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**Original Research Article**

# Review on Updated Management of Prurigo Nodularis (PN)

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## Abstract

***Background:*** Prurigo Nodularis (PN) presents as a challenging chronic dermatological condition characterized by intensely pruritic nodules on the skin, leading to significant morbidity. Despite its prevalence and impact on patients' quality of life, treatment options remain limited, necessitating evidence-based approaches to address this complex condition effectively. ***Objective:*** This study aims to provide an updated overview of evidence-based management strategies for PN, highlighting recent advancements in treatment modalities. ***Method:*** A systematic review of clinical studies on PN treatment was conducted by searching the PubMed and Scopus databases from January 1, 2001, to December 1, 2023. A total of 706 unique studies published in English were identified and screened for inclusion criteria. Only primary clinical studies investigating treatment strategies in PN patients were included, while case reports and series with fewer than five patients were excluded. Relevant publications were further supplemented by searching bibliographies for additional studies meeting the inclusion criteria. ***Results:*** The review identified significant advancements in evidence-based management strategies for PN, driven by a growing body of clinical research and therapeutic innovation. Pharmacological interventions targeting pruritus, inflammation, and lesion resolution have shown efficacy, including topical agents such as corticosteroids, emollients, Vitamin D3 analogues, tacrolimus creams, and systemic therapies like antihistamines, gabapentinoids, immunosuppressant and anti-inflammatory agents, JAK inhibitors, retinoids, and sometimes selective serotonin reuptake inhibitors (SSRIs). Additionally, emerging biological agents and non-pharmacological approaches, such as multidisciplinary interventions, have demonstrated promise in improving patient outcomes. ***Conclusion:*** Evidence-based management of PN represents a dynamic field with evolving treatment modalities. While challenges persist, including limited efficacy and safety concerns of certain treatments, recent developments in targeted therapies, systemic immunomodulators, and novel pharmacological approaches offer hope for improved patient care. Further research into genetic underpinnings and personalized therapies is warranted to address the heterogeneous nature of PN and enhance treatment efficacy and safety.

**Keywords:** Prurigo nodularis, pharmacological interventions, chronic pruritus.

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## INTRODUCTION

Prurigo nodularis, a chronic dermatological condition characterized by intensely itchy nodules on the skin, poses significant challenges in management due to its complex etiology and limited treatment options. In recent years, there has been a growing emphasis on evidence-based approaches to address this debilitating condition. This introduction provides an overview of the current landscape of evidence-based management strategies for prurigo nodularis, highlighting key updates and advancements in treatment modalities [1-3].

Prurigo nodularis is a chronic inflammatory skin disorder characterized by the formation of firm, intensely pruritic nodules, often leading to excoriation, ulceration, and secondary infections. Despite its prevalence and impact on patients' quality of life, the pathogenesis of prurigo nodularis remains incompletely understood, encompassing neuroimmune,

neurovascular, and psychosocial factors. Traditional management approaches have often been unsatisfactory, emphasizing the need for evidence-based interventions tailored to address the multifactorial nature of the condition.

Recent years have witnessed significant advancements in evidence-based management strategies for prurigo nodularis, driven by a growing body of clinical research and therapeutic innovation. One notable development is the recognition of neuroimmune dysregulation as a central mechanism in the pathogenesis of prurigo nodularis, leading to the exploration of targeted therapies aimed at modulating neuroinflammatory pathways. Additionally, advances in understanding the role of sensory nerves and itch signaling molecules have paved the way for novel pharmacological interventions targeting pruritus, a hallmark symptom of the condition [4-7].

A cornerstone of evidence-based management for prurigo nodularis involves pharmacological interventions aimed at alleviating pruritus, reducing inflammation, and promoting lesion resolution. Topical agents such as corticosteroids, calcineurin inhibitors, and capsaicin have demonstrated efficacy in managing localized prurigo nodularis lesions, while systemic therapies including antihistamines, gabapentinoids, and antidepressants may be utilized for widespread or refractory cases. Notably, emerging biologic agents targeting cytokines and immune mediators implicated in prurigo nodularis pathogenesis hold promise as future treatment modalities [8-9].

In addition to pharmacotherapy, evidence-based management of prurigo nodularis encompasses non-pharmacological approaches aimed at addressing psychosocial factors, optimizing patient education, and promoting self-management strategies. Multidisciplinary interventions combining dermatological care with psychological support, cognitive-behavioral therapy, and patient-centered education have shown promise in improving patient outcomes and enhancing adherence to treatment regimens.

**Objective**

To asses the up-to-date management of prurigo nodularis.

## METHODOLOGY

A systematic review of clinical studies on the treatment of prurigo nodularis (PN) was conducted by searching the PubMed and Scopus databases from January 1, 2001, to December 1, 2023. A total of 706 unique studies published in English were identified through a search strategy developed in collaboration with a research librarian. Only primary clinical studies that investigated treatment strategies in PN patients were included, while studies lacking treatment outcomes were excluded. Additionally, case reports and series with fewer than five patients were excluded to minimize selection bias. Relevant publications were further supplemented by searching the bibliographies for additional studies meeting the inclusion and exclusion criteria.

## RESULTS

**Table-1: Randomized controlled trials for prurigo nodularis treatment with published results. [10-14]**

| Studied Intervention | Control Group Intervention | N | Key Findings | Side Effects |
|---|---|---|---|---|
| Betamethasone valerate 0.1% tape once daily | Moisturizing itch-relief cream twice daily | 11/12 | Subjects completed treatment course. Betamethasone-treated side exhibited better clinical response at week 4 compared with Aveeno-treated side. Mean VAS reductions from baseline: Betamethasone 4.85 points, Aveeno 3.15 points. | None reported |
| Calcipotriol 50 µg/g ointment twice daily | - | 10 | Number and size of nodules decreased: calcipotriol group (49%, 56% respectively) vs betamethasone group (18%, 25% respectively) after 8 weeks. | Self-resolving mild perilesional skin irritation with calcipotriol |
| Pimecrolimus 1% cream twice daily | - | 30 | Significant mean VAS reduction from baseline with both pimecrolimus (2.7 points) and hydrocortisone (2.8 points) treatments at day 10. Improved prurigo lesions at 10 days, 4 weeks, and 8 weeks with both treatments. | Progression, suspected contact allergy to wound dressing |
| 308-nm excimer weekly | - | 13 | PAIS with ≥40% improvement in 8 excimer-treated sites at week 34 compared with 3 clobetasol-treated sites. VAS with 63% improvement with excimer treatment at week 34 compared with 49% improvement with clobetasol treatment. | Hyperpigmentation, erythema, burning, vesicles, and blistering |
| PUVA plus 308-nm excimer twice weekly | Betamethasone valerate 0.1% ointment twice daily | 21 | 6/11 patients receiving PUVA alone achieved complete remission, while 7/10 patients receiving combination therapy achieved complete remission. | PUVA alone: moderate erythema Combination therapy: erythema, vesicles and edema |

Besides the aforementioned treatment, there are other options that show promise in the treatment and management of Prurigo Nodularis.

Cyclosporin is an immunosuppressant that helps reduce inflammation and immune activity in prurigo nodularis, potentially relieving itching and skin lesions by modulating the overactive immune response. Cyclosporine lowers inflammation and immune-mediated skin injury by inhibiting T-cell activity, which is hypothesized to play a role in the pathogenesis of prurigo nodularis. It is an effective treatment option for prurigo nodularis, particularly in patients who have not responded to other treatments. Cyclosporine may be considered a second line agent for this condition. Frequently, high dosages of 3 mg/kg/day to 4.5 mg/kg/day for 24 to 36 weeks are required. In some patients, significant improvement in the lesion and reduction of pruritus may be seen [19].

Pregabalin is used for its neuropathic pain-relieving properties, which can help reduce the chronic itch and discomfort associated with prurigo nodularis by inhibiting nerve signaling involved in itching. Pregabalin decreases the release of excitatory neurotransmitters like glutamate by attaching to the alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system. In disorders like prurigo nodularis, where itching is frequently neuropathic in origin, this activity helps control pain signals and can lessen the itchy sensation. In an open and non-controlled study, pregabalin was seen to be effective for the treatment of PN. However, a properly powered randomized controlled validation study was still required [20].

Baricitinib and other JAK inhibitors target specific pathways in the immune response, reducing inflammation and potentially controlling the severe itching and lesions seen in prurigo nodularis by interrupting the signaling involved in the condition. JAK inhibitors function by preventing the action of one or more enzymes in the Janus kinase family, including TYK2, JAK1, JAK2, and JAK3. These enzymes are involved in the signaling pathways of different cytokines which are important for inflammation and the immunological response. JAK inhibitors work by blocking these pathways, which in turn lessens inflammation, immunological activation, and the skin lesions and persistent itching associated with prurigo nodularis. In a preliminary investigation of a pilot study, treatment with baricitinib in twelve adult patients with long-standing recalcitrant PN yielded highly favorable outcomes. Larger and longer randomized controlled trials are essential to determine the effectiveness, longevity, and safety of baricitinib in managing PN [21].

Isotretinoin, a retinoid, helps reduce inflammation and keratinization in the skin, potentially improving the nodules and chronic itching in prurigo nodularis by normalizing skin cell turnover. The main ways that isotretinoin acts are via decreasing keratinization and sebaceous gland activity. Its effects in relation to prurigo nodularis are thought to stem from its capacity to control epidermal differentiation and lower skin inflammation. Isotretinoin also possesses certain immunomodulatory properties that may aid in mitigating the persistent inflammation and itching associated with PN.

Methotrexate, an immunosuppressant and anti-inflammatory agent, is used in prurigo nodularis to reduce immune system activity, helping to alleviate inflammation and the formation of pruritic nodules. Methotrexate reduces DNA synthesis and cell proliferation by blocking the dihydrofolate reductase enzyme. In context of PN Methotrexate is thought to be helpful by lowering immune activation and the inflammatory response, which are factors in the nodular lesions and persistent itching. Use of Methotrexate in PN has been little studied.

SSRIs (Selective Serotonin Reuptake Inhibitors) can help manage prurigo nodularis by addressing the psychological aspects of chronic itching, such as anxiety or depression, which may exacerbate the condition. SSRIs work by increasing the levels of serotonin in the brain by inhibiting its reuptake into the presynaptic neuron In addition to regulating mood, serotonin influences how senses perceive their surroundings, including itching. SSRIs may lessen the persistent itching that causes prurigo nodularis patients to scratch by regulating serotonin levels. SSRIs can be an effective adjunct treatment for prurigo nodularis, especially in patients where psychological factors or neuropathic itch are significant contributors to their condition. SSRIs can be an alternate treatment option for PN but this should be confirmed in future double-blind studies.

Cryotherapy involves freezing the pruritic nodules, which can help reduce their size and alleviate itching by destroying abnormal tissue and reducing inflammation in prurigo nodularis [3]. The cold temperatures cause the destruction of the abnormal skin cells that form the nodules. By destroying the nerve endings within the treated area, cryotherapy can reduce the sensation of itch, which helps to break the cycle of scratching that exacerbates PN. It is typically used as an adjunctive therapy when other treatments have not provided sufficient relief. According to the American Academy of Dermatology, cryotherapy can be a viable option when other treatments fail to relieve the itch and pain.

Separate studies done by Siepmann *et al.*, and Müller & Zeidler showed that these drugs can be used as an alternative treatment [17-18].

