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Metabolic Drivers of Itch: Neural Dysregulation in Prurigo Nodularis Linked to Obesity and Diabetes Metabolic Itch and Neural Dysregulation in PN

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Abstract

Background: Prurigo nodularis (PN) is a chronic skin condition characterized by intense itching, recognized as a neuroimmune disease linked to an "itch-scratch" cycle and neural sensitization. Recent evidence suggests that metabolic syndrome, including obesity and type 2 diabetes, may exacerbate chronic inflammation in PN.

Objectives: This study aims to systematically review the recent literature (2015-2025) on peripheral neural changes and central itch pathways in PN, highlighting their clinical implications and how they intersect with metabolic dysregulation.

Methods: A systematic search was conducted for original studies on PN published from 2015 to 2025, focusing on neural and neuroimmune mechanisms.

Results: Forty-three studies were included, consisting of 5 clinical trials, 4 interventional studiesm, 10 observational studies, 15 translational lab studies, and 10 mechanistic studies. Key findings indicate significant peripheral neural changes, such as altered intraepidermal nerve fiber density and increased levels of pruritogenic neuropeptides. Immune mediators like interleukin-31 interact with cutaneous nerves, creating a cycle of itch and inflammation. Central sensitization, similar to chronic pain, is also observed, with PN linked to various comorbidities. Biologic therapies targeting IL-31 or type-2 cytokines (e.g., nemolizumab, dupilumab) have shown promise in reducing itch.

Conclusions: PN exemplifies a disorder of neural dysregulation that necessitates an integrated approach. Addressing both local neurogenic inflammation and central sensitization is crucial for breaking the itch-scratch cycle and improving patient outcomes.

Keywords: Prurigo Nodularis; Chronic Pruritus; Neuroimmune Dysregulation; Peripheral Sensitization; Central Sensitization; Metabolic Syndrome; Type 2 Diabetes; Obesity; Interleukin-31; Translational Dermatology

Abbreviations: PN- Prurigo Nodularis; T2DM- Type 2 Diabetes Mellitus; IL- Interleukin; AD- Atopic Dermatitis; IENFD- Intraepidermal Nerve Fiber Density; SP- Substance P; CGRP- Calcitonin Gene-Related Peptide; NK1R- Neurokinin-1 Receptor; NGF: Nerve Growth Factor; OSMRβ: Oncostatin M Receptor Beta; ETAR- Endothelin A Receptor; CGRPR- CGRP Receptor; JAK- Janus Kinase; CRP- C-Reactive Protein; CNS- Central Nervous System; TRP- Transient Receptor Potential; RAAS- Renin-Angiotensin-Aldosterone System; HbA1c- Hemoglobin A1c

Introduction

Prurigo nodularis (PN) is a chronic skin disorder characterized by its classic morphology of dome-shaped, firm, hyperkeratotic nodules that may appear excoriated or crusted due to persistent scratching. These lesions typically develop on the extensor surfaces of the arms, legs, and trunk. Patients often suffer from intense pruritus, which contributes to sleep disturbances and significant psychological distress. The typical clinical presentation of PN is shown in Figure 1 through a pictographic depiction, which demonstrates both the distribution and the associated symptoms, including pruritus and sleep disruption. PN has shifted from being viewed as only a skin disorder to being recognized as a primary neuroimmune disease impacting both the nervous and immune systems' functions [1,2]. The persistent severe itching experienced by PN patients causes significant quality of life deterioration, which triggers sleep disturbances along with anxiety and depression. People with PN experience greater quality of life impairment than patients with other chronic skin conditions, which cause itching due to the extreme intensity and treatment resistance of PN symptoms [1,3]. The burden of PN increases due to its high healthcare utilization and patient distress, while many patients express dissatisfaction with available treatment options (Figure 1).

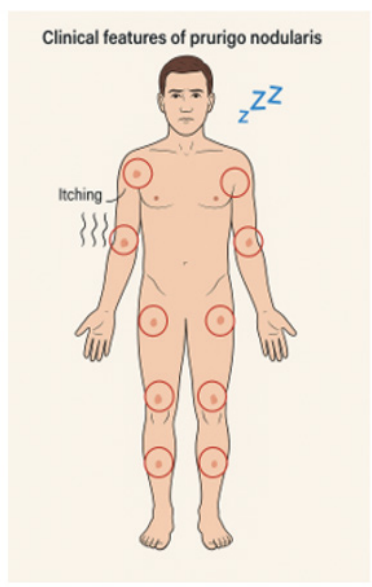

Figure 1: Classical clinical distribution of prurigo nodularis.
Multiple hyperkeratotic, excoriated nodules (red circles) are distributed on extensor surfaces of the arms and legs. These lesions are intensely pruritic (itch indicated by wavy lines), leading to an "itch-scratch" cycle, and are often accompanied by sleep disturbances (illustrated by the 'Zzz' icon), highlighting the systemic impact of chronic pruritus [1-3].

Recent findings show that PN commonly presents alongside systemic metabolic dysfunction. Research reveals PN patients have higher occurrences of metabolic syndrome and its elements than the general population, which includes type 2 diabetes mellitus (T2DM), obesity, dyslipidemia, and hypertension [4-6]. A recent meta-analysis study found that around one-third of patients dealing with PN also suffer from T2DM [5]. The relationship between chronic metabolic inflammation and insulin resistance indicates they play a role in PN pathogenesis through a neuroinflammatory environment that promotes itch [6]. PN-associated itching intensifies due to the low-grade systemic inflammation in obesity and diabetes. Patients showing severe PN along with sleep disturbances experience higher levels of C-reactive protein, which leads to a fourfold elevation in their risk of developing metabolic syndrome [7]. Clinicians often evaluate PN patients for systemic causes of itch, like diabetes and renal disease, after identifying these connections [1].

A self-sustaining "itch-scratch" cycle dominated by neural dysregulation forms the core of PN pathophysiology. When scratching occurs repeatedly, the skin barrier gets damaged, causing neural hyperplasia, which releases pruritogenic mediators, thus forming a vicious cycle of chronic itch. Recent conceptual advances describe PN through four key pathogenic domains: The pathogenic mechanism behind PN involves type 2 inflammation, epidermal hyperplasia, dermal fibrosis, and neuroimmune dysregulation [8]. The concept of "neural sensitization" now functions as the principal connecting mechanism between these various domains. PN's chronic itch condition stems from peripheral nerve fiber sprouting, skin sensitization, and central nervous system alterations resembling chronic pain mechanisms. PN lesions demonstrate chronic neuronal hyperexcitability and sensitization that extends beyond the lesion area and represents widespread neural circuit dysregulation in processing itch [9,10]. Additionally, neuropeptide-mediated inflammation and immune cell recruitment in PN skin indicate active neuroimmune cross-talk. According to Chisolm et al. (2023), PN manifests as a "chronic neural-and immune-mediated disease" where nerve fibers and immune cells mutually facilitate each other's activation [1]. The combined understanding of PN reveals it as a neurocutaneous syndrome that extends beyond skin disorders, including dysfunctional interactions between the skin's nervous and immune systems.

Current research advancements have yet to produce a comprehensive review that analyzes PN's neural dysregulation and how it connects peripheral and central itch pathways. Although prior research has examined PN's immunopathogenesis and new treatments [3,11] and its clinical management [12,13], no studies have brought together recent mechanistic discoveries about peripheral nerve alterations and central sensitization which led to chronic itching in PN patients. Understanding these neural pathways is not only important academically but also has significant translational implications: This research establishes the foundation for creating new targeted treatments (such as Interleukin-31 (IL-31) blockers and inhibitors of other neuroactive cytokines) alongside complete management strategies that treat skin conditions and nervous system issues.

