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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 and herpes viral infections.[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. Similar , 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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