization and spending.[30-32] A retrospective study of 15,818 patients with PN showed a disproportionate burden of comorbid tuberculosis infection in patients with PN compared to the general population, which could be attributed to Th2 immune skewing.[33] Lastly, PN may have an association with malignancies of the skin, hematopoietic system, and solid organs.[34]

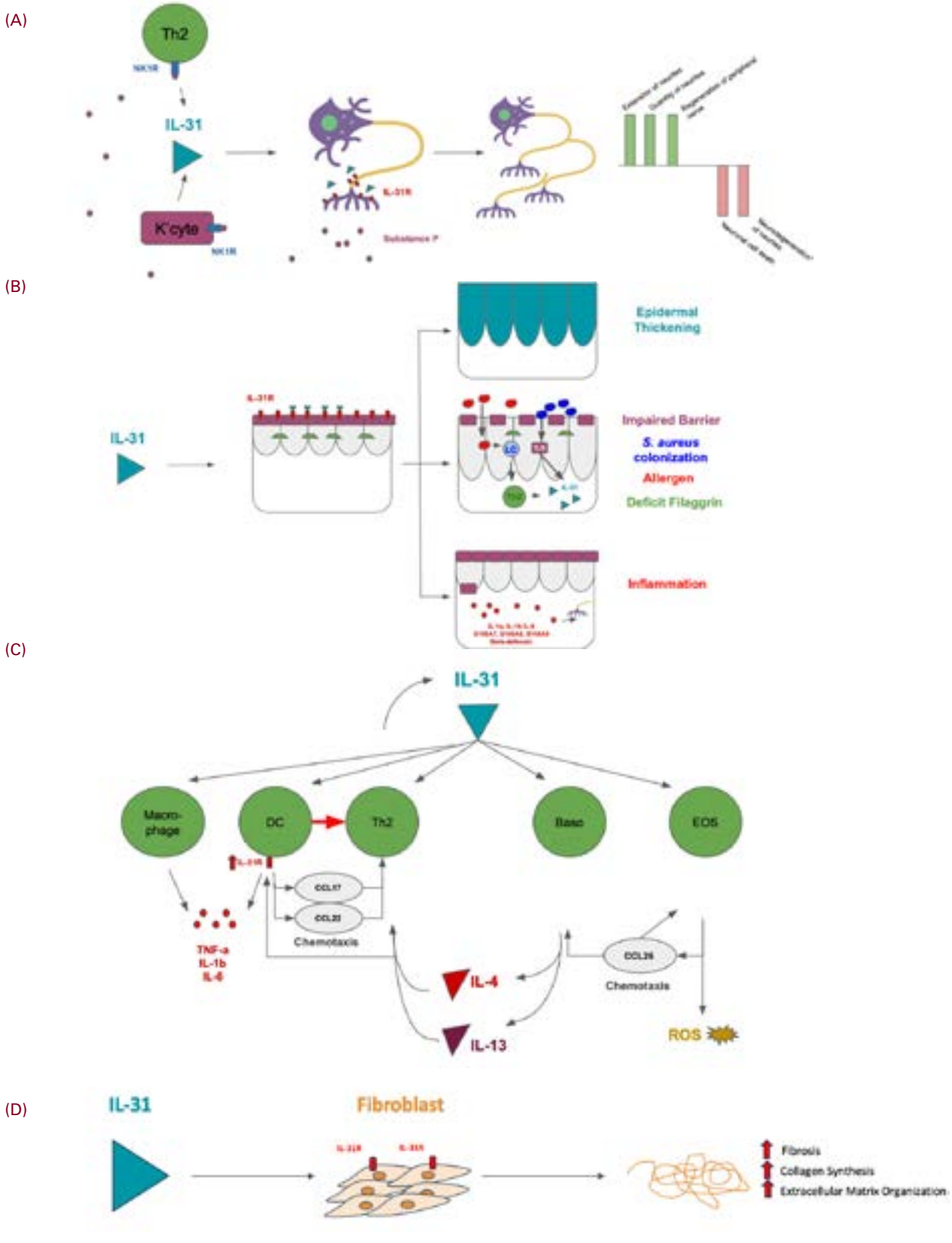
**Pathophysiology of PN**

Immune and neural dysregulation are central to the pathogenesis of PN.[35,36] The brain and skin are of the same ectodermal embryological origin. The term *brain-skin axis* describes the connection between our nervous/psychiatric and dermatological systems. While it is debated which aspect (immune or neural) occurs first in the initiation of PN, it is clear that both are inextricably intertwined and act in tandem (Figure 1).

Neural sensitization results in intense itching and scratching. The act of scratching causes disruption of the epidermal skin barrier resulting in the release of pro-inflammatory mediators by keratinocytes (eg, IL-1A, S100A), penetrance of allergens that activate epidermal Langerhans cells and T helper 2 (Th2) cells which secrete IL-31, and bacterial colonization with *Staphylococcus aureus* and other microbes that activate keratinocyte toll-like receptors (TLRs) to cause further secretion of IL-31 by keratinocytes.[37,38] IL-31 interacts with IL-31 receptors on numerous cells resulting in pleiotropic effects. On nerve cells, IL-31 stimulates the sensation of itch and proliferation and regeneration of nerve endings, thus causing neural sensitization and release of substance P, which feeds back onto keratinocytes and Th2 cells causing further release of IL-31.[39] IL-31 also acts on numerous immune cells causing a further inflammatory cascade; IL-31 interacts with (1) basophils to stimulate release of Th2-related cytokines IL-4 and IL-13 that then bind to Th2 lymphocytes, (2) eosinophils to release reactive oxygen species (ROS) and CCL26 which causes chemotaxis of basophils, (3) dendritic cells to release CCL17 and CCL 22 to recruit Th2 cells, and (4) macrophages to release TNF-alpha, IL-1b, and IL-6 (Figure 1).[40-43]

Recent gene expression and proteomic data have also identified fibroblasts as key players in PN.[44-49] A single-cell RNA sequencing study comparing individuals with PN to AD and healthy controls found that PN exhibited a unique population of CXCL14-/IL-24+ papillary fibroblasts and upregulation of gene expression signatures corresponding to the activation of cellular pathways involved in fibrosis, extracellular matrix organization and collagen synthesis.[45] While both PN and AD had type 2 immune skewing, PN also exhibited less activation of immune pathways relative to AD.[45] Another single-cell RNA sequencing study also identified 7 unique subclusters of fibroblasts in lesional PN skin compared to non-lesional PN skin with a shift toward a cancer-associated fibroblast (CAF)-like phenotype.[46] This

**FIGURE 1.** Pathophsyiologic mechanisms of prurigo nodularis. IL-31 is the key orchestrator of disease progression with pleotrophic effects on numerous cell types: (A) neurons, (B) epidermal cells, (C) immune cells, and (D) fibroblasts.



may explain the epidemiological observation that patients with PN have increased risk of CAF-associated malignancies such as squamous cell carcinoma compared to patients with AD.[34] Furthermore, fibroblast-derived secretory proteins WNT5A and periostin were found to interact with several neuronal receptors suggesting a novel fibroblast-neuronal axis. Activation of profibrotic responses and enrichment of fibroblast populations in PN skin relative to AD skin were also confirmed by Ma et al in a third independent single-cell RNA sequencing study.[47] Treatment with nemolizumab, a monoclonal antibody targeting IL-31 receptor α (IL-31RA), reverses the pro-fibrotic transcriptomic and proteomic profiles in both the skin and serum.[39,47,48] These findings strongly suggest a role of fibroblasts and mesenchymal dysregulation in the induction and maintenance of PN as well as their connection with the immune and neural axes, which is unique to PN compared to AD.

**Psychodermatological Perspectives of PN**

Chronic pruritus, the most defining characteristic of PN, along with unsightly skin lesions, bleeding, pain, sleep loss, and mental health symptoms, is associated with a negative impact on patients' quality of life (QoL).[50-52] Several studies have investigated the impact of PN-associated itch on QoL with the Dermatology Life Quality Index (DLQI) being the most frequently used assessment tool.[51,53,54] A systematic review and meta-analysis also found all studies to have moderate-to-severe pruritus and a very large or extreme effect on QoL.[51]

Pruritus worsens in the evening with the severity of nocturnal pruritus (NP) having a directly correlated impact on the severity of sleep disturbance.[54,55] A recent study of 39 patients with PN found that the majority reported sleep disturbance to a great extent and that it correlated significantly with pruritus timing in the evening.[56] Ständer et al further validated the Sleep Disturbance Numeric Rating Scale (SD NRS) in patients with PN.[57] The SD NRS is a single-item patient-reported outcome (PRO) assessing day-to-day sleep disturbance in patients with pruritic conditions and has been previously validated in AD.[58] Its use as a PRO for assessing PN impact on QoL in the clinic and in clinical trials remains to be determined.

In addition to its impact on QoL, PN also imparts an economic burden. A cohort study of 36 patients with PN by Whang et al found that when compared to controls, patients with PN had worse health performance, which they correlated to an average of 6.5 lifetime quality-adjusted life years (QALYs) lost per patient. This translated to an individual lifetime economic burden of $323,292 and a total societal burden of $38.8 billion.[52]

*Psychiatric Conditions in PN*

The intense pruritus of PN, as well as the disfiguring skin lesions, can have profound negative effects on the patient's mental health. Likewise, stress and psychological factors can significantly impact the development and severity of PN. While etiology of PN has not been fully elucidated, neuronal sensitization to itch and the development of the itch-scratch cycle has been hypothesized as a simplified origin of the condition. In fact, PN is associated with neural sensitization disorders of pain.[59] Nonetheless, there are significant interplays between dermatology, neurology, and psychiatry in the development and disease process.

Psychocutaneous conditions are those conditions, such as psoriasis, atopic dermatitis, or prurigo, in which psychological stress is a key element in causing exacerbations or flare-ups of the skin conditions.[60] Another classifying term for prurigo is a psychophysiologic disorder, which is a skin condition that is inherently susceptible to psychological stress in disease precipitation or exacerbation.[61]

Patients with PN have higher rates of systemic illnesses (eg, autoimmune conditions) and mental health disease.[62,63] Psychiatric conditions are significantly more prevalent in individuals with PN than in the general population.[64,65] Those found more commonly in patients with PN include eating disorders, self-harm, attention deficit/hyperactivity disorder, schizophrenia, mood disorders, anxiety, and substance use disorders.[13]

Underlying psychiatric conditions can influence the patient's perception of their disease; for example, a patient with comorbid major depressive disorder and pruritic cutaneous conditions might experience an increased sensation of itching.[66] Stress and emotional tensions can contribute to worsening the itching sensation in pruritic conditions such as PN and lichen simplex chronicus.[62]

*Effect of PN on Mental Health*

Patients with PN have a more than six-fold chance of having body dysmorphic disorder (BDD) symptoms in an observational, cross-sectional multicenter study.[67] BDD is defined in the DSM-5 as preoccupation with one or more perceived defects or flaws in physical appearance that are not observable or appear slight to others. This study also found that BDD symptoms were significantly related to factors including higher psychological stress and feelings of stigmatization.[67] This aptly draws attention to the chicken-or-egg discussion considering the interplay between the dermatological and psychological aspects in PN and demonstrates the close interrelation between the skin condition and mental health.

The increased self-consciousness and feelings of shame and stigmatization experienced in disfiguring skin conditions can easily become preoccupying or debilitating thereby significantly affecting one's daily life. Fear of what others may think of the cutaneous lesions exacerbates the individual's stress and worsens the itching, resulting in further trauma and worsening of the lesions. Patients often report significantly worse itch and scratching when alone and becoming hyper focused on the lesions. Patients often describe avoiding social situations and purposefully altering their dress, for example, wearing long sleeves and pants even in hot climates out of self-consciousness. One study found a direct correlation between severity of PN and increased stigma scores as well as increased likelihood of abstaining from social activities.[68] The study found that in the last 3 months because of their PN, 21.4% missed at least 1 day of work, learning, training, school or university; 72.9% gave up a leisure or sport activity; and 62.9% refused an invitation to a dinner or a party.[68]

PN also exhibits a significant psychological burden and has been linked to anxiety, depression, and suicidal ideation.[69] In a multicenter study from 13 European countries, the investigators reported 19% of total patients with prurigo had suicidal ideations related to their skin condition.[53] A cross-sectional study in 39 patients with PN and healthy controls found patients with PN exhibited higher serum IL-6 and lower serotonin levels, which significantly correlated with the severity of pruritus, but the association of these fluctuations with depression is not yet conclusive.[69]

*Mental Health Assessment Tools*

A helpful tool, in addition to clinical assessment, to assess the extent to which stress is affecting the patient's function and condition is the use of a patient survey questionnaire initially and possibly on follow-up to quantitatively track psychological measures over time. Examples of these include the Patient Health Questionnaire with 2 (PHQ-2) or 15 (PHQ-15) questions to screen for depression, or the Modified Mini Screen (MMS) for a more global assessment of depression, anxiety, obsessive-compulsive disorder, post-traumatic stress, and psychosis.[70]

Other assessments useful to assess and track psychological aspects of patients affected by PN include DLQI,[71] Patient Unique Stigmatization Holistic tool in Dermatology (PUSH-D),[72] and Epworth sleepiness scale.[73]

## CONCLUSION

To conclude, PN has inextricable interplays between psychiatry, immunology, and dermatology. Growing our understanding of the psychodermatology of PN is paramount to improving our treatment of this difficult-to-treat condition and identifying patients at risk for neuropsychiatric comorbidities that may need early intervention.

## DISCLOSURES

Naiem Issa is an advisor, consultant, and speaker for Galderma. Mohammad Jafferany and Hannah Riva have no conflicts of interest to declare.

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ORIGINAL ARTICLE

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# Patient Journey and the Burden of Systemic Comorbidities and Sequalae in Prurigo Nodularis

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## ABSTRACT

**Background:** Prurigo Nodularis (PN) is a relatively rare chronic inflammatory skin disease characterized by firm pruritic nodules. PN is associated with significantly increased rates of many systemic and non-systemic comorbidities. This results in a higher burden of disease and utilization of specialty care compared to non-PN United States (US) adults. Psychiatric comorbidities associated with PN include depression and anxiety. In this article, we describe the burden of comorbidities. sequelae of disease, inflammatory disease signatures, and the impact of PN in African American and Asian patients. Furthermore, we explore challenges in the recognition and diagnosis of PN and describe methods to increase awareness of PN among dermatologists.

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## INTRODUCTION

**Patient Journey and the Burden of Systemic Comorbidities and Sequalae in Prurigo Nodularis**

Prurigo Nodularis (PN) is a relatively rare condition with prevalence estimates as low as 18 per 100,000 in the US, that disproportionately affects adults in their fifth and sixth decades of life.[1,2] An analysis of the data from the Johns Hopkins Health System found that during the last 5 years, 958 patients were diagnosed with PN with 50% of those patients ranging in age from 45 to 64 years and an additional 17% ranging from 65 to 74 years of age.[3] A nationwide analysis of claims data identified increasing rates of PN with 2658 patients in 2016 and 9,426 patients in 2019.[4] A study using data from All of Us, a National Health Institute database containing health information from US adults similarly found increased prevalence with increasing age, ranging from 0.02% in those under 30 years of age to 0.35% in those over 70 years of age. The same study found that participants with PN had statistically significantly higher rates of comorbidities than US adults without PN, including atopic dermatitis (15.5% vs 1.5%), chronic hepatitis C (6.4% vs 1.4%), chronic kidney disease (29.4% vs 5.7%), congestive heart failure (20.3% vs 3.4%), COPD (23.3% vs 5.2%), depression (54.4% vs 18.0%), HIV (7.4% vs 1.2%), and type 2 diabetes (43.2% vs 12.1%).[5] These comorbidities place a higher systemic burden of disease on patients resulting in higher utilization of specialty care. In a multicenter cohort phase 2 clinical trial, nemolizumab was shown to reduce systemic inflammation, it will be necessary to see in future studies if this lowers comorbidity risk.[6]

A national-representative study looking at private insurance claims data found that patients with PN saw dermatologists more frequently than age-matched controls and patients with atopic dermatitis and psoriasis.[4] This increase in visits when compared to patients with atopic dermatitis and psoriasis provides support for the claims that patients with PN experience a greater disease burden as PN is believed to be the most severe of the pruritic dermatoses.[7]

This chronically severe dermatosis presents a substantial financial burden on patients. An analysis found that the lifetime financial impact was estimated to be $ 323,292 per individual. In addition to the large financial burden, PN also has a large negative impact on the patient's quality of life (QoL). The same analysis found that PN can have greater impairments on QoL than chronic diseases such as strokes and has a comparable impact on chronic kidney disease.[8] Patients with PN are also impacted by many nonsystemic diseases including xerosis cutis (OR 8.02), neurotic excoriations (OR 71.2), atopic dermatitis (OR 9.48), asthma (OR 1.67), and urticaria (OR 2.78).[2]

**Impact on Mental Health**

Prurigo Nodularis has been associated with psychiatric disorders such as depression and anxiety. Additionally, consumption of anxiolytics and antidepressants is significantly higher among patients with PN.[9] In addition to the psychiatric conditions, other mental health disorders such as schizophrenia, mood disorder, eating disorder, ADHD, substance use, and self-harm also showed increased rates in patients with PN.[2] A study that combined PN and lichen simplex chronicus (LSC) using the National Inpatient Sample Database corroborated this as they found these patients were 2.26 times more likely to have a mental health diagnosis. Furthermore, patients with PN/LSC admitted for any mental health condition were hospitalized 2.18 longer on average and had an increased cost of care of $1,617 compared to those without PN/LSC.[10] There also appears to be gender differences in the prevalence of PN and psychiatric conditions, with women being more commonly affected.[11] This is consistent with the findings of a single institution study of patients seen for pruritus in which females were more likely than males to be diagnosed with comorbid psychiatric conditions.[12]

**Inflammatory Disease Signatures in PN**

PN is often grouped with atopic dermatitis and psoriasis, however, a recent study found that it has a distinct circulating and cutaneous Th22 immune dysregulation. The source of increased IL-22 secretion was found to be circulating $CD4^+$ and $CD8^+$ T-cells.[13] Plasma assays have demonstrated increases in inflammatory mediators in the systemic response, which likely play a role in the systemic comorbidities seen in patients with PN.[14] A recent proteomic analysis found that among all patients with PN, levels of CDCP1 (a transmembrane protein found in T cells) and MCP-3 (a marker of innate immunity that stimulates monocytes and dendritic cell chemotaxis toward inflammatory skin sites) were elevated. More specifically 2 clusters were identified, providing support for 2 unique endotypes: an inflammatory phenotype, with a predisposition towards atopy, and a neuropathic phenotype, with a predisposition towards myelopathy.[15] Little information is known about PN on a single-cell level, but a recent single-cell transcriptomic profiling (scRNA-seq) provided better insight into this. A unique fibroblast cell population in the skin of patients with PN and the presence of another phenotype in PN fibroblasts characterized by the presence of cancer-associated fibroblasts (CAF) was identified.[16] A multicenter cohort study found that therapy with nemolizumab, a novel IL-31RA inhibitor, was able to reverse circulating blood inflammation.[6] Future registry studies are needed to understand more about the pathogenesis of PN and to evaluate if early treatment may reduce the development of subsequent disease comorbidities.