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The recent approval of nemolizumab (an anti-IL-31 receptor antibody) for PN management combined with active research into additional neural targets makes an updated review of peripheral and central itch mechanisms in PN extremely relevant [14,15].

Based on current findings, the systematic review intends to fill this research gap through a detailed investigation of neural dysregulation in PN. We synthesize evidence from recent primary studies (2015-2025) on: The research examines neural dysregulation in PN through three main areas: (1) peripheral neural modifications including nerve fiber density changes and neuroimmune interactions in the skin; (2) neural sensitization processes in central itch pathways along with associated central nervous system alterations and neural comorbidities; and (3) potential clinical applications of these findings to enhance existing and develop new treatment approaches. By merging these research results, we aim to understand the interactions between peripheral and central itch pathways in PN and how focusing on these pathways can enhance patient treatment results.

Methods

Search Strategy

Our systematic literature search aimed to locate primary research studies on prurigo nodularis that focused on neural and neuroimmune mechanisms and itch-related processes. Our search covered PubMed, Scopus, and Embase databases to locate articles published between January 1, 2015, and April 31, 2025. Our search strategy included keyword combinations such as "prurigo nodularis," "itch," "neural," "nerve," "neuropeptide," "pruritus mechanism," and "sensitization." We completed a manual review of reference lists from relevant review articles like those by Liao et al. (2024) and Müller et al. (2023) to include all relevant studies [3,11]. Articles published in non-English languages were included in the study only if an English translation was available.

Inclusion and Exclusion Criteria

We included studies that met the following criteria: The selected studies examined PN patients or designated PN as a separate group alongside laboratory work using human PN samples and explored neural dysregulation along with itch mechanisms and neuroimmune interactions such as nerve fiber modifications and itch-related biological mediators and neuroimmune cells as well as central neural itch responses in PN. Our research included clinical trials, cohort studies, case-control and cross-sectional studies, and translational research. Translational research included tissue analyses and molecular or cellular experiments on PN biopsies. Review articles, editorials, and expert opinions did not make it into our study, but we used them to build the background of the introduction. Case reports were also excluded from the systematic analysis to focus on generalizable data, with one exception: The review included small case series from extensive studies when these series provided valuable mechanistic information.

Data Extraction and Synthesis

The two researchers (blinded) conducted separate evaluations of titles and abstracts to determine relevance before independently reviewing complete articles of selected studies. Discrepancies were resolved by consensus. The included studies provided us with detailed information about their design structures and sample sizes, as well as their methods, which encompassed clinical assessments and molecular or histological techniques, along with their principal discoveries about itch pathways and neural characteristics in PN. Because study designs and outcomes varied extensively, we decided against a meta-analysis and opted for qualitative synthesis. We organized study findings into thematic categories, including peripheral mechanisms, central mechanisms, neuroimmune mediators, and therapeutic interventions for narrative reporting.

Study Characteristics

Our selection process identified 43 distinct studies that satisfied the inclusion criteria. We categorized these by study type: The study types included five interventional studies which were randomized controlled trials or interventional cohort studies that tested PN therapies and their mechanisms, as well as observational clinical studies and mechanistic laboratory studies which looked at clinical, histological data in PN patients and conducted transcriptomic, proteomic or cellular analyses of PN tissue using animal or ex vivo models to study PN itch mechanisms. Each study received no formal assessment for risk of bias. However, most observational studies had small single-center samples that likely restrict their generalizability. In contrast, mechanistic studies frequently did not include non-PN control groups beyond comparisons with healthy skin or atopic dermatitis (AD). These limitations are noted in our discussion (Table 1).

Results

Research articles comprehensively picture neural dysregulation in PN by combining clinical data with molecular discoveries. Figure 2 shows how study designs are distributed across the research. Among the 43 studies reviewed, 5 (11.4%) were randomized controlled trials or interventional therapy studies, often incorporating mechanistic analyses; 10 (22.7%) were observational studies involving patient populations; 4 (9.1%) were uncontrolled interventional studies; 15 (36.4%) were translational laboratory investigations focused on molecular or immunologic mechanisms; and 9 (20.9%) were case reports or case series. Research utilized patient samples and models to perform single-cell sequencing and cytokine analysis. The research field of PN has adopted sophisticated translational methods such as single-cell RNA sequencing and spatial proteomics in conjunction with clinical research during the last ten years. The subsections below summarize the key characteristics and findings from these studies. The majority of PN patients in these studies showed metabolic issues like obesity and T2DM, which indicates

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a relationship between neuro-itch dysregulation and systemic metabolic dysfunction [5,6] (Figure 2).

Table 1: Categories of included studies (2015-2025) and number of studies in each design type.

Study Design	Number of Studies (n)
Randomized controlled trials (placebo-controlled)	5
Uncontrolled interventional studies (open-label/longitudinal)	4
Observational studies (cross-sectional or correlational)	10
Translational laboratory studies (molecular/immunologic)	15
Case reports/series	9
Total	43

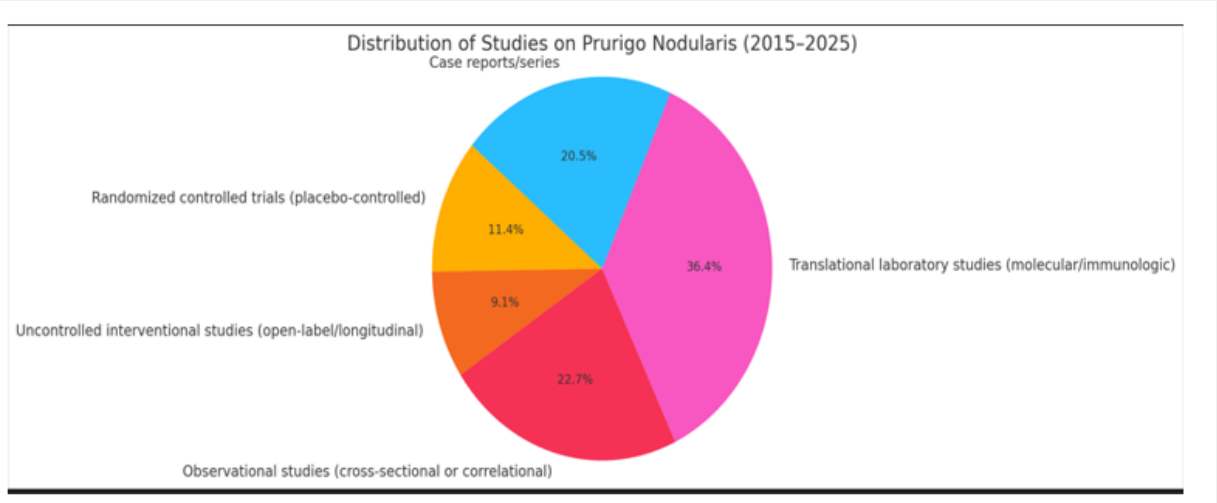

Figure 2: Distribution of included study types in this systematic review (N = 43 studies).
This pie chart illustrates the relative proportions of 43 studies categorized into translational laboratory studies (36.4%), observational designs (22.7%), case reports/series (20.5%), randomized controlled trials (11.4%), and open-label/uncontrolled interventional studies (9.1%). These data reflect the growing emphasis on molecular and immunologic mechanisms in PN research.
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Peripheral Neural Alterations in PN

The skin affected by PN exhibits distinct changes in its peripheral cutaneous nerves. Research consistently demonstrates variations in intraepidermal nerve fiber density within PN lesions. Interestingly, studies have reported seemingly paradoxical results regarding nerve fiber density: Initial histological assessments reveal reduced intraepidermal nerve fibers density (IENFD) in chronic PN lesions because nerve fibers endure damage from extended inflammation and scratching. Research by Bobko et al. (2016) revealed that lesional and peri-lesional PN skin exhibited much lower IENFD than healthy skin [16].

Meanwhile, nerve fibers showed reinnervation of the epidermis after lesion healing. The disease state causes epidermal nerve fiber loss, which is followed by nerve regrowth once recovery begins. Clinical evaluation of PN lesions reveals nodules exhibiting hyperesthesia or heightened sensitivity, indicating potential functional hyperinnervation or increased neural sensitization, even though visible nerve fibers appear diminished [16]. The immunohistochemical research by Agrawal et al. (2023) demonstrated that PN lesions contain more S-100 positive neural elements compared to controls and feature elevated mast cell density in the dermal layer as revealed by toluidine blue staining [17]. This study indicates enhanced reactivity of S-100 protein, which points to damaged intraepidermal free nerve endings, yet simultaneous dermal nerve growth in PN. PN lesions demonstrate concurrent hypertrophy or hyperplasia of dermal nerve fibers despite the damage to intraepidermal free nerve endings. These findings align with the concept of "neural plasticity" in chronic itch: The skin's nerve cells alter their structure when affected by PN because chronic inflammation destroys certain nerve fibers [17]. In contrast, others grow thicker or produce new branches, resulting in a dysfunctional nerve network [18].

PN lesions show abnormal expression of neurotrophic factors and neuropeptides beyond nerve fiber density, which drives neural hypersensitivity. Nerve Growth Factor (NGF) is a primary neurotrophin that facilitates peripheral nerve growth alongside sensitization. In a comparative analysis. The study by Deng et al. (2022) demonstrated that PN lesional skin exhibits much higher

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NGF concentrations than AD lesions and healthy skin, aligning with greater neural density observed in PN derma. Expression levels of NGF and its receptors TrkA and p75NTR increased in PN skin, which suggests NGF plays a role in abnormal nerve growth within PN. Recent studies propose that artemin participates in the development of itch neuron hyperplasia [19]. However, direct PN evidence remains scarce, and studies of other chronic itch conditions reveal that artemin/GFRα3 signaling triggers itch neuron sprouting. The upregulation of NGF in PN might occur alongside other growth factors to create a nerve-dense environment within the skin tissue [3].

PN lesional skin presents elevated pruritogenic neuropeptide release from cutaneous nerves as structural changes occur. Skin nerve fibers release substance P (SP) and calcitonin gene-related peptide (CGRP), which transmit itch and pain signals while also triggering inflammatory responses in immune cells and blood vessels [18,20,21]. PN skin biopsies display increased SP immunoreactivity within nerve fibers while showing raised dermal levels of both SP and CGRP, particularly in pruritic lesions [3]. Substance P's interaction with neurokinin-1 receptors on neurons and immune cells increases itch sensation, while neurokinin-1 receptor (NK1R) antagonists remain investigated as potential itch relief treatments [21]. The scientific basis for NK1R antagonists in PN remains valid despite varied clinical trial results because neuropeptidergic signaling plays a role in PN's neurogenic inflammation [22]. CGRP functions as a vascular dilator and inflammatory cell recruiter, and its elevated levels in PN skin help maintain neurogenic inflammation that triggers itch. In summary, PN lesions are biochemically primed for itch: PN lesions contain neuron-derived peptides that directly trigger pruritus and neurogenic inflammation.

The close relationship between skin nerves and immune cells stands as another marker of peripheral neural dysfunction observed in PN. Mast cell numbers usually rise in PN lesions, where they typically gather near nerve fibers. The mast cells produce a variety of mediators, including histamine, tryptase, IL-4, and nerve growth factors that can activate or damage nearby nerves. Research using electron microscopy and immunostaining in PN demonstrates degranulating mast cells positioned near neural structures, which indicates bidirectional communication between nerves and mast cells where nerves release neuropeptides that activate mast cells and mast cells release substances that either stimulate nerves or promote their growth [17]. Mast cell-nerve interactions play a significant role in sustaining PN itch through pathways that do not depend on histamine, since antihistamines do not alleviate most PN itch. Research shows that eosinophils and dendritic cells play a role in this process. Eosinophil infiltration occurs in PN lesions, which produce neurotoxic granules along with pruritogenic cytokines such as IL-31 that affect nerve function [18,20]. The study by Liu et al. (2023) showed that PN lesional skin has elevated levels of CD11c^+ myeloid dendritic cells compared to non-lesional and healthy skin which correlated with patient itch severity. The interaction between dendritic cells and nerve fibers occurs through cytokines such as IL-31, which dendritic cells produce, and antigen presentation that triggers neuroimmune responses [23]. These findings collectively underscore that peripheral sensitization in PN is not only due to inherent nerve fiber abnormalities, but also due to a pro-pruritic cutaneous microenvironment: A pathological communication exists between skin immune cells and structural cells with nerve fibers, which reduces the activation threshold for itch nerves.

Neuroimmune Mediators Linking Skin and Nerves

The discovery of specific cytokines and receptors that link the immune system to the nervous system within skin tissue marks an important advancement in PN research. Interleukin-31 (IL-31), which is known as the "itch cytokine," functions as a key component because Th2 helper T cells and certain dendritic cell subsets produce it to activate IL-31 receptors on sensory neurons directly, which leads to pruritus. Patients with PN exhibit a significant increase in the expression of IL-31. In their 2022 study, Chaowattanapanit et al. demonstrated elevated serum IL-31 levels in PN patients compared to healthy controls. They verified through immunohistochemistry that IL-31 expression rose within PN lesions both in immune cells and the epidermis. The association between elevated IL-31 levels and increased itch severity suggests IL-31 drives pruritus in PN [24]. Research by Afratakhti et al. (2022) showed a group of PN patients with higher levels of circulating IL-13 and periostin (both fibrogenic type 2 biomarkers) who also had elevated IL-31, suggesting a specific PN subgroup with type 2 cytokine bias and intense pruritus [25]. The critical role of IL-31 in PN is further supported by therapeutic evidence: The monoclonal antibody nemolizumab works by targeting IL-31RA and has shown significant reductions in itch and lesion improvement for PN patients [26,27]. The nemolizumab results validate IL-31 as a central pathogenic factor within the PN neuroimmune network, which we will address later.

The classic type 2 cytokines IL-4 and IL-13, which drive atopic inflammation, significantly contribute to neural dysregulation in PN. PN presents a Th2-skewed immune microenvironment that does not reach the severity of atopic dermatitis. Research by Shao et al. (2023) indicates that lesional PN skin demonstrates increased IL-4 and IL-13 expression levels, while IL-4 directly correlates with itch intensity. Sensory neurons become directly excitable and are induced to produce itch when IL-4 and IL-13 bind to IL-4 receptor α [28]. Research shows that IL-4/IL-13 signaling decreases neuronal sensitivity to pruritogens and triggers scratching behavior in mice during cutaneous injection. Type 2 inflammatory processes leading to PN itch are confirmed through significant patient improvement from IL-4/IL-13 inhibition by dupilumab (an IL-4Rα antagonist that blocks both cytokines). Dupilumab affects skin lesions and itching in PN patients through simultaneous or separate actions, showing that these cytokines affect neural itch circuits and skin inflammation independently or together [26]. IL-4 and IL-13 stimulate fibroblast activation

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and periostin production within dermal layers, establishing a connection between neural dysfunction and fibrotic changes found in persistent PN nodules [28]. IL-4/13 triggers itch through neurons and immune cells while facilitating the tough-to-treat fibrotic core of nodules.

Additional cytokines and mediators involved in the neuroimmune dialogue of PN include IL-17 and oncostatin M (OSM), among other key players. IL-17 levels increase in specific PN lesions due to Th17 cells and neutrophil production, but its effect on itch remains less defined when compared to IL-31 or IL-4/13. Researchers focus on OSM because its receptor OSMRβ joins with IL-31RA to create the IL-31 signaling complex, but OSM has alternate signaling capabilities through OSMRβ-gp130 complexes. Research by Shao et al. (2023) shows that pruritic inflammatory skin exhibits higher OSM levels while PN lesions demonstrate increased OSMRβ expression. Research is ongoing for therapies like vixarelimab that target OSMR with the expectation of treating both pruritus and inflammation simultaneously. Sensory nerve endings express transient receptor potential (TRP) channels, which function as critical mediators of itch signals derived from different chemical stimuli, with TRPV1 and TRPA1 being particularly notable. These ion channels undergo sensitization in chronic pruritic skin, but this process is not exclusive to PN [28]. The latest research review shows that TRP channel dysfunction (stimulus-induced overactivity) lies at the heart of chronic itch conditions and serves as a focus for developing precise antipruritic treatments [29]. The continuous presence of cytokines such as IL-31 and epidermal irritants in PN may cause an increase in TRPV1/A1 activity, which results in heightened nerve sensitivity. Patients report their PN nodules to be itchy and, at times, painful or burning, resulting from activation of polymodal nociceptive channels.

Skin-derived cells like mast cells and keratinocytes release pruritogenic mediators such as Substance P and endothelin-1 that target specific receptors and channels on sensory nerve endings in the skin [18,20,21]. The central neuronal receptors and channels involved in PN itch signaling are NK1R (neurokinin-1 receptor for SP), MRGPRX2 (mast cell receptor for SP/CST), endothelin A receptor (ETAR), CGRP receptor (CGRPR), TRPV1 and TRPA1 (ion channels for various itch stimuli with Ca^2+ influx) and the receptors for IL-4/13 (IL-4Rα/IL-13Rα1), IL-31 (IL-31RA/OSMRβ), and OSM (gp130/OSMRβ). When these pathways become active, they trigger nerve depolarization, which causes nerve endings to release additional neuropeptides, thereby creating positive feedback loops. These pathways are denoted below: Dupilumab functions by blocking IL-4Rα, which stops IL-4/13 signaling, while Tralokinumab targets IL-13 explicitly. Nemolizumab binds IL-31RA, and Vixarelimab inhibits OSMRβ with Janus Kinase (JAK) inhibitors (abrocitinib, tofacitinib, upadacitinib, baricitinib) targeting multiple cytokines signaling pathways. The drug Barzolvolimab functions by binding to the KIT receptor, decreasing the mast cell population [18,20,21]. These therapies disrupt skin-nerve communication to stop the itch-scratch cycle.

(Figure 3) demonstrates how prurigo nodularis (PN) neuropeptide systems and their receptors present multiple potential treatment targets. Therapeutic interventions focusing on the SP-NK1R axis and IL-31-neuron signaling through IL-31RA antagonism target the neural components responsible for chronic itch. Neuropeptide-based treatments, including NK1R antagonists, show inconsistent clinical results, but their effectiveness can be explained by the molecular sensitization of PN nerves to pruritogenic stimuli [18,21,22]. PN lesions feature numerous neuroactive substances, including classic neuropeptides such as P and CGRP and endothelin-1 from epithelial sources, which target peripheral nerve endings to maintain itch responses [18,20,21]. Clinical trials demonstrate that pruritus relief results from interrupting neuroimmune signaling pathways by blocking IL-31 and IL-4/13 cytokines.

Figure 3. Schematic overview of peripheral neuroimmune interactions driving itch in prurigo nodularis.

PN's neuroimmune crosstalk is dominated by a type 2 inflammatory milieu that feeds directly into neural activation: The cytokines IL-31, IL-4, and IL-13 function as key regulators bridging immune cells with itch fibers. Additional regulatory layers come from Th17 cytokines, along with other cytokines. Cytokine-targeting treatments in PN demonstrate translational medicine success by proving that neural symptoms like itch can be controlled through immune modulation at the neuroimmune interface. (Table 2) compares major cytokines and neural factors that affect PN by detailing their origins and nerve impacts alongside reviewed study evidence (Table 2).

Central Sensitization and Neural Pathways in PN

The pathophysiology of PN originates in the skin, yet research shows chronic itch in PN involves central nervous system activity. PN patients display central sensitization characteristics, which is a condition that triggers heightened responses of the spinal cord and brain to peripheral stimuli as studied in chronic pain research [8,18]. Central sensitization in itch leads to allokinesis, which results from harmless stimuli or the extension of itch beyond localized skin regions. PN provides examples of both. Patients suffering from PN experience itching near lesions or unaffected skin when light touch occurs, which implies central amplification [10,19]. Research in the field of epidemiology has identified connections between PN and neural sensitization disorders. A study by Choragudi and Yosipovitch (2023) examined a comprehensive inpatient database and discovered a significant connection between PN and chronic pain syndromes, together with neuropathic disorders. Patients who have PN more frequently are prone to developing fibromyalgia as well as migraines and diabetic neuropathy according to central sensitization syndrome

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studies when researchers remove potential confounders [30,31]. The simultaneous appearance of PN with these conditions indicates that people with PN may possess inherent or common biological pathways that result in increased neural sensitivity. Similarly, Hughes et al. (2020) found that most PN patients display peripheral neuropathy conditions like small fiber neuropathy or radiculopathy through neurological examination. The treatment of neuropathy in their cases sometimes reduced the itching, which supported the theory that neuropathic signals play a role in PN pruritus [10]. The evidence demonstrates that PN functions beyond skin symptoms and affects wider itch processing mechanisms.

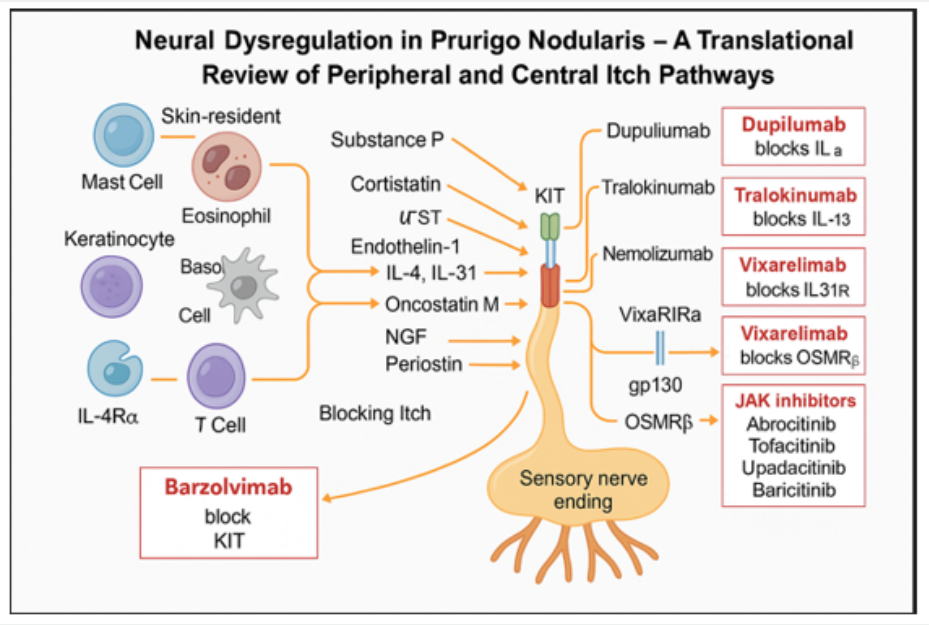

Figure 3: Schematic overview of peripheral neuroimmune interactions driving itch in prurigo nodularis.
Skin-resident cells (e.g., mast cells, eosinophils, keratinocytes, T cells) release mediators-Substance P, IL-4, IL-31, oncostatin M, NGF, periostin-that activate sensory nerve endings via KIT, IL-4Rα, IL-31R, OSMRβ, and gp130. Agents such as dupilumab, tralokinumab, nemolizumab, vixarelimab, barzolvimab, and JAK inhibitors (abrocitinib, tofacitinib, upadacitinib, baricitinib) block these pathways to reduce chronic itch [3,9,11,26].

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Table 2: Key cytokines and neural alterations in prurigo nodularis and their roles in itch pathogenesis.

Mediator/Factor	Source in PN lesions	Effect on Itch/Nerves	Evidence in PN (2015-2025 studies)
IL-31 [8]	Th2 T cells, mast cells	Activates IL-31RA; boosts Th2	↑ IL-31 in PN; nemolizumab ↓ itch
IL-4 / IL-13 [15,26]	Th2 cells, basophils, eosinophils	Sensitizes nerves; causes fibrosis	↑ IL-4/13 in PN; dupilumab effective
IL-17 [28]	Th17, ILCs	Drives neutrophils; boosts keratinocytes	↑ IL-17A in PN; reduced post-nemolizumab
Oncostatin M [28]	T cells, macrophages, keratinocytes	Inflammation/fibrosis via OSMRβ	↑ OSM in PN; vixarelimab ↓ itch
NGF [19]	Skin cells, neurons	Promotes nerve sprouting, lowers firing threshold	↑ NGF in PN vs AD; enriched nerve growth genes
Substance P [22]	Sensory nerves	Stimulates NK1R; degranulates mast cells	↑ SP/NK1R activity; partial relief with antagonists
CGRP [30]	Sensory nerves	Modulates inflammation; vasodilates	IL-31 induces CGRP; present in PN nerves
Mast cells [13]	Dermal mast cells	Releases mediators; activates PAR2	↑ Mast cells, tryptase, histology supports role
↓ IENF [16]	Structural finding	Fewer fibers; neuropathic itch	↓ IENF in lesional/non-lesional PN
↑ Dermal fibers [17]	Structural finding	More dermal fibers; stronger signal	↑ Thickened dermal nerves, myelin geneupreg.
Central sensitization [9,31]	CNS (brain, spinal cord)	Amplifies CNS itch processing	PN linked to fibromyalgia; suggests CNS role

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Abbreviations: IL- Interleukin; Th2- T-helper type 2; Th17- T-helper type 17; ILC- Innate lymphoid cell; OSM-Oncostatin M; OSMRβ-Oncostatin M receptor beta; NGF- Nerve growth factor; SP-Substance P; NK1R- Neurokinin-1 receptor; CGRP- Calcitonin gene-related peptide; PAR2-Protease-activated receptor 2; IENF- Intraepidermal nerve fiber; AD- Atopic dermatitis; CNS- Central nervous system

Research suggests chronic pruritus at the spinal cord level involves neurons in the dorsal horn that become hyperexcitable. Research on animal models and human conditions demonstrates that persistent itch produces transcriptional and synaptic changes within the spinal cord that mirror chronic pain characteristics, such as heightened excitatory neurotransmitters and reduced inhibitory tone alongside gliosis development. Human data about PN remains limited, yet available evidence allows us to conclude these changes. Steinhoff et al. (2022) proposed that persistent itch in chronic atopic dermatitis and PN causes NMDA receptor-driven sensitization of neurons within the spinothalamic tract through continuous spinal cord stimulation, which mirrors the pain "wind-up" effect. Eventually, these changes mean that minor stimuli or self-generated nerve impulses in PN skin become amplified at the central level, which produces intense itch sensations that exceed the actual peripheral damage [8,18]. Advanced neuroimaging methods are now revealing the mechanisms of central itch processing in PN. A recent systematic review of functional MRI in PN summarized preliminary findings: Functional MRI results demonstrate that PN patients activate distinct brain regions, including the prefrontal cortex, insula, and cingulate cortex, when exposed to itch stimulation differently from healthy individuals. The brain regions activated during chronic itch intersect with salience and emotion processing areas, which indicates that circuits involved in attention and pain perception reinforce the itch experience [32]. Future research must confirm that PN leads to remodeling of central neural circuits, which transform the central nervous system into an active player in maintaining chronic itch.

The involvement of both the autonomic nervous system and circadian rhythms presents a fascinating dimension to studying neural dysregulation in PN. PN patients experience itch patterns throughout the day, with symptoms intensifying during nighttime. According to Steinhoff et al. (2022), PN itch intensifies at night because of decreased distractions, which increase itch perception and circadian variations in cytokine or neural mediator levels. The autonomic nervous system may control itch through stress-induced responses, leading to increased sympathetic activity that worsens itch symptoms in those vulnerable to such reactions [18]. Some evidence points to dysautonomia in chronic pruritus conditions: Recent small studies show changes in heart rate variability and sweat responses among chronic itch patients, which suggest dysfunction in the ANS [33]. Although no published research has confirmed an ANS abnormality in PN cases, researchers find it feasible because stress appears to trigger PN flare-ups. Nerve growth factor and substance P, which show elevated levels in PN, appear to interact with autonomic nerve fibers like cutaneous sympathetic nerves, leading to vasodilation and other lesion trophic modifications [21]. The understanding of this area remains theoretical but suggests additional neural regulation mechanisms that might be disrupted in PN.

