Prurigo nodularis

Pathogenesis and management

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Learning objectives
After completing this learning activity participants should be able to discuss the pathogenesis of prurigo nodularis and describe current management practices and approaches for treating patients with prurigo nodularis.

Disclosures
Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

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Dr Kwatra is an advisory board member for Pfizer Inc, Regeneron Pharmaceuticals, and Menlo Therapeutics and has received grant funding from Pfizer and Kiniksa Pharmaceuticals. The other authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Prurigo nodularis is a chronic skin condition characterized by severely pruritic nodules that cause a profound negative impact on quality of life. The second article in this 2-part continuing medical education series focuses on reviewing the pathogenesis of prurigo nodularis and exploring management algorithms for this condition. In addition, we discuss some emerging and novel therapies for treating prurigo nodularis. The first article in this 2-part series describes the broader epidemