Practical approaches for diagnosis and management of prurigo nodularis: United States expert panel consensus

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Background: Prurigo nodularis (PN) is a chronic disease characterized by intensely pruritic, raised, nodular lesions. Because there are currently no United States Food and Drug Administration-approved therapies specifically for PN, management is highly variable, and no consensus exists on treatment regimens.

Objective: To provide practical guidance to help United States dermatologists diagnose and effectively treat patients with PN.

Methods: We participated in a roundtable discussion to develop consensus recommendations on diagnosis and treatment of PN from a United States perspective.

Results: The core findings in PN are the presence of firm, nodular lesions; pruritus lasting at least 6 weeks; and a history or signs, or both, of repeated scratching, picking, or rubbing. The diagnostic workup involves a complete review of systems, considering potential systemic diseases, and assessment of disease severity,

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including disease burden and pruritus intensity. Treatment should be selected based on a patient's clinical presentation, comorbidities, and response to prior treatments and should address both neural and immunologic components of pruritus.

Limitations: Data on PN are from anecdotal or small clinical trials, and all treatments are currently used off-label.

Conclusion: An effective treatment approach for patients with PN should be based on clinical judgment and tailored to the individual needs of the patient. (J Am Acad Dermatol 2021;84:747-60.)

Key words: chronic nodular prurigo; diagnosis; prurigo nodularis; pruritus; treatment.

Prurigo nodularis (PN) is a distinct clinical disease defined by the presence of chronic pruritus and multiple localized or generalized, elevated, firm, and nodular lesions. Although the underlying cause of PN is unknown, neural and immunologic processes both appear to play a role in its development.[1,2]

Limited data are available on the incidence and prevalence of PN, likely because PN is relatively uncommon and, until recently, was grouped with other pruritic conditions in disease classification systems. A distinct *International Classification of Diseases, 10th Revision* (*ICD-10*) code for PN was introduced in 2015 (*ICD-10*: L28.1). A study using this *ICD-10* code to identify patients with PN estimated a prevalence of 72 per 100,000 United States (US) residents aged between 18 and 64 years; however, this is likely an underestimation because only insured patients were included and a lack of disease awareness exists among both patients and general practitioners.[3] PN is more common among older adults (mean age, 50-55 years), women, and African Americans.[3-7]

PN is associated with a significant disease burden, including sleep disruption, anxiety, and depression. National Inpatient Sample 2016 data show hospital inpatients with a PN diagnosis have a longer length of stay (6.5 vs 4.6 days, respectively; $P < .001$) and higher cost of care ($14,772 vs $11,728; $P < .001$) than inpatients without PN.[4] Patients with PN also incur significantly higher health care costs in the outpatient setting compared with age- and sex-matched controls.[8]

Dermatologic conditions such as atopic dermatitis, and other diseases, such as chronic kidney disease, diabetes, heart failure, chronic hepatitis B/hepatitis C virus, HIV, and non-Hodgkin lymphoma, may be associated with PN.[3,6,9-11] Although some of these conditions may be causative, the precise relationship remains to be fully delineated.

Currently, no treatments are approved specifically for PN, and available treatments demonstrate variable success.[12] The recommendations presented here represent our expert opinions.

CAPSULE SUMMARY

- Prurigo nodularis is a chronic disease with no United States Food and Drug Administration-approved therapies or consensus on appropriate treatment regimens.
- Treatment should be tailored to the individual needs of the patient, considering their clinical presentation, comorbidities, and response to prior treatments, and should include therapies targeting both neural and immunologic mechanisms of pruritus.

TERMINOLOGY

The terminology used in the US to describe this disease is PN. In Europe, the disease is also described as chronic prurigo of the nodular type.[1] European terminology uses the overarching term of chronic prurigo, with subclassification as nodular, papular, plaque, or umbilicated type based on size and morphology. In the US, the general term PN is preferred to encompass all variants because it is considered sufficiently descriptive of the basic clinical picture and has an existing *ICD-10* code.

PN can arise without any identifiable disease association or as a secondary manifestation of another condition (eg, atopic dermatitis). PN is easily recognized by morphology and is often treated directly and independently of other underlying disease(s). This is consistent with the definition proposed by the European Academy of Dermatology and Venereology Task Force,[13] which states that chronic prurigo is defined as a distinct disease within the spectrum of pruritus based on the following characteristics: symptoms may develop independent of underlying causes of pruritus, PN is perpetuated by both the sensitization induced by the

Abbreviations used:

AE: adverse event
ICD-10: *International Classification of Diseases, 10th Revision*
IL: interleukin
mAb: monoclonal antibody
NK_1: neurokinin 1
PN: prurigo nodularis
PUVA: psoralen plus ultraviolet A
RCT: randomized controlled trial
US: United States

pruritus and the scratching behavior, and treating any underlying cause alone may not provide sufficient relief.[13]

Classifying PN as a disease allows patients to distinguish their disorder from other conditions and provides reassurance that they have a defined disease. Furthermore, PN has a sufficient clinical distinction to identify patients for new and upcoming targeted therapies.

DISEASE SIGNS AND SYMPTOMS

The core findings in PN are the presence of firm, nodular lesions; pruritus lasting at least 6 weeks; and history or signs, or both, of repeated scratching, picking, or rubbing (Table I).[1,14] Additional signs and symptoms often present in PN include symmetrical distribution of nodules on areas of the skin accessible to scratching; sparing of the face, palms, and soles; presence of additional lesions induced by scratching, picking, or rubbing; and accompanying symptoms of pruritus such as burning, stinging, and pain.[1,15]

Table I. Core symptoms and common additional features

Variable	Description
Core symptoms	• Presence of firm, nodular lesions • Pruritus lasting ≥6 weeks • History and/or signs of repeated scratching, picking, or rubbing
Common additional features	Signs and symptoms • Nodules are usually symmetrically distributed on areas of the skin accessible to scratching • Face, palms, soles, scalp, and genitals are rarely affected • Additional lesions induced by scratching/picking/rubbing may be present (eg, lichenified plaques, excoriations, ulcerations, and/or scars) • Pruritus may be accompanied by additional burning, stinging, pain, and other sensations Burden of disease • Impaired quality of life, sleep deprivation, missed work/school, emotional impact (depression, anxiety, anger, shame, helplessness), and social isolation • Associated comorbidities include impaired liver, renal, or thyroid function, diabetes, HIV or hepatitis B/C virus, and malignancy

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of PN includes perforating disorders, such as Kyrle disease (although some experts consider perforating lesions to be a subtype of PN[16]), hypertrophic lichen planus, atopic dermatitis with lichen simplex chronicus, autoimmune blistering diseases, such as bullous pemphigoid and dermatitis herpetiformis, neurotic excoriations, and skin picking syndromes/body-focused repetitive behaviors, lichen amyloidosis, multiple keratoacanthomas, arthropod bites, and scabies.

To distinguish between PN and the aforementioned diagnoses, a skin biopsy may be performed and the sample sent for hematoxylin and eosin or special stains to confirm suspected collagen perforation, immune infiltration, or signs of infection. Characteristic histolopathologic features of PN include thick compact orthohyperkeratosis, pseudoepitheliomatous hyperplasia, focal parakeratosis, and hypergranulosis in the epidermis.[17] In the dermis, papillary dermal fibrosis with vertically arranged collagen fibers, increased numbers of capillaries, increased fibroblasts, and a mixed superficial, perivascular, or interstitial inflammatory infiltrate may be observed.[17] Direct immunofluorescence may be indicated to rule out autoimmune disorders. In addition, skin scrapings may be useful if scabies or underlying fungal infections are suspected.

DIAGNOSTIC WORKUP

The diagnostic workup should begin with a clinical examination that includes a complete review of systems, including the consideration of potential systemic disease.[14,15] Patients should be assessed for PN severity, including pruritus intensity and disease burden; for example, quality of life, sleep deprivation, anxiety/depression, and associated comorbidities (Table II).

The initial laboratory assessment for all patients should include a complete blood count with differential and liver and renal function tests.[14,15] Thyroid function testing and screening for diabetes and

Table II. Diagnostic workup

Variable	Description
Initial visit (can initiate treatment)	Clinical examination, including a complete review of systems Assess for prurigo nodularis severity: • Extent of prurigo nodularis (number and firmness of lesions) • Pruritus intensity (mild, moderate, severe, or very severe; or use the numeric rating scale*) • Disease burden (quality of life, sleep disturbance, anxiety/depression, and associated comorbidities) Assess the need for behavioral and emotional support related to anxiety or depression
Laboratory tests	All patients: • Complete blood cell count with differential • Liver function tests • Renal function tests If risk factors exist or as indicated by review of systems: • Thyroid function tests • Diabetes assessment • HIV and hepatitis B/C virus serologies
Additional tests to consider	If malignancy is suspected and patient has had pruritus for <1 year, refer for age-appropriate malignancy screening Biopsy, if suspicion of an alternative or other contributing condition

*The numeric rating scale is a useful, quick, and validated tool to reliably assess and monitor the severity of pruritus; however, patients may need some guidance on how to use it.

underlying infectious etiologies, including HIV and hepatitis B/C virus, should also be assessed if risk factors are present or suggested by the review of symptoms and physical examination. At the initial visit, clinicians should also assess disease burden and the need for behavioral or emotional support related to anxiety or depression. During the second visit, clinicians should consider additional psychologic comorbidities.

Pruritus for >1 year in the absence of other systemic symptoms is unlikely to be related to malignancy. However, it is important to note that in rare cases, persistent generalized pruritus without an identifiable cause may be a manifestation of hematologic or other malignancies. All patients should be encouraged to follow-up with their primary care provider for routine care and age-appropriate malignancy screening and for additional targeted screening if a specific malignancy concern exists.

Treatment can be initiated based on the initial clinical workup while the patient undergoes screening for potential contributors or associated diseases.

TREATMENT

Treatment options for patients with PN are limited, and there are currently no US Food and Drug Administration-approved treatments specifically for PN. Consequently, all treatments are currently used off-label, and there is high variability in treatment selection and lack of consensus on dosing regimens.

Treatment goals are to reduce pruritus, interrupt the itch-scratch cycle, and completely heal PN lesions.[1,14] Adequate treatment of PN must address both the neural and immunologic components of pruritus. Current PN treatments include gentle skin care, antipruritic emollients, topical corticosteroids, topical calcineurin inhibitors, topical capsaicin, neuromodulators (eg, gabapentinoids, cannabinoids, or anesthetics), antidepressants, phototherapy, and immunosuppressants.[18] Other agents sometimes used or that are in development include μ-opioid receptor/κ-opioid receptor antagonists/agonists, Janus kinase (JAK) inhibitors, neurokinin 1 (NK_1) receptor antagonists, oncostatin M inhibitors, and anti-interleukin (IL) 4 and anti−IL-31 receptor-α monoclonal antibodies (mAbs).[1,19,20]

Treatment of PN should be based on clinical judgment rather than on a strict stepwise approach. Factors to consider when selecting appropriate treatment include the patient's age, comorbidities, severity of PN, impaired quality of life, and possible adverse events (AEs).[1] Histamine H_1/H_2 receptor antagonists are unlikely to be effective and are not recommended for PN treatment, unless a comorbid histamine-mediated condition is suspected.[21]

Fig 1 illustrates a 4-tier treatment ladder that addresses both neural and immunologic mechanisms. Patients can enter the treatment ladder at any tier based on clinical presentation and move up

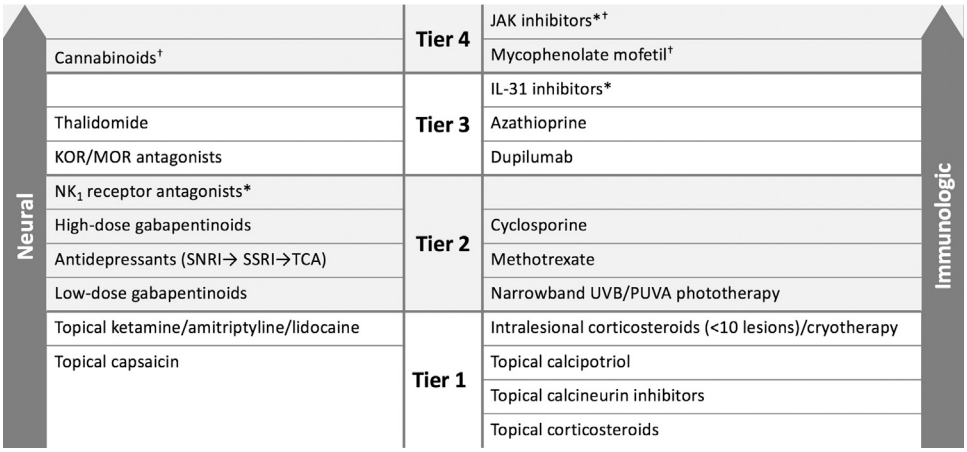

Fig 1. Prurigo nodularis treatment ladder. This 4-tier treatment ladder addresses both neural and immunologic mechanisms. Patients can enter the treatment ladder at any tier based on clinical presentation and move up or down the ladder based on treatment response. *IL-31*, Interleukin 31; *JAK*, Janus kinase; *KOR*, κ-opioid receptor; *MOR*, μ-opioid receptor; NK_1, neurokinin 1; *PUVA*, psoralen plus ultraviolet A; *SNRI*, serotonin and norepinephrine reuptake inhibitor; *SSRI*, selective serotonin reuptake inhibitor; *TCA*, tricyclic antidepressant; *UVB*, ultraviolet B. *Investigational therapies. †Therapies that have been helpful in chronic pruritus but currently lack data in prurigo nodularis. **Therapy may function via multiple mechanisms, immunologic or otherwise.

or down the ladder based on treatment response. Of note, most data included here to support these therapeutic options for PN are based on small clinical trials, observational studies, or case reports (Table III).[22-57] Additionally, some therapies with antipruritic activity in other patient populations lack data in PN. Potential therapies and suggested regimens that reflect the consensus of the expert panel are provided (Table IV).

Tier 1: mainly topical therapies

Neural. Treatments that address the neural component of PN include topical capsaicin and topical ketamine in combination with lidocaine and amitriptyline. The limited clinical evidence and our experience show these treatments tend to have short-term efficacy.[22,23] AEs associated with these treatments are typically transient burning, redness, and itching at the application site.

Immunologic. Therapies that address the immunologic component of PN include topical corticosteroids, topical calcineurin inhibitors, topical calcipotriol, and intralesional corticosteroid injections, which have been performed with or without adjunctive cryotherapy. Data to support the use of these topical therapies are predominantly based on small open-label or intraindividual randomized controlled trials (RCTs).[24-27] AEs associated with these treatments are typically limited to transient intense burning or skin irritation.[24,25] For patients who have been previously treated with topical corticosteroids without success, topical calcineurin inhibitors may be used at the provider's discretion if a prolonged course of a topical immunomodulator is desired.

Thicker lesions may require direct injection of corticosteroids into PN lesions, which can be accompanied by cryotherapy.[58,59] Data to support the use of these therapies in PN are limited to case reports from the 1980s.[28,29] However, a more recent review indicated a 2.5-mg/mL corticosteroid dilution was safe and effective for patients with localized dermatitis, including PN.[59] We generally recommend limiting the use of intralesional corticosteroids to patients with <10 lesions. Although uncommon and associated with higher doses, AEs of intralesional corticosteroids can include telangiectasia, hypopigmentation, and hyperpigmentation.[59] AEs of cryotherapy include hypopigmentation, particularly in patients with dark-colored skin, and edema and pain, especially if multiple nodules are treated simultaneously on one extremity.[29]

Tier 2: mainly widespread skin-directed or systemic therapies with reasonable tolerability

Phototherapy. Ultraviolet phototherapy including narrowband ultraviolet B and psoralen plus ultraviolet A (PUVA) phototherapy may address immune and neural components that contribute to the development of PN.[60] Data from 2 small RCTs of

Table III. Data supporting use of various antipruritic treatments in patients with prurigo nodularis (*PN*)

Therapy	Study design	Patient population	No.	Outcome	Adverse events	LOE*
Tier 1: Mainly topical therapies						
Neural						
Topical capsaicin 0.025%-0.3% 4-6 times/d for 2 wk to 10 mo[22]	Open-label, uncontrolled	PN	33	Complete elimination of pruritus within 12 d; pruritus returned after cessation of treatment in 16 of 33 pts (48%)	Transient burning sensations, erythema, and increase in itch	2b
Topical ketamine 5%-10%, amitriptyline 5%, and lidocaine 5% ≤3 times a d[23]	Retrospective	PN	18	Significant reduction in NRS	Burning sensation, redness, and itching at application site	4
Immunologic						
Pimecrolimus cream 1% BID for 57 d[24]	Intraindividual RCT	PN	30	Significant reduction in pruritus VAS at d 11, 29, 57, and 85; no significant difference vs 1% hydrocortisone cream	Contact allergy to wound dressing (not related)	1b
Pimecrolimus cream 1% BID to maximum achievable relief (range, 8 d-25 mo)[25]	Open-label, uncontrolled	PN	7	Complete (100%) or near-complete (70%) cessation of itch in 4 pts; 50%, 20%, and no reduction of itch in 1 pt each	Transient intense burning	2b
Tacrolimus 0.1% BID to maximum achievable relief (range, 3 wk-3 mo)[25]	Open-label, uncontrolled	PN	4	100%, 50%, 20%, and no reduction of itch in 1 pt each	Transient intense burning	2b
Betamethasone valerate tape 0.1% once daily for 4 wk[26]	Intraindividual controlled	PN	12	Greater reduction in pruritus VAS at wk 4 vs feverfew-containing moisturizing antipruritic cream applied BID	None reported	2b
Calcipotriol ointment 50 μg/g BID for 8 wk[27]	Intraindividual RCT	PN	10	Significant reduction in number and size of nodules vs betamethasone valerate ointment 0.1% at wk 4 and 8	Transient perilesional skin irritation	1b
Cryotherapy, followed by injection of intralesional triamcinolone acetonide 10 mg/mL + lidocaine 0.75% every 4-6 wk for 4 or 8 treatments[28]	Case report	PN	2	Complete resolution of all lesions (n = 1); marked reduction in pruritus and complete flattening of the lesions with resultant hyperpigmented scars (n = 1)	None reported	5
Blistering cryotherapy for 2-4 freeze-thaw cycles[29]	Case report	PN	1	Nodules blistered and healed within 2-4 wk resulting in hypopigmented macules; no further complaints of pruritus during 3-mo follow-up	Edema, pain, and hypopigmentation	5
Tier 2: Mainly widespread or systemic therapies with reasonable tolerability						
Phototherapy						

UVB 308-nm excimer light for 10 wk[30]	Intraindividual RCT	Prurigo form of AD	13	Significant improvement in PAIS from BL to wk 10 with both UVB and CP; significant difference between groups at wk 14, 22, and 34 Significant reduction in VAS pruritus scores with both UVB and CP at wk 10; no significant difference between groups	Transient burning sensation, erythema, vesicles, and blistering; hyperpigmentation	1b
PUVA ± UVB 308-nm excimer light[31]	RCT	PN	22	PUVA alone: CR in 6 of 11 pts (55%); PR in 5 of 11 (45%) PUVA + UVB: CR in 7 of 11 pts (64%); PR in 3 of 11 (27%); 1 dropout (9%) No significant difference between groups; 30% less PUVA radiation needed with combination therapy	Moderate UV erythema, formation of vesicles, and edema in some nodules (combination therapy only)	1b
Neural						
Gabapentin 300 mg/d, titrated up to 1200 mg/d[32]	Case report	PN	1	Complete resolution of pruritus and disappearance of lichenified papules and plaques leaving slight hyperpigmentation	Slight drowsiness	5
Pregabalin 75 mg/d for 3 mo[33]	Open-label, uncontrolled	PN	30	CR in 23 pts (76%) and slight improvement in 6 (20%); significant reduction in VAS from BL to 3 mo	Sedation, dizziness, and headache	2b
Paroxetine 10 mg/d for 3 d, followed by 20 mg/d up to 60 mg/d or fluvoxamine 25 mg/d for 3 d, followed by 50 mg/d up to 150 mg/d[34]	Open-label, prospective proof-of-concept	PN	50	Complete lesion healing in 14 pts (28%) and partial lesion healing in 17 (34%)	Fatigue, vertigo, nausea, drowsiness, and gastrointestinal pain	2b
Duloxetine hydrochloride 20-40 mg/d[35]	Case report	PN	2	Resolution of pruritus and flattened nodules in 1 pt and improvement of pruritus and skin lesions in 1 pt	None reported	5
Amitriptyline 60 mg for 3 wk, 30 mg for 2 wk, 10 mg for 1 wk[36]	Open-label, uncontrolled	PN	17	Response in 14 pts (82%); relapse within 7 mo in 5 pts	Reduced concentration during the day	2b
Serlopitant 5 mg/d for 8 wk[37]	RCT	PN	127	Significant reduction in average-itch VAS score from BL to wk 8 with serlopitant vs PBO. Two subsequent studies showed no statistically significant difference in reduction in WI-NRS from BL to wk 10 between serlopitant and PBO.	Nasopharyngitis, diarrhea, and fatigue	1b
Aprepitant 80 mg/d for 3 to 13 d[38]	Open-label, uncontrolled	PN	13	Significant reduction from BL in mean VAS	Nausea, vertigo, and drowsiness	2b

Continued

Table III. Cont'd

Therapy	Study design	Patient population	No.	Outcome	Adverse events	LOE*
Aprepitant 80 mg/d for 4 wk[39]	RCT	PN	58	No significant differences between aprepitant and PBO in pruritus, lesions, or QOL	No differences between aprepitant and PBO in safety analysis	1b
Topical 1% aprepitant gel BID for 28 d[40]	RCT	PN	19	Mean VAS pruritus scores decreased from BL to d 28 with aprepitant and PBO; no significant difference between groups	Administration-site pain and cutaneous reactions	1b
Immunologic						
Methotrexate 7.5-20 mg/wk[41]	Retrospective cohort	PN	13	Remission or marked improvement in 10 of 13 pts (77%)	Fatigue, nausea, and elevated liver enzymes	4
Methotrexate 5-25 mg/wk[42]	Retrospective	PN	39	Moderately/very much improved pruritus reported in 32 of 36 pts (89%) at 3 mo; 29 of 32 (91%) at 6 mo; and 25 of 28 (89%) at 12 mo	Elevated transaminases, anemia, and nausea	4
Cyclosporine microemulsion 3-5 mg/kg/d[43]	Observational	PN	14	Very good response (80-100%) in 10 of 14 pts (71%), good response (40-70%) in 3 of 14 (21%), and no/slight response (0-30%) in 1 of 14 (7%)	Disturbed renal and hepatic functions, hypertrichosis, gingival hyperplasia, gastric upset, diarrhea, hypertension, reversible elevation of serum lipids, and weight gain	4
Cyclosporine 2-4 mg/kg/d[44]	Retrospective	PN	8	Remission (no active or new lesions) achieved in 6 of 8 pts (75%), improvement in 1 of 8 (13%), and 1 lost to follow-up	Migraines, nausea, hypertension, dizziness, blurry vision, keratoacanthoma, hypercholesterolemia, and folliculitis	4
Tier 3: Less tolerable, less well-established, or experimental therapies						
Neural						
Naltrexone 50 mg/d[45]	Observational	Elderly PN	4	Reduction in VAS from BL to mo 2	Transient insomnia and fatigue	4
Naltrexone 50 mg/d[46]	Open-label, uncontrolled	PN	17	Reduction in pruritus: 100% in 8 of 17 pts (47%), 50%-70% in 4 of 17 (24%), 10%-30% in 3 of 17 (18%), none in 4 of 17 (24%)	Tachyphylaxis and transient nausea, fatigue, and dizziness	2b
Intranasal butorphanol 1-3 mg/d[47]	Case report	PN	1	Reduction in itch and improvement in sleep	None in this patient; somnolence, dizziness, and nausea or vomiting are associated with intranasal butorphanol	5
Thalidomide 50 or 100 mg/d[48]	Retrospective	PN	42	Skin condition improved in 32 of 42 pts (76%): clearing, n = 1; marked improvement, n = 5; moderate improvement, n = 20; slight improvement, n = 6	Neuropathy, sedation, dizziness, rash, depression, and nausea	4

Thalidomide 33-200 mg/d[49]	Open-label, uncontrolled	HIV and PN	8	100% of pts had >50% reduction in itch; 7 of 8 pts had >50% reduction in skin involvement	Peripheral neuropathy	2b
Thalidomide 50-100 mg/d[50]	Retrospective	PN	13	Complete improvement in 7 of 13 pts (54%); slight improvement in 4 of 13 pts (31%)	Neuropathy, sedation, dizziness, and renal toxicity	4
Thalidomide 50-100 mg/d[51]	Case series	PN	6	All pts reported reduction in pruritus and improvement in skin lesions; 1 pt had recurrence and responded to second course	Sedation and transient generalized erythema with lower leg edema	4
Immunologic						
Dupilumab 600-mg induction dose, then 300 mg every 2 wk for 16 wk[52]	Retrospective	PN form of AD	9	Significant improvement from BL to wk 16 in EASI, DLQI, and pruritus VAS score	None reported	4
Dupilumab 600-mg induction dose, then 300 mg every 2 wk[53]	Retrospective	PN	9	Substantial reduction in itch NRS; complete resolution in 7 of 9 pts (78%)	None reported	4
Dupilumab[54]	Cohort	PN	16	Significant reduction in itch NRS from BL to mo 3, with pruritus CR in 5 pts (31%), PR in 9 (56%), and no response in 2 (13%)	Conjunctivitis, worsening of celiac disease, and eosinophilia	4
Dupilumab 600-mg induction dose, then 300 mg every 2 wk[55]	Case report	PN	4	After 2 wk to 3 mo, all 4 pts achieved an itch NRS score of 0; mean itch NRS reduction was −8.8	None reported	5
Azathioprine 50 mg BID[56]	Case report	PN	2	Improved pruritus and less prominent nodules in both pts; recurrence after 2 mo in pt 1 (less severe) and after 3 y in pt 2 (disease was controlled with mildly potent topical corticosteroid)	Nausea, diarrhea, and epigastric pain; monitoring for bone marrow suppression recommended	5
Nemolizumab 0.5 mg/kg every 4 wk[57]	RCT	PN	70	Significantly greater percentage change in peak pruritus NRS score at wk 4 with nemolizumab vs PBO	Gastrointestinal (abdominal pain and diarrhea) and musculoskeletal symptoms	1b
Tier 4: Therapies that may prove useful but currently lack data in PN						
Neural						
Cannabinoids	No data available in patients with PN					5
Immunologic						
Mycophenolate mofetil	No data available in patients with PN					5
Janus kinase inhibitors	No data available in patients with PN					5
Anti-IL-31/oncostatin M receptor antibodies	No data available in patients with PN					5

AD, Atopic dermatitis; *BID*, 2 times daily; *BL*, baseline; *CP*, clobetasol propionate; *CR*, complete remission; *DLQI*, Dermatology Life Quality Index; *EASI*, Eczema Area and Severity Index; *IL-31*, interleukin 31; *LOE*, level of evidence; *NRS*, numeric rating scale; *PAIS*, Physician Assessment of Individual Signs; *PBO*, placebo; *PR*, partial remission; *pt(s)*, patient(s); *PUVA*, psoralen plus ultraviolet A; *QOL*, quality of life; *RCT*, randomized controlled trial; *UV*, ultraviolet; *UVB*, ultraviolet B; *VAS*, visual analog scale.

*LOE rating and criteria: *1a*, systematic review of RCTs; *1b*, individual RCT; *2a*, systematic review of cohort studies; *2b*, individual cohort study; *3a*, systematic review of case-control studies; *3b*, individual case-control study; *4*, case series and poor-quality cohort and case-control studies; *5*, case reports or expert opinion.

Table IV. Suggested regimens for systemic medication for prurigo nodularis

Therapy	Recommended dosages	Efficacy*
Topical		
Neural		
Topical capsaicin	Capsaicin 0.025%-0.3% 4-6 times daily	1
Topical ketamine, amitriptyline, lidocaine	Ketamine 5%-10%, amitriptyline 5%, and lidocaine 5% Use 3 times daily	1
Immunologic		
Pimecrolimus cream	Pimecrolimus 1% cream BID, may be used indefinitely	1
Tacrolimus ointment	Tacrolimus 0.1% ointment BID, may be used indefinitely	1
Betamethasone valerate	Betamethasone 0.05% cream or ointment BID, limit use to 2-4 consecutive wk	2
Intralesional triamcinolone acetonide	5-20 mg/mL, 0.05-0.1 mL per prurigo nodularis lesion	2
Systemic		
Neural		
Gabapentin	300-1200 mg PO TID SR: Start 300 mg PO at night and increase every 2 d by 300 mg for 1-2 wk then increase by 300 mg TID increments every 1-2 wk as tolerated.†	3
Pregabalin	75-100 mg PO BID SR: Start 25 mg PO BID for 1-2 wk, then increase by 25-mg BID increments every 1-2 weeks as tolerated.†	3
Paroxetine	10 mg to 40 mg PO daily SR: Start 10 mg PO daily for 2-4 wk, then increase by 10-mg increments every 2-4 wk as tolerated.†	3
Duloxetine	30 mg to 60 mg PO daily SR: Start 30 mg PO daily at night for 2-4 wk, then increase by 30-mg increments every 2-4 wk as tolerated.†	3
Amitriptyline	10 mg to 60 mg PO daily SR: Start 10 mg PO daily at night for 1 wk, then increase by 10 mg increments every 2-4 wk as tolerated.†	3
Aprepitant	80 mg PO daily	3
Butorphanol	1 mg to 3 mg intranasal daily SR: Start 1 mg daily at night for 1-2 wk, then increase by 1-mg increments every 2 wk as tolerated.†	3
Thalidomide	50 or 100 mg PO daily SR: Start 50 mg PO daily for 4 wk, then increase to 100 mg as tolerated.†	3
Naltrexone	50 mg to 150 mg PO daily SR: Start 25 mg PO daily for 3 d, if tolerating, increase to 50 mg daily for 1 wk, then increase by 25- to 50-mg increments every 2-4 wk as tolerated.†	3
Immunologic		
Methotrexate	7.5-15 mg PO weekly SR: Start 7 .5 mg PO once weekly for 2 wk, then increase by 2.5- to 5.0-mg weekly as needed.†	4
Cyclosporine	3-5 mg/kg body weight PO daily SR: Start 3.0 mg/kg PO daily for 2-4 wk, if tolerating, increase by 0.5-1.0 mg/kg daily every 2-4 wk as tolerated.†	4
Dupilumab	600 mg SC initial dose, then 300 mg SC every other wk	3
Azathioprine	50 mg to 200 mg PO daily SR: Start 50 mg PO daily for 2-4 wk, increase by 50 mg daily every 2-4 wk as tolerated.†	3

BID, 2 times daily; *PO*, per os (oral); *TID*, 3 times daily; *SC*, subcutaneous; *SR*, suggested regimen.

*Efficacy rating reflects the quality of the published data and a consensus opinion of the authors on this panel. Ratings on this 6-point scale include *0* (no effect), *1* (may help in rare cases or to a very low degree), *2* (may help to some extent in 5% to 10% of individuals), *3* (may help to some extent in 10% to 40% of individuals), *4* (may help to some extent in 40% to 60% of individuals), and *5* (may help to a great extent in majority of individuals).

†Regimen provided is a general guideline. Medication dosage and frequency of increase should be evaluated on an individual basis in light of response to therapy, potential adverse effects, or concerns in light of medical comorbidities or polypharmacy.

ultraviolet B 308-nm excimer light and PUVA alone or in combination showed improvement in pruritus with phototherapy.[30,61] AEs were generally mild and transient and included burning sensation, erythema, vesicles, blistering, and hyperpigmentation; erythema and vesicles were more common with combination therapy.[30,61] There was no difference in remission rates between PUVA alone or in combination with narrowband ultraviolet B; however, combination therapy required a lower number of PUVA treatments to achieve remission.[30]

Neural. Therapies that address the neural component include gabapentinoids, antidepressants (serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, or tricyclic antidepressants), and NK_1 receptor antagonists.

One case report and a cohort study suggest that gabapentinoids may be effective at reducing pruritus in patients with PN.[32,62] Sedation is the main AE observed with these therapies, 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 100-300 mg at night; pregabalin 75 mg) and increase the dose as tolerated, up to 3600 mg for gabapentin or 600 mg for pregabalin, in divided doses throughout the day.[32,62]

When treating PN with antidepressants, we typically start with a serotonin and norepinephrine reuptake inhibitor, followed by a selective serotonin reuptake inhibitor and then a tricyclic antidepressant. Two open-label studies and a case report have provided support for an antipruritic effect of the antidepressants paroxetine, fluvoxamine, amitriptyline, and duloxetine in patients with PN.[34-36] The most common AEs observed with selective serotonin reuptake inhibitors were fatigue, vertigo, drowsiness, nausea, gastrointestinal pain, and weight gain.[34] The main AE reported with amitriptyline was reduced concentration during the day.[36] The most common AEs with duloxetine are nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, and hyperhidrosis.[63]

Two NK_1 receptor antagonists have been evaluated in patients with PN: aprepitant, approved for prevention of chemotherapy-induced or postoperative nausea and vomiting, and the investigational agent serlopitant. Although aprepitant use was supported by an initial uncontrolled study in 20 patients with chronic pruritus, including 13 patients with PN, these findings were not supported by RCTs of oral or topical aprepitant.[38-40] Serlopitant was evaluated in the largest RCT conducted in patients with PN to date, demonstrating a significant reduction in pruritus visual analog scale scores compared with placebo.[37] Serlopitant received Food and Drug Administration breakthrough designation for treatment of pruritus associated with PN in January 2019.[61] However, Menlo Therapeutics (Bridgewater, NJ) recently announced the results of 2 phase 3 clinical trials evaluating the efficacy of serlopitant in 580 patients with PN, who were randomized to once-daily dosing of serlopitant 5 mg or placebo. Serlopitant showed a slight numerical advantage over placebo, but neither study met its primary end point of a statistically significant difference in the number of patients achieving a 4-point or greater reduction in the worst-itch numeric rating scale for patients treated with serlopitant from baseline to week 10 (Menlo Therapeutics press release April 6, 2020; https://menlotherapeutics.gcs-web.com/news-releases/news-release-details/menlo-therapeutics-announces-results-two-phase-3-clinical-trials). AEs reported for NK_1 receptor antagonists are generally mild and similar to placebo. The most commonly reported AEs were nausea, vertigo, and drowsiness with oral aprepitant; nasopharyngitis, diarrhea, and fatigue with oral serlopitant; and administration-site pain and cutaneous reactions with topical aprepitant.[37,39,40]

Immunologic. Therapies that address the immunologic component include methotrexate and cyclosporine. Results from 2 retrospective studies evaluating methotrexate in patients with PN showed a marked improvement in lesions and reduction in pruritus.[41,42] The most common AEs were nausea, fatigue, anemia, and elevated aminotransaminases.[12,41,42] Limited data suggest that cyclosporine reduces pruritus and is associated with clinical improvement in patients with PN.[43,44] Regular monitoring of blood pressure and renal/hepatic function is required, and cyclosporine is not recommended for patients with impaired renal function.[12,43,44]

Tier 3: less tolerable, less well-established, or experimental therapies

Neural. Therapies that address the neural component include κ-opioid receptor/μ-opioid receptor agonists/antagonists and thalidomide. Some observational studies and case reports of patients with PN reported improvements in pruritus with naltrexone or butorphanol.[45-47] AEs associated with κ-opioid receptor/μ-opioid receptor agonists/antagonists are generally transient and include dizziness, headache, fatigue, somnolence, nausea, vomiting, and diarrhea.

A few uncontrolled studies have reported improvements in skin lesions and reduced itch

among patients with PN treated with thalidomide; however, thalidomide use is limited by its poor safety profile, including peripheral neuropathy and a risk of thromboembolism and teratogenicity.[12,49,54,64] Limited evidence exists to support the efficacy of lower doses (50-100 mg/day) with fewer AEs.[50,51]

Immunologic. Therapies that address the immunologic component include dupilumab, azathioprine, methotrexate, and investigational IL-31 receptor mAbs. Dupilumab, a mAb that blocks the shared α-subunit of the IL-4 receptor and thereby prevents IL-4 and IL-13 signaling, was evaluated in 3 retrospective case series in patients with PN.[52,54,55] These studies reported a significant reduction in pruritus with the standard dupilumab dose (600-mg induction dose, then 300 mg every 2 weeks). Similar results were reported in 3 smaller case series of 2 to 4 patients with PN.[53,55,65,66] AEs of dupilumab appear to be mild. Conjunctivitis, worsening of celiac disease, eosinophilia, herpes labialis, and alopecia were reported in 1 to 2 patients each. Results from the ongoing phase 3 study of dupilumab in PN (NCT04183335) are expected to help guide treatment.

Limited data suggest that azathioprine reduces pruritus in patients with PN; however, the effects appear to be short-term.[56] Azathioprine is also associated with significant AEs, including nausea, diarrhea, and epigastric pain, and monitoring for potential bone marrow suppression is recommended.[56] In a retrospective case review of 96 patients treated with azathioprine for pruritus, 65% of patients experienced suspected drug-related AEs, and 33% permanently discontinued treatment.[67]

Long-term therapy with systemic corticosteroids, such as prednisone, may lead to systemic complications because of the duration and dose of treatment usually required, thus limiting their utility in PN. Prednisone use should be limited to a short trial period (<4 weeks).

The investigational anti—IL-31 receptor mAb nemolizumab has shown promise for the treatment of PN. A phase 2 RCT of nemolizumab in patients with PN reported a significantly greater reduction in pruritus numeric rating scale itch scores with nemolizumab vs placebo.[57] AEs included gastrointestinal and musculoskeletal symptoms. Nemolizumab received Food and Drug Administration breakthrough therapy designation for the treatment of pruritus associated with PN in December 2019.[68]

Tier 4: therapies that may prove useful but currently lack data in PN

Neural. Although antipruritic effects have been reported for both systemic and topical cannabinoids, no studies are currently evaluating cannabinoids in patients with PN.[69,70]

Immunologic. Mycophenolate mofetil is sometimes used to treat chronic dermatitis; however, no studies have been reported in patients with PN. Likewise, several inhibitors of cytokine signaling, including Janus kinase inhibitors and anti—IL-31/oncostatin M receptor mAbs, are reported to have antipruritic effects but have not been evaluated in patients with PN.

CONCLUSIONS

Defining PN as a distinct clinical entity will allow for clearer diagnostic and management approaches as well as support investigational studies to advance understanding of the pathogenesis of PN and provide effective treatment options. All treatments for PN are currently used off-label, and all data supporting the use of various treatments are based on anecdotal or small clinical trials. An effective treatment approach should be based on clinical judgment and tailored to the individual needs of the patient, considering their clinical presentation, comorbidities, and response to prior treatments. These expert panel recommendations are intended to provide practical guidance to US dermatologists for the diagnosis and effective treatment of patients with PN as well as offer researchers a simplified PN classification for investigational studies.

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