Therapeutic Modulation of Itch Pathways

The success of innovative treatments that target neural pathways demonstrates the translational significance of understanding PN's neural pathways. Targeting neuroimmune cytokines through biologic therapies and JAK inhibitors leads to exceptional PN treatment results, which confirms these cytokines as disease drivers. Research findings in 2023 revealed two essential Phase 3 studies concerning nemolizumab, which functions as an anti-IL-31 receptor antibody. The OLYMPIA 2 trial revealed that subcutaneous nemolizumab administration every 4 weeks achieved a minimum 4-point reduction in itch scores for about 60% of patients after 16 weeks, while only approximately 20% of patients receiving placebo saw similar results [27]. Patients taking nemolizumab experienced significant nodule healing and improved sleep and life quality. The research documented by Kwatra et al. (2023b) established that patients treated with nemolizumab plus topical steroids experienced a significant reduction in itch and skin lesions compared to those treated with placebo plus steroids. Significantly, these trials demonstrate efficacy and provide mechanistic insight: The studies demonstrate that IL-31 signaling plays a crucial role in causing PN itch. The inhibition of IL-31R from a neural perspective reduces IL-31-triggered activation of itch neurons and likely decreases neuroimmune responses in skin tissue because IL-31 interacts with keratinocytes and immune cells [26]. Research conducted by Deng et al. (2023) backs these findings through their translational study. They analyzed skin biopsies on PN patients before and after 16 weeks of nemolizumab treatment. The treatment with nemolizumab resulted in both decreased expression of type 2 inflammatory genes and pruritic pathways in the affected skin areas while simultaneously restoring the expression of some epidermal barrier genes. After treatment, IL-31 and IL-13 downstream gene signatures showed reduction and a rise in proteins, including filaggrin, which is key to barrier function. Nemolizumab disrupts the IL-31 neuronal feedback loop, which leads to itch relief and initiates skin repair by breaking the biochemical itch–scratch cycle [14]. In line with this, Tsoi et al. (2022) showed that blocking IL-31 reverses PN's transcriptomic profile, which depends on IL-31/IL-4 response genes and neuropeptide pathways, demonstrating the molecular disease modification through neural cytokine targeting [34]. Sonkoly (2022) pointed out that inhibiting IL-31, which serves as "the itch cytokine," shuts down a substantial portion of the PN disease network, resulting in clinical improvement [2].

Dupilumab represents another therapeutic breakthrough because it targets IL-4Rα to stop IL-4 and IL-13 from transmitting

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signals. Dupilumab first emerged as a treatment for atopic dermatitis before Phase 3 studies in 2022 showed its effectiveness against PN, which resulted in its FDA approval for this use. According to combined PN trial results, dupilumab treatment led to significant itch relief for 45-60% of patients after 24 weeks while only 30% of placebo recipients experienced similar improvement. Skin lesions also improved, albeit gradually [15]. Clinical observations indicate that some patients experienced early itch relief before their nodules flattened.

In contrast, other patients showed skin lesion improvement first, suggesting that IL-4/13 signaling influences itch sensation and skin pathology through separate yet intersecting pathways. Dupilumab functions by blocking IL-4 and IL-13, which likely diminishes their itch-inducing effects on neurons and limits the production of IL-31 and other immune cell mediators. Blocking IL-4 and IL-13 should decrease dermal fibrosis because these cytokines activate fibroblasts, and this reduction will help dissolve nodules and normalize nerve distribution in the skin over time. Recent single-cell research supports these findings. Single-cell RNA sequencing of PN lesions by Ma et al. (2023) revealed COL11A1^+ pro-fibrotic fibroblasts highly enriched in PN that showed decreased expression of fibrosis and neural interaction genes, including periostin, fibronectin, and WNT5A, after IL-31 or IL-4/13 blockade therapy [7]. Joel et al. (2024) discovered specific fibroblast subpopulations within PN that expressed excessive levels of pruritogens and proteins related to scarring, which suggests that treatments must target this fibroblast-driven aspect of PN [35].

Small-molecule JAK inhibitors, which inhibit various cytokine pathways including IL-31 and IL-4/13, show anecdotal results in PN treatment beyond biologics. Case series describe how oral tofacitinib, Upadacitinib, and Abrocitinib treatments resulted in quick itch relief for severe PN patients who did not respond to other treatments [17,34,36,37]. JAK inhibitors function by simultaneously reducing the activity of multiple pruritic cytokines, including IL-2, IL-4, IL-13, and IL-31. JAK inhibitors function by reducing skin neuroimmune activity [38]. The long-term safety profile for these treatments in PN patients has yet to be fully determined.

Traditional treatments for PN, including thalidomide, gabapentinoids, and phototherapy, suggest neural mechanisms as part of their therapeutic effects. Thalidomide operates in PN by reducing TNF-α and other inflammatory mediators. However, its neuropathy side effect leads to questions about whether its anti-itch capabilities stem from nerve function suppression. Gabapentinoids (gabapentin and pregabalin) function by targeting neuronal calcium channels for off-label use in PN to lower central sensitization; their effectiveness in some patients confirms that central nervous system intervention can alleviate PN itch [12]. Nonspecific older treatments uphold the theory that PN treatment needs comprehensive management through both immunologic and neurologic strategies.

In summary, the therapeutic data strongly corroborate the mechanistic findings: The PN itch pathway depends on IL-31 and IL-4/13 as central elements because their inhibition causes notable clinical improvement, while treatments that lower neural sensitivity, such as nemolizumab and gabapentinoids, show effectiveness. The response to treatment varies among patients because other mechanisms contribute to the condition, since some people experience continuing itch after nemolizumab treatment, which indicates other itch-producing factors. Our progress thus far highlights that PN's neural dysregulation stems from multiple factors. Current effective therapies focus on the type 2 neuroimmune axis, while present research investigates alternative targets including NK1 (neurokinin-1), OSMR, and TRP channels. Figure 2 shows that different points in the neuroimmune network can be targeted for therapy, and combining these targets may produce greater benefits, like simultaneous treatment of IL-31 and central sensitization. In clinical settings, the primary obstacle involves discerning which patients require immune-targeted treatment compared to those who could gain from neural-modulating therapies such as antidepressants or anticonvulsants, along with psychotherapy for habit reversal.

Discussion

PN represents a disease where pathologic neuroimmune interaction possibly results in a neuro-immuno-metabolic disorder characterized by peripheral itch sensitization through nerve fiber proliferation and neuroimmune skin activation that merges with central sensitization to maintain chronic pruritus. Recent studies demonstrate that patients with PN exhibit neuroimmune dysregulation, which interacts with systemic metabolic dysregulation because these patients frequently present with metabolic syndrome and inflammatory comorbidities that increase itch signaling [4,7]. The neuro-itch dysregulation mechanism provides insights into PN's resistance to treatment and directs the development of new therapeutic strategies. Treatment of the pruritic environment in PN could benefit from metabolic health management by patients, which includes optimizing weight and glycemic control. However, this approach requires validation through direct research studies. Our conversation covers the practical implications of these findings, including new biologics that target itch-specific cytokines and the necessity to treat metabolic inflammation and central neural hyperexcitability in PN patients (Table 3).

This systematic review establishes prurigo nodularis as a neural dysregulation disorder between dermatology and neurology disciplines. The studies demonstrate how peripheral and central itch pathways merge to maintain continuous itchiness in PN. In the skin, a pathologic neuroimmune circuit is established: The cutaneous nerve fibers, particularly those small C-fibers which sense itch, undergo structural changes and become hyperreactive. At the same time, immune cells at the lesion site release pruritogens such as IL-31, IL-4, IL-13, NGF, and neuropeptides, increasing nerve activity and proliferation [8]. The

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lowered itch threshold means standard triggers or random nerve activity generate intense itching through peripheral sensitization. When itch signals repeatedly reach the spinal cord and brain, they cause central sensitization, which leads neural circuits in the dorsal horn and brain to intensify incoming itch signals and may create phantom itch sensations. The net effect is a self-reinforcing itch-scratch cycle: Scratching behavior in patients triggers further activation of the skin's neuroimmune network while causing the central nervous system to predict and intensify itch sensations [18,19].

Table 3: Key Metabolic and Systemic Comorbidities in Prurigo Nodularis.