**Patient Spectrum: Skin of Color, Asian, and Caucasian**

A study of 909 patients with PN found that African American (AA) patients were 3.4 times more likely to have PN than White patients. Additionally, AA patients with PN were 10.5 times more likely to have HIV than were race-matched controls with atopic dermatitis, and 8 times more likely to have HIV than were African American patients with psoriasis.[17] In a study using TriNetX, a health research network of approximately 64 million patients in 45 large healthcare organizations, all patients with PN were found to have higher all-cause mortality (HR 1.75) than control patients. More specifically subgroup analysis showed that Black patients had the highest mortality (HR 2.07).[14] AA patients with PN favor a Th22/IL-22 profile in both systemic and cutaneous immune response, leading to the possibility that Black patients with PN may experience greater systemic inflammation and this is the cause of their higher mortality.[13,18] It is also important to note that a survey of 6,000 US veterans randomly sampled from the US Veterans Hospital Patient Database found that AA patients had a greater emotional impact and were more likely to visit their primary care providers for pruritis, although they had a similar number of visits to a dermatologist.19 The patient population of this sample rules out the insurance as the main culprit, but still leaves questions about the racial disparities in medical treatment of PN. Single center and national studies have shown PN to be more common overall in women than men, however, a Korean study based on a large dermatology outpatient cohort found PN to be more prevalent in males (56.8%) than females (43.2%). This supports the findings by Boozalis et al in Asian prevalence (58.1% male, 41.9% female).[1,17,20]

**Challenges in Recognition and Diagnosis and Increasing Awareness Among Dermatologists**

A biopsy of PN may show hyperplastic dermal nerve fibers and decreased density of intraepidermal nerve fibers, but PN remains a clinical diagnosis.[1] Some of the typical features clinicians should look out for include grouped and symmetrically distributed nodules on the extensor surfaces of the extremities and trunk, and the butterfly sign, which is when skin on the upper aspect of the back is spared. In addition to these findings, pruritis is necessary for the diagnosis of PN, but patients may also report a burning or stinging sensation.[1,21,22] Aside from these typical features PN may also have varying presentations and can be recalcitrant to treatment, making it difficult for providers to appropriately manage PN. Dupilumab is currently the only drug approved by the US Food and Drug Administration for the treatment of PN in the US.[23] A survey of 30 providers from 14 European countries highlights the amount of uncertainty around the diagnosis and management of PN, as respondents reported that 90% have prescribed antihistamines despite unanimous agreement that antihistamines are generally ineffective for PN-associated pruritus.[22] In addition to initiating appropriate treatment, in the right clinical context providers should consider screening for psychiatric disorders, HIV, the presence of cognitive impairment, and many of the systemic comorbidities already discussed.[10,11,17]

## CONCLUSION

PN has an impact on patients' lives due to the many systemic and nonsystemic comorbidities associated with a higher burden of disease. In addition to these comorbidities, there are also psychiatric comorbidities that are important to understand to improve outcomes. It is worth noting that the burden is augmented in patients with skin of color thus highlighting the importance of addressing racial disparities in the medical treatment of PN. Though diagnosis of PN remains challenging, increasing awareness of common exam and biopsy findings can improve the clinical decision-making process.

## DISCLOSURES

Dr Kwatra is an advisory board member/consultant for Abbvie, Amgen, Arcutis Biotherapeutics, Aslan Pharmaceuticals, Bristol Myers Squibb, CaraTherapeutics, Castle Biosciences, Celldex Therapeutics, Dermavant, Galderma, Genzada Pharmaceuticals, Incyte Corporation, Johnson & Johnson, Leo Pharma, Novartis Pharmaceuticals Corporation, Pfizer, Regeneron Pharmaceuticals, and Sanofi and has served as an investigator for Galderma, Incyte, Pfizer, and Sanofi. Dr Chisolm has served as an investigator, scientific advisor, or received research support, from Pfizer, Incyte, Amgen, Galderma, Trevi, Menlo, Abbvie, Janssen, Kiniksa, AstraZeneca, Sanofi, Regeneron, Lilly, and Vifor. Dr Puerta-Durango has no conflicts of interest to declare. Dr Mollanazar has served as an advisory board member for Boehringer Ingelheim, Janssen, Novartis, Regeneron Pharmaceuticals, Inc., Sanofi, Trevi Therapeutics, Menlo Therapeutics Inc, Galderma, Leo Pharma, Abbvie; investigator for Sanofi; and consultant for Novartis, Regeneron, Janssen, and Sanofi.

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ORIGINAL ARTICLE

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# Management of Prurigo Nodularis

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## ABSTRACT

**Background:** Prurigo nodularis (PN) is a chronic disease characterized by intense pruritus and nodular lesions associated with reduced quality of life. Until recently, no US Food and Drug Administration (FDA)-approved therapies have been available for the management of PN. Treatment regimens have been highly variable and clinical management guidelines are lacking overall; formal treatment guidelines do not exist within the US. In 2022, dupilumab became the first FDA-approved medication for PN. Multiple novel agents that target the neuroimmune underpinnings of the disease are currently in development and show promise for this challenging disorder.
**Objective:** To review current treatments and emerging therapies for effective management of patients with PN.
**Methods**: We reviewed publications on PN management identified from PubMed, Embase, Web of Science, and the Cochrane Library. We also included publicly available data on clinical trials for PN therapies reported on the US National Library of Medicine ClinicalTrials.gov, the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) Database, and the European Clinical Trials (EudraCT) Database.
**Results:** The recommended management of PN begins with an assessment of disease severity, including disease burden and pruritus intensity, and evaluation of comorbid medical disorders. Treatment goals include resolution of itch, improvement in nodules or cutaneous lesions, and improvement in quality of life. Therapies should be selected based on a patient's clinical presentation and comorbidities. Treatment should simultaneously address the neural and immunologic components of PN. Combination therapy, particularly with conventional agents, may be beneficial.
**Limitations:** Data on most conventional PN treatments are limited to anecdotal reports, small clinical trials, or expert consensus recommendations. No head-to-head comparative trials have evaluated the relative efficacy of conventional and/or emerging agents, or combination therapy.
**Conclusion:** An effective treatment approach for patients with PN should reduce pruritus, allow nodular lesions to heal, and improve individual quality of life. The treatment landscape for PN is rapidly evolving with one FDA-approved agent and several new promising therapies on the horizon.

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## INTRODUCTION

Prurigo nodularis (PN) is a chronic skin disease classically characterized by refractory pruritus and nodular skin lesions, although a wide spectrum of variation in both sensory symptoms and lesional appearance may exist.[1] Whereas PN was once considered a psychiatric disorder, accumulating data demonstrate that neural dysfunction and immune dysregulation are central to PN pathophysiology.[2,3] Studies comparing burden of disease and health utility scores in patients with PN to those with other cutaneous and/or systemic disorders have consistently shown that PN patients not only suffer from higher disease burden and more severely reduced quality of life (QoL) compared to other skin diseases (including psoriasis, atopic dermatitis (AD), and cutaneous T cell lymphoma),[4,5] but PN imposes a greater burden on individuals than hypertension, diabetes, stroke, bronchitis and chronic kidney disease requiring hemodialysis.[6] Despite the overwhelming disease burden in this patient population, conventional treatments for PN have fallen short of providing meaningful symptomatic relief and durable disease control.

Until recently, FDA-approved treatments were not available for PN and management consisted of single item or combination therapy with topical corticosteroids, systemic immunosuppressants or phototherapy, antihistamines, anticonvulsants, and/or antidepressants. Data on the majority of such agents are sparse, and limited to observational studies, case reports, and small clinical trials that demonstrate variable success.[7] In 2021, a panel of US dermatologists with expertise in managing PN published a consensus statement with recommendations for disease management consisting of a 4-tier treatment ladder that addressed both neural and immunologic mechanisms underlying the disease.[1] The authors highlighted that treatment should be tailored to the individual needs of the patient, considering their clinical presentation as well as individual systemic and mental health comorbidities. Furthermore, it was noted that therapies targeting both neural and immunologic mechanisms of pruritus may be of benefit in some patients, often necessitating combination therapy.

Success with off-label use of dupilumab in PN patients ultimately prompted randomized controlled trials (RCTs) that demonstrated substantial improvement in itch and disease control in PN. In 2022, dupilumab became the first FDA-approved medication for PN, bringing much needed attention to this devastating disease and heralding an expansion in the therapeutic landscape. Inspired by rapidly evolving insights into itch physiology and PN-specific pathophysiology, several promising agents are now in development for PN including an anti-interleukin (IL)-31 receptor alpha monoclonal antibody, an oncostatin M inhibitor, mu opioid receptor (MOR)/kappa opioid receptor (KOR) antagonists/agonists, and Janus kinase (JAK) inhibitors.[2,8]

## RESULTS

The goals of treatment in PN are to reduce pruritus, disrupt the itch-scratch cycle, and completely heal PN lesions.[2,9] Adequate treatment of PN must address both the neural and immunologic components of pruritus. Despite an actively evolving treatment pipeline, current treatment options for patients with PN are limited. At the time of this review, there is only one approved agent for PN available in the US. Consequently, most treatments are used off-label, and there is high variability in treatment selection and a lack of consensus on dosing regimens.

### Current Treatment Landscape

Current PN treatments include gentle skin care, antipruritic emollients, topical corticosteroids, topical calcineurin inhibitors, capsaicin, and other compounded topical neuromodulators (eg, gabapentin, cannabinoids, or anesthetics such as lidocaine or ketamine), phototherapy, systemic immunosuppressants, and systemic antidepressants and anticonvulsants.

Treatment of PN should be based on clinical judgment rather than a strict stepwise approach.[1] Factors to consider when selecting appropriate treatment include the patient's age, comorbidities, severity and distribution of PN lesions, impact on QoL including sleep disturbance, and possible adverse events (AEs).[2] In some instances, particularly those with localized or mild disease, single modality therapy may be sufficient to control PN symptoms. However, in patients with more widespread, refractory, or severe involvement, combination therapy which consists of topical and systemic medications (eg, topical corticosteroids and/or topical anesthetic plus systemic immunosuppressive agent and/or systemic neuromodulator) may be warranted. In general, histamine H1/H2 receptor antagonists are not recommended for PN treatment due to lack of efficacy and potential for sedation, unless a comorbid histamine-mediated condition is suspected.[10]

### Topical Anesthetics and Neuromodulatory Agents

Treatments that address the neural component of PN include topical capsaicin, camphor, menthol, ketamine, lidocaine, and amitriptyline, with the latter 3 often compounded together.[11] Based on limited clinical evidence, these treatments tend to have short-term efficacy.[12,13] These topical agents may provoke transient burning, itch, or redness at the application site, most commonly experienced with capsaicin; however, such reactions typically subside within minutes to hours, and become less troublesome with repeat applications.

### Topical Immunomodulatory Agents

Therapies that address the immunologic component of PN include topical calcipotriol, topical and intralesional corticosteroids, topical calcineurin inhibitors (TCIs), and cryotherapy. Data to support the use of these topical therapies are predominantly based on small open-label or intraindividual randomized controlled trials (RCTs).[14-17]

*Topical and Intralesional Corticosteroids*

Despite widespread use in daily clinical practice, the efficacy of topical corticosteroids has only been evaluated for PN in a few studies. In one study, Betamethasone valerate tape 0.1% once daily for 4 weeks resulted in a greater reduction in pruritus on the visual analogue scale (VAS) after 4 weeks of treatment compared to a moisturizing antipruritic cream applied twice daily.[14] A recent review demonstrated intralesional triamcinolone (2.5 mg/mL dilution) was safe and effective for patients with localized dermatitis, including PN.[18] This finding is consistent with isolated case reports published in the 1980s which showed benefit from intralesional corticosteroids directly injected into PN lesions followed by cryotherapy.[19,20] Based on these limited data and potential side effects including atrophy, telangiectasia, and altered pigmentation, intralesional corticosteroids in PN should be limited to those patients with <10 lesions or localized disease.[1,18] Similarly, the use of cryotherapy should be limited to localized disease, and patients should be counseled on the potential for altered pigmentation and pain.[20]

*Topical Calcineurin Inhibitors*

In several uncontrolled, open-label trials, tacrolimus 0.1% ointment and pimecrolimus 1% cream demonstrated improvement and reduction of itch in isolated PN patients. A randomized, controlled, double-blind study comparing pimecrolimus 1% cream with hydrocortisone 1% creams in non-atopic PN patients demonstrated improvement in itch, scratch lesions, and QoL in both treatment arms, although no statistical differences were seen between the 2 topicals.[21] In a surveillance study in patients with chronic pruritus, which included PN patients, TCIs offered only modest benefit in a small subset of patients.[22] Burning and irritation at the application site are well-established side effects associated with TCIs, but are usually transient and fade with repeat use.[15,17]

*Topical JAK Inhibitors*

JAK inhibitors are small molecule inhibitors that suppress intracellular signaling mediated by one or more Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways that lay downstream of multiple cytokines. Numerous studies, including multiple RCTs, have demonstrated their efficacy in reducing inflammation and pruritus in several dermatologic diseases including atopic dermatitis (AD) and psoriasis. Moreover, topical JAK inhibitor formulations including tofacitinib 2% ointment (JAK 1/ 3 inhibitor), delgocitinib 0.05% ointment and cream (pan-JAK inhibitor), and ruxolitinib 1.5% cream (JAK1/2 inhibitor; currently approved in the US for AD) have shown a benefit in managing atopic and eczematous hand dermatitis. However, data supporting the use of topical JAK inhibitors in PN remains limited. A 12-week double blind, vehicle-controlled trial followed by a 40-week open label extension period evaluating the use of ruxolitinib 1.5% cream twice daily for PN is currently underway (NCT05755438).[23]

**Systemic and/or Widespread Skin-Directed Therapies**

*Phototherapy*

Narrowband ultraviolet B (UVB) and psoralen plus ultraviolet A (PUVA) phototherapy have been used in the management of PN for decades. Several case series, retrospective observational studies, and a few open-label prospective trials have reported between 50% to 100% improvement in PN severity with narrowband (NB) or broadband (BB) UVB phototherapy, and 75% to 100% improvement in response to PUVA.[24,25] Data from 2 small RCTs of UVB 308-nm excimer light and PUVA alone or in combination showed improvement in pruritus with phototherapy. There was no difference in remission rates between PUVA alone or in combination with narrowband UVB; however, the number of PUVA treatments required to achieve remission was lower with combination therapy.[26] Phototherapy is generally well tolerated, although side effects may include burning, erythema, blistering, and hyperpigmentation.[26,27]

*Immunosuppressive Agents*

Cyclosporine reduces itch in many pruritic dermatoses and is associated with clinical improvement in patients with PN. In one case series of 14 patients, cyclosporine at doses 3 to 5 mg/kg led to improvement in 13 patients (92%) within weeks to months.[28] Similar results were observed in a small case series of 8 patients in which a mean dose of 3.1 mg/kg brought about improvement after approximately 3 weeks in all patients.[29] Regular monitoring of renal/hepatic function is required, and cyclosporine is not recommended for patients with impaired renal function.[7,28,30]

Azathioprine has been reported to reduce pruritus in PN patients, as a single agent or in combination with amitriptyline[31,32]; however, the effects appear to be short-lived.[31] Azathioprine is also associated with significant AEs, including nausea, diarrhea, and epigastric pain. Monitoring for potential bone marrow suppression is also recommended.[31]

Two retrospective studies evaluating methotrexate in patients with PN demonstrated marked improvement in lesions and reduction in pruritus with doses ranging from 5 to 25 mg weekly.[33,34] The most common AEs were nausea, fatigue, anemia, and elevated aminotransaminases.[7,33,34] Mycophenolate is sometimes used to treat chronic dermatitis; however, no studies have been reported in patients with PN.

*Anti-IL4 and IL13 Biologics*

Dupilumab is a human monoclonal antibody directed against IL-4 receptor alpha, initially introduced and FDA-approved for adult and pediatric AD. Following several case reports and case series suggesting benefits for the management of PN,[35-40] the LIBERTY-PN PRIME (n=151; NCT04183335) and PRIME2 (n=160; NCT04202679) phase 3 RCTs confirmed that dupilumab significantly reduced itch and skin lesions in PN patients. In the PRIME trial, dupilumab resulted in a ≥4-point worst itch-numerical rating scale (WI-NRS) reduction in 44.0% and 15.8% of patients at week 12, and 60% and 18% at week 24 in the dupilumab and placebo arms respectively. Investigator global assessment for PN (IGA-PN) of clear to almost clear (0-1) was achieved in 32% vs 11.8% at week 12, and 48% vs 18.4% at week 24 in dupilumab and placebo arms, respectively. Similar results were observed in the PRIME 2 trial (≥4-point reduction in WI-NRS: 57.7% vs 19.% at week 24, IGA 44.9% vs 15.9% at week 24 in dupilumab and placebo arms, respectively.) Dupilumab is generally well tolerated with only mild and transient AEs reported including conjunctivitis, worsening of celiac disease, eosinophilia, and herpes labialis.[41] Based on these positive findings, dupilumab was approved by the US FDA for the management of PN in September 2022.