## DISCUSSION

Numerous treatments for prurigo nodularis (PN) are hindered in their clinical application due to either low efficacy or a high incidence of side effects. Moreover, among the 35 studies analyzed, only 8 were randomized controlled trials (RCTs), and merely 9 reports encompassed over 25 patients. The challenge of achieving successful outcomes with existing PN treatments likely stems from the heterogeneous etiology of chronic pruritus. In addition to cutaneous origins, various systemic conditions, as well as neurologic, psychiatric, and somatoform factors, may contribute to pruritus onset. Hence, careful patient-directed therapeutic selection emerges as pivotal in disease management [14].

The management of prurigo nodularis involves a multifaceted approach targeting both the immune system and symptomatic relief. Cyclosporin, by modulating the overactive immune response, and methotrexate, with its dual immunosuppressant and anti-inflammatory effects, play crucial roles in reducing inflammation and preventing the formation of pruritic nodules. Baricitinib and other JAK inhibitors further refine this immune-targeted therapy by specifically interrupting the signaling pathways responsible for severe itching and lesion formation. Meanwhile, isotretinoin works by normalizing skin cell turnover, helping to reduce inflammation and keratinization [12]. Pregabalin provides relief from chronic itch through its neuropathic pain-relieving properties, addressing the discomfort associated with nerve signaling. SSRIs offer psychological support by managing the anxiety and depression that can exacerbate itching. Finally, cryotherapy serves as a localized treatment, reducing nodule size and inflammation by freezing and destroying abnormal tissue, thereby offering symptomatic relief. This comprehensive therapeutic strategy highlights the importance of addressing both the underlying immune mechanisms and the symptomatic burden of prurigo nodularis [11].

The utilization of thalidomide for PN is restricted due to its poor safety profile. Its analogue, lenalidomide, has been introduced with expectations of similar clinical efficacy and improved safety. Although several recent case reports support such efficacy, concerns about possible drug-induced neuropathy or myopathy led to the termination of treatment in one reported case. Additionally, increased risks of thromboembolism, myelosuppression, and Stevens-Johnson syndrome have been associated with lenalidomide use. Current studies exploring lenalidomide for PN did not achieve sufficient power for inclusion in this review [15-16].

Systemic immunomodulatory agents like methotrexate (MTX) and cyclosporine demonstrate effective PN treatment but are accompanied by significant safety concerns. Conversely, antiepileptics and antidepressants present promise as treatment options for PN with fewer side effects. Gabapentin, acting similarly to pregabalin by modulating γ-aminobutyric acid neurotransmitter signaling through calcium channels, has shown anecdotal success in chronic pruritus and PN patients. However, reports detailing gabapentin's efficacy in PN lacked sufficient power for inclusion in this article [13-14].

In addition to neurokinin-1 receptor antagonists, newer therapeutic avenues for PN include targeting IL-31 signaling and opioid receptor modulation. Nemolizumab, an IL-31 receptor A antagonist, is currently undergoing phase II studies in PN patients. Nalbuphine, acting as an opioid κ-receptor agonist and μ-receptor antagonist, has demonstrated beneficial effects in PN patients in a recent multicenter, double-blind, RCT, with preliminary results suggesting efficacy trends for nalbuphine extended-release 180 mg twice daily compared with placebo. No serious drug-attributed adverse events were noted in this study.

## CONCLUSION

This comprehensive overview offers evidence-based recommendations for healthcare practitioners, aiding in informed decision-making while also pinpointing areas for further research and advancement in prurigo nodularis (PN) treatment. Beyond addressing the condition directly, patients with PN stand to gain from the development of safer and more efficacious systemic therapies. Recent investigations into neurokinin-1 receptor antagonists, κ-opioid receptor modulators, and IL-31 receptor antibodies demonstrate promising potential in this regard. Furthermore, exploring the genetic basis of the disease holds promise for the development of targeted and personalized therapies. As new findings emerge, the array of options available to practitioners will expand, catering to the diverse needs of PN patients with evolving precision and efficacy.

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