Condition	Association with PN	Mechanism
T2DM [5,6]	Higher prevalence (~30% in PN)	Insulin resistance, small fiber neuropathy, elevated IL-31/ Th2 cytokines
Obesity [4,6]	More frequent in PN vs. controls	Low-grade inflammation, Th2/Th17 bias, autonomic dysfunction
Metabolic Syndrome [4,7]	Increased risk (up to 4-fold with severe PN)	Systemic inflammation, IL-4/IL-13-driven neuroimmune activation
Hyperlipidemia [4]	Elevated cardiometabolic risk and mortality	Shared inflammatory drivers; endothelial dysfunction

Comparison with Other Pruritic Conditions

Researchers have extensively studied atopic dermatitis (AD), which provides a basis for comparison with PN findings. PN and AD demonstrate type 2 inflammation, involving shared mediators such as IL-4, IL-13, and IL-31. PN represents the end of the spectrum where persistent scratching leads to nodular chronic lesions accompanied by neural hypertrophy and dermal fibrosis, which do not typically occur in AD. AD presents primary epidermal barrier dysfunction, while PN shows epidermal changes as secondary outcomes from scratching. Neuroimmune dysregulation occurs in both conditions, yet PN's itch displays greater severity and persistence, which indicates increased neural sensitization. The reduced density of IENF in PN, as reported by Bobko et al. (2016), resembles the neural damage seen in brachioradial pruritus and other neuropathic itch disorders, where damaged peripheral nerves generate unexpected itching. Researchers suggest that PN exhibits characteristics of cutaneous small-fiber neuropathy, which presents as itching instead of pain in some patients [16]. The connection between PN and diabetes, along with neuropathic symptoms, according to Hughes et al. (2020), confirms this perspective. PN exhibits strong type 2 immune activation marked by elevated levels of IL-31. PN displays type 2 immune activation with elevated IL-31, comparable to atopic dermatitis and chronic prurigo disorders. Therefore, PN straddles categories: This condition displays characteristics of inflammatory pruritic dermatitis and neuropathic itch conditions [10]. The dual nature of PN demands multipronged strategies for effective treatment because it exhibits characteristics of both inflammatory and neuropathic conditions.

Clinical Implications

Recognizing neural dysregulation in PN has direct implications for clinical practice. Firstly, it justifies the use of therapies targeting neural-immune signaling (e.g. IL-31 or IL-4/13 inhibitors), as evidenced by their success. Clinicians should view PN not simply as steroid-responsive dermatitis, but as a chronic neuroinflammatory condition that may need chronic therapy akin to how one manages chronic pain. Secondly, the presence of central sensitization means that treating the skin alone may not suffice in long-standing cases - patients might benefit from systemic neuromodulators (such as gabapentin, pregabalin, or certain antidepressants) to help "reset" central itch processing. In severe PN, adding such agents has been reported to improve sleep and overall itch control [12]. Thirdly, patients with PN should be evaluated for coexisting neurologic conditions. Given the association with peripheral neuropathies, a focused neurologic exam or nerve conduction study could be warranted in atypical cases (for instance, unilateral PN or PN with dysesthesias). Treating an underlying neuropathy (if found, e.g., treating B12 deficiency or diabetes aggressively) might lessen the itch trigger [39]. Moreover, the link with psychiatric comorbidity (anxiety/depression in ~50% of PN patients) calls for integrated care -addressing mental health may help break the itch–anxiety cycle that can exacerbate central sensitization [40].

Our review also underscores some gaps in current knowledge. While peripheral immunologic pathways in PN have been well-characterized in recent years, the central mechanisms remain under-investigated. There is a paucity of direct data on spinal cord or brain changes in PN - an area ripe for further research. Functional MRI and electroencephalography studies of itch are still in early stages but could reveal how chronic PN itch is represented in the brain and whether interventions normalize those patterns. Another gap is in understanding why certain patients develop PN. Many people have eczema or itch and scratch, but not all develop nodules. Genetic or systemic factors likely predispose some individuals to this extreme itch phenotype. The finding by Sutaria et al. (2022) that there are racial differences in RAAS (renin-angiotensin-aldosterone system) dysregulation in PN hints that systemic neuroendocrine factors could influence the expression of PN [41]. Angiotensin II, for example, can stimulate pruritus via mast cell activation; differences in angiotensin or aldosterone levels might subtly affect chronic itch propensity.

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Additionally, Marani et al. (2024) demonstrated involvement of a "skin-liver" axis in PN, where PN patients showed altered liver enzyme patterns and gene expression links between skin and liver metabolism [42]. This raises interesting questions about systemic metabolic or immunologic conditions contributing to PN - for instance, could chronic liver inflammation or metabolic syndrome predispose to a pro-pruritic state via systemic inflammation? These systemic insights, while not directly neural, shape the milieu in which neural dysregulation manifests.

The concept of PN as a neuroimmune (and systemic) disease has practical clinical implications. For one, it emphasizes the importance of multidisciplinary care. Dermatologists treating PN should be aware of the high rates of diabetes, obesity, and cardiovascular risk factors in this population and coordinate with primary care or endocrinology to optimize those conditions. Improved control of a patient's metabolic syndrome could hypothetically reduce systemic inflammatory load and itch intensity. Likewise, neurologists and pain specialists may provide valuable input for refractory cases where neural sensitization is prominent. The recent success of IL-31 and IL-4Rα inhibitors illustrates that tackling immune-driven neural activation can dramatically relieve PN; however, some patients will still experience residual itch, perhaps due to entrenched central sensitization or unidentified drivers. This underscores the need for continued research into neural targets (such as new antipruritic that penetrate the central nervous system (CNS) or therapies addressing sympathetic dysregulation).

From a pathophysiological perspective, PN sits at the crossroads of dermatology, neurology, immunology, and systemic medicine. It can be viewed as an exemplar of neurogenic inflammation exacerbated by systemic inflammatory priming. The co-occurrence of PN with obesity and insulin resistance raises interesting questions about shared cytokine pathways (for example, IL-6, TNF-α, and other inflammatory mediators elevated in metabolic syndrome could conceivably contribute to pruritus) [5]. Conversely, chronic severe itch and poor sleep might worsen metabolic control via stress and hormonal pathways. These interconnections highlight a vicious cycle: PN causes stress and inflammation, which might aggravate metabolic dysfunction, in turn fueling more inflammation and itch [43]. Breaking this cycle requires a holistic therapeutic strategy.

Recent data hint that treating PN's skin and neural aspects can have benefits beyond the skin - for instance, patients on dupilumab or nemolizumab have shown improvements in sleep, mood, and even systemic inflammation markers. Such outcomes support the notion that effectively quelling the itch–scratch cycle may allow the body to reset some of its metabolic and inflammatory perturbations (Yosipovitch et al., 2024; [27]. This is particularly relevant for PN patients with comorbid diabetes or heart disease, where reducing chronic itch and improving sleep could positively impact glycemic control and cardiovascular risk. Future dedicated studies could examine whether aggressive PN treatment leads to measurable improvements in metabolic indices (e.g., Hemoglobin A1c (HbA1c), weight, C-reactive protein (CRP)) over time.

Ultimately, recognizing PN as not just a localized skin disorder but a systemic neuroinflammatory condition has widened the scope of management. Therapies that combine anti-inflammatory, neuromodulatory, and metabolic interventions hold promise for improving patient outcomes. As new treatments emerge, clinicians should remain vigilant for any unaddressed aspect - be it persistent central itch, comorbid depression/anxiety, or unchecked metabolic syndrome - and tailor a comprehensive plan accordingly. The goal is to break the itch-scratch cycle on all fronts and restore patients' quality of life.