Tralokinumab is a fully human IgG4 monoclonal antibody directed against IL-13, which downregulates T helper (TH) inflammation by inhibiting the cytokine's interaction with IL-13 a1 and a 2 receptors. The efficacy of tralokinumab in patients with moderate-to-severe PN-like phenotype AD was evaluated in a multicenter, prospective, open-label case series.[44] Patients demonstrated a significant improvement in EASI reaching EASI-50 within 4 weeks, EASI-75 within 12 weeks, and EASI-90 within 32 weeks (mean EASI reduction from 27.2-1.7, *P*<.001). Thirteen of 17 patients (76%) achieved either complete or almost complete clinical remission (IGA 0 or 1). The mean NRS-itch value significantly decreased as early as week 4 (*P*<.001) and progressively reduced after 16 weeks with continuous treatment.[42] At the time of this review, the anti-IL-13 monoclonal antibody lebrikizumab has been shown to effectively reduce itch and clinical lesions in AD but has not yet been evaluated in the management of PN.

*Anti-IL-31Ra and Oncostatin M Receptor Antagonists*

IL-31 is a TH2 cytokine that has been shown to induce acute itch in animal models when it binds to the heterodimer receptor complex composed of IL-31Ra and oncostatin M receptor beta subunit (OSMRb). IL-31 mRNA levels are increased in PN, and itch intensity and PN severity correlate with the number of dermal IL-31+ cells, dermal IL-31 RA+ cells, and dermal OSM(+) cells.[43]

Nemolizumab, a monoclonal humanized anti-IL-31Ra antibody, has been evaluated for its efficacy in reducing pruritus and disease severity in AD and PN. In a 12-week, double-blind, phase 2 RCT (n=70; NCT03181503) in moderate-to-severe PN, nemolizumab subcutaneous injection (0.5mg/kg) led to a statistically significant reduction in peak pruritus NRS (PP-NRS) at 4 weeks compared to baseline (nemolizumab: -4.5 (50.3% change) and placebo: -1.7 (-20.2% change)).[44] In the multicenter, phase 3 OLYMPIA 2 RCT (n=274; NCT04501679),[45] 41 % of subjects receiving nemolizumab monotherapy (after initial 60mg loading dose, every 4 weeks < 90 kg: 30 mg, ≥90 kg 60 mg) achieved a ≥4 point improvement in PP-NRS at week 4 compared to 7.7% of those receiving placebo (*P*<0.0001). By week 16, 56.3% and 20.9% of subjects in the nemolizumab and placebo arms, respectively, achieved this primary endpoint (*P*<0.0001).[46] In addition, significant improvement in the proportion of patients achieving IGA success (IGA of 0-1 and ≥2 point IGA improvement) was observed with nemolizumab (37.7%, compared to 11.0% in placebo, *P*<0.0001) at week 16. Similarly, improvement in sleep (51.9%, compared to 20.9% of placebo, *P*<0.0001), ≥4 point improvement in dermatology quality of life index (DLQI; 74.9%, compared to 39.6% placebo), and improvement in mood based on the Hospital Anxiety and Depression Scale (HADS) scores for anxiety (-2.60 (± 0.27), compared to -1.40 (± 0.36) placebo) and for depression (-2.30 (± 0.27), compared to -0.80 (± 0.36) placebo) were observed at week 16. Nemolizumab was generally well tolerated in both trials, with few serious AEs in both the treatment and placebo arms, although peripheral edema and worsening of atopic eczema were reported.[46]

Vixarelimab is a human monoclonal antibody that targets OSMRβ and thereby interferes with IL-31 signaling in target cells. It was granted Breakthrough Therapy designation status by the FDA in 2020 and is under evaluation for PN. In a recent multicenter, phase 2a RCT in moderate-to-severe PN patients (n=50) comparing weekly vixarelimab 360 mg subcutaneous injection to placebo, vixarelimab achieved a 4-point reduction in WI-NRS score in 52.2% subjects (12/23) compared to 30.8% (8/26) subjects receiving placebo (*P*= 0.11) at week 8, and improvement of PN-IGA score of 0 (clear) or 1 (near clear) in 30.4% (7/23) versus 7.7% (2/26) on placebo (*P*= 0.03) (NCT03816891).[47] Improvements were also observed in sleep and QoL. Vixarelimab was well tolerated with few AEs, which included nasopharyngitis, upper respiratory infection, nummular eczema, and injection site reactions.[48]

*Systemic JAK Inhibitors*

Although not currently approved by the FDA for PN, oral JAK inhibitors (including tofacitinib, upadacitinib, baricitinib, and abrocitinib) have been reported in several case reports and case series to improve PN.[49,50] In a recent retrospective study comparing dupilumab (n=36) to oral JAK inhibitors (baricitinib (n=10) and upadacitinib (n=3)) for PN, no difference in WI-NRS or PN-IGA was observed between treatment arms (≥4 point improvement in WI-NRS: 60% dupilumab vs 58.3% JAK inhibitor, *P*=0.921); % patients with PN-IGA of 0 or 1: 40.0% dupilumab vs 25.0% JAK inhibitors, *P*=0.485). JAK inhibitors showed a faster onset of response than dupilumab (3.65 ± 2.27 weeks for JAK inhibitors compared to 10.7 ± 13.4 weeks for dupilumab; *P*=0.004), after adjusting for confounders (*P*=0.042). Disease flare and skin infections were more common with JAK inhibition.[51]

**Systemic Neuromodulators**

*Gabapentinoids*

Although widely used in the management of chronic pruritic disorders including PN, gabapentinoids have not been extensively studied in controlled trials for benefit in this disorder. Several case reports and a cohort study suggest that gabapentinoids may be effective at reducing pruritus in patients with PN.[52-54] Sedation is a commonly observed side effect with these therapies, particularly at initiation or at high doses, although dizziness, peripheral edema, and headache have also been reported. Although no RCTs are available to evaluate gabapentin or pregabalin dosing in patients with PN, it is recommended to start at a low dose to limit sedation (eg, gabapentin 100 to 300 mg at night; pregabalin 25 to 50 mg) and increase the dose as tolerated, up to 3600 mg for gabapentin or 600 mg for pregabalin, in divided doses throughout the day.[52,55]

*Antidepressants*

Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) have been reported to benefit patients with PN and are frequently used off label for this indication. Although the goal of antidepressant therapy in PN is to reduce the severity of pruritus, these agents also offer the added potential benefit of mood stabilization given the high co-morbid burden of depression and anxiety in this population.[56-58]

Open-label studies have provided support for an antipruritic effect of SSRIs paroxetine and fluvoxamine and showed similar efficacy between these 2 agents with several months of use.[59] Similarly, an open-label trial with amitriptyline was reported to benefit patients with PN within several weeks to months at doses ranging from 10 to 60 mg daily.[62] Nortriptyline 25 to 50 mg daily and doxepin 25 mg daily have also been reported to improve itch and lesional severity in PN patients.[60]The most common AEs observed with SSRIs were fatigue, vertigo, drowsiness, nausea, gastrointestinal pain, and weight gain.[59] Side effects of tricyclic antidepressants include sedation, dizziness, reduced daytime concentration, dry mouth, constipation, and weight gain.[60]

*Opioid Modulators*

Several observational studies and case reports of patients with chronic pruritus, including patients with PN, reported improvements in pruritus with naltrexone or butorphanol.[61-64] Clinical and pre-clinical studies evaluating the role of M and K opioids in itch underscore the potential of opioid modulation in pruritic conditions such as PN, although the use of these agents may be limited by tolerability. AEs associated with kappa opioid receptor (KOR)/mu opioid receptor (MOR) antagonists are generally transient and include dizziness, headache, fatigue, somnolence, nausea, vomiting, and diarrhea.

Naltrexone, nalmefene, and naloxone are mu opioid receptor (MOR) antagonists. Naltrexone is FDA approved in the treatment of alcoholism and opioid addiction, but it has been used off label at both high and low doses with variable success in the treatment of chronic pruritus of diverse etiologies.[65] In a recent meta-analysis, naltrexone (high dose, low dose, or topical application) treatment resulted in improvement in itch due to atopic dermatitis, prurigo nodularis, cholestasis, burn injury, and autoimmune disorders.[66] In a separate open label trial, naltrexone 50 mg daily led to symptoms and lesion improvement in 9 of 17 PN patients.[67] Naloxone has also been used anecdotally and reported in open label studies to be beneficial for the treatment of itch of multiple etiologies including urticaria, cholestatic, uremic and postburn pruritus. It is available in both the oral and intravenous formulations, the latter being utilized more often due to low oral bioavailability.[68]

Butorphanol and nalbuphine (KOR agonists/MOR antagonists), nalfurafine, and difelikefalin (selective KOR agonists) have been reported to improve itch in several chronic pruritic conditions including uremic pruritus and PN.[69] In a phase 2 RCT comparing nalbuphine extended release (NAL-ER) at 81 mg or 162 mg twice daily to placebo in PN patients (n=62; NCT02174419), 44.4% ($P$=0.32) of subjects on the higher dose NAL-ER and 27.3% ($P$=0.78) of subjects on the lower dose achieved ≥30% reduction from baseline in 7-day WI-NRS at week 10.[70] Additional improvement in itch was observed in the 50 week OLS extension trial period. In the phase 2b/3 PRISM trial (n=344; NCT03497975), NAL-ER 162 mg twice daily treatment led to a statistically significant reduction in itch (25% of subjects) compared to placebo (14% of patients) ($P$=0.0157).[71] Nalbuphine was generally well tolerated, with mild AEs of nausea, dizziness, headaches, and constipation.

Difelikefalin is a peripherally active KOR agonist that holds promise for the management of multiple pruritic conditions. In a Phase 3 RCT (n=378; NCT03422653), treatment with difelikefalin IV formulation (0.5 mg/kg) resulted in ≥3 point improvement in WI-NRS in 51.9% patients compared to 30.9% receiving placebo ($P$<0.001) in patients with chronic kidney disease (CKD) receiving hemodialysis, leading to FDA approval for this indication in August 2021.[72,73] Patients treated with difelikefalin experienced AEs of diarrhea, vomiting, and dizziness. An oral formulation is currently being studied for the treatment of itch in AD and notalgia paresthetica, but no data are currently available regarding its use in PN.

*Neurokinin Antagonists*

Despite initial excitement about the use of NK1 receptor antagonists in the management of idiopathic pruritus and PN, both aprepitant and serlopitant failed to meet primary endpoints in RCTs for PN leading to the abandonment of these agents for FDA approval for PN indication. However, it is important to note that in the phase 2 RCT comparing serlopitant 5 mg daily (n=65) to placebo (n=63) over 8 weeks, serlopitant treatment resulted in itch reduction as early as 2 weeks, and significantly reduced itch compared to placebo at weeks 4 ($P$=0.02) and 8 ($P$<0.001).[74] AEs reported for NK1 receptor antagonists are generally mild and similar to placebo. The most commonly reported AEs were nasopharyngitis, diarrhea, and fatigue with oral serlopitant; nausea, vertigo, and drowsiness with oral aprepitant; and administration-site pain and cutaneous reactions with topical aprepitant.[75-77]

*Thalidomide and Lenalidomide*

Thalidomide and/or its analogue lenalidomide have been used in the management of PN for decades, although formal RCTs evaluating their efficacy for PN are not available, and data to support its use are limited to case reports, case series, and small observational studies.[78,79] A systematic review that pooled from 18 publications studying these agents for PN reported that thalidomide (50-300 mg used for <1 year) and (5-10 mg for <24 months) resulted in improvement in 71.7% of patients treated.[80] In another study evaluating low dose (<100 mg) thalidomide in severe and refractory PN patients (n=17), 9 patients achieved complete clearance, and 4 achieved partial clearance of their disease.[78] Although individuals in this study tolerated thalidomide well without neuropathy, thalidomide is often limited by sedation, gastrointestinal discomfort, the potential for peripheral neuropathy, risk of thromboembolism, and teratogenicity.[7,79,80] Limited evidence exists to support the efficacy of lower doses (50-100 mg/day) with fewer AEs.[81,82]

## CONCLUSIONS

Although most treatments for PN are currently used off label with minimal data from double-blind RCTs to support their use, a rapid surge in clinical trials evaluating anti-itch therapeutics for PN holds promise for a broader therapeutic arsenal to help manage this challenging disorder. An effective treatment approach should be tailored to the individual needs of the patient, considering their clinical presentation,

comorbidities, and associated quality of life concerns including sleep and mood disturbance. Combination therapy of immunomodulatory and neuromodulatory agents may promote faster itch resolution and/or lesion control than individual therapy, although formal studies to evaluate this approach are needed. Newer agents, including dupilumab, nemolizumab, JAK inhibitors, and others may exert their effects by targeting immune and nerve populations, which may explain their rapid and often dramatic impact on the PN population.

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## DISCLOSURES

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