Limitations

It is important to acknowledge the limitations of the evidence and of this review. Many included studies had small sample sizes; PN is relatively uncommon and often misdiagnosed, making large studies challenging. Thus, some findings (e.g., particular cytokine elevations) need confirmation in larger cohorts. There is also a bias in the literature toward severe, treatment-refractory PN (since those patients are often seen in tertiary centers that publish), so these mechanistic insights might be most applicable to severe PN. Milder cases might have less pronounced neural changes. Additionally, as a systematic review, our analysis is limited by the quality of reported data – heterogeneity in methods sometimes precluded direct comparison or pooling of results. However, the consistency of certain themes (like IL-31 involvement) across different studies lends credibility to those conclusions.

Future Directions

Identifying neural dysregulation in PN offers significant practical applications for medical treatments. This finding supports the application of therapies that influence neural-immune interactions. Their effectiveness proves the validity of therapies aimed at neural-immune signaling (for example, IL-31 or IL-4/13 inhibitors). Medical professionals must understand PN as a persistent neuroinflammatory disorder that requires long-term treatment strategies similar to those used for chronic pain management. Patients with long-term conditions may need systemic neuromodulators alongside skin treatments because central sensitization can make isolated skin treatments ineffective. Adding these agents to severe PN treatment protocols leads to improved sleep quality and better itch control [12]. A comprehensive evaluation for neurological conditions should be performed in patients diagnosed with PN. A focused neurologic examination or nerve conduction study should be considered in unusual peripheral neuropathies such as unilateral PN or PN involving dysesthesias. Treating an underlying neuropathy (if diagnosed, such as correcting B12 deficiency or aggressively managing diabetes) may help reduce the itch trigger. The association between psychiatric comorbidity (anxiety/depression

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in about 50% of PN patients) demonstrates the need for integrated care because treating mental health issues might disrupt the itch-anxiety cycle that worsens central sensitization.

Our review points to several existing gaps in present understanding. Researchers have extensively studied PN's peripheral immunologic pathways, but central mechanisms are far less understood. Direct data about spinal cord or brain alterations in PN remains scarce, which creates a promising opportunity for future investigations. Although research on functional MRI and electroencephalography of itch remains nascent, these studies could demonstrate brain representation of chronic PN itch and identify normalization effects of treatments. Scientists have yet to determine what causes certain patients to develop PN. While countless individuals experience eczema or continuous itching and scratching activities, not everyone progresses to form nodules. This extreme itch phenotype probably emerges from genetic or systemic factors predisposing specific individuals. The discovery by Sutaria et al. (2022) about racial variations in RAAS (renin-angiotensin-aldosterone system) dysregulation among PN patients suggests systemic neuroendocrine factors may control PN expression. Angiotensin II triggers pruritus through mast cell activation, and variations in angiotensin or aldosterone levels may slightly alter chronic itch likelihood [41].

Additionally, Marani et al. (2024) established that PN involves a "skin-liver" axis that connects altered liver enzyme patterns with skin and liver metabolic gene expression in PN patients. The role of systemic metabolic or immunologic conditions in PN development remains intriguing. Chronic liver inflammation or metabolic syndrome could lead to a pro-pruritic state because of systemic inflammation [42]. The systemic factors that influence PN do not directly affect neural pathways but establish the environment where neural dysregulation occurs.

Understanding PN as a neuroimmune systemic disease leads to practical applications in clinical treatment strategies. Multidisciplinary care becomes essential through this approach. Medical professionals who manage PN need to understand the elevated incidence of diabetes, obesity, and cardiovascular risks within this group and work alongside primary care or endocrinology specialists to manage these health concerns. Controlling metabolic syndrome in patients might decrease systemic inflammation and lessen itch severity. Neurologists and pain specialists offer essential guidance for complex cases that display significant neural sensitization. IL-31 and IL-4Rα inhibitors demonstrate breakthroughs in relieving PN through immune-driven neural activation suppression, yet some patients continue to experience persistent itching because of central sensitization or other unidentified factors. Research into neural targets remains essential to develop solutions like CNS-penetrating antipruritic and sympathetic dysregulation therapies.

PN represents the intersection of dermatology with neurology, immunology, and systemic medicine from a pathophysiological standpoint. The condition represents a classic case of neurogenic inflammation worsened by systemic inflammatory priming. The simultaneous presence of PN with obesity and insulin resistance prompts investigation into common cytokine pathways because inflammatory mediators like IL-6 and TNF-α that increase during metabolic syndrome may play a role in causing pruritus. Long-term intense itching and insomnia can exacerbate metabolic health through mechanisms related to stress and hormonal activity. These interconnections highlight a vicious cycle: PN generates stress and inflammatory responses that can worsen metabolic dysfunction and subsequently trigger more inflammation and itching. A comprehensive therapeutic approach is essential to break this cycle.

Recent findings demonstrate that addressing skin and neural symptoms in PN treatment leads to additional benefits beyond skin health because patients receiving dupilumab or nemolizumab treatments experience better sleep and mood and exhibit reduced systemic inflammation markers. When the itch-scratch cycle is adequately controlled, the body can restore balance to its metabolic and inflammatory processes (Yosipovitch et al., 2024). Improving sleep and reducing chronic itch can benefit patients with PN who also have diabetes or cardiac conditions by enhancing glycemic control and minimizing cardiovascular risk [27]. Subsequent research initiatives should investigate how intense PN treatment produces measurable metabolic benefits, including HbA1c, weight reduction, and CRP improvements.

The understanding that PN represents a systemic neuroinflammatory condition beyond just skin issues expands treatment approaches. Patient outcomes could improve through therapies that integrate anti-inflammatory, neuromodulatory, and metabolic interventions. When new treatments become available, clinicians must stay attentive to any untreated issues, including continuous central itch, comorbid depression/anxiety, or metabolic syndrome, to develop a complete treatment strategy. Healthcare providers aim to disrupt the itch-scratch feedback loop comprehensively while enhancing the quality of life for patients.

Conclusion

Prurigo nodularis exemplifies how chronic diseases emerge from complex interactions between the immune system, metabolic dysfunction, and neural dysregulation. The condition is characterized by abnormal signaling from cutaneous nerve endings to central itch-processing centers, highlighting the role of the nervous system as a key element of PN pathogenesis. Patients suffering from PN experience a complex condition consisting of peripheral sensitization due to abnormal nerve fiber density and skin neurochemical changes, and central sensitization from extended itch signal exposure while battling type 2 inflammation, systemic metabolic dysfunction, and developing dermal fibrosis. Over the last ten years, translational research has discovered principal drivers of the disease process, especially IL-31 and IL-4/13, leading to successful targeted treatments, significantly

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reducing disease symptoms. Achieving complete remission in PN proves difficult because all elements of the itch circuitry need to be addressed.

Future therapeutic strategies that combine treatments for immune inflammation and metabolic dysregulation with neural function modulation will likely provide PN patients with more comprehensive symptom relief. Medical professionals must follow a comprehensive treatment strategy for PN by addressing skin lesions and neural modulators while managing metabolic risk factors and supporting psychosocial needs. Research focused on itch neural pathways necessitates ongoing investigation, including advanced neuroimaging techniques and the discovery of new neuron-specific targets. The PN model provides crucial insights into chronic itch mechanisms at a systems level, which could benefit research on other long-term pruritic conditions. To effectively manage prurigo nodularis, patients must interrupt the itch circuit through multiple strategies, including treatment of metabolic inflammation, which can greatly enhance the quality of life for sufferers of this challenging condition. Continuous translational research that connects dermatology with neuroscience makes the goal more achievable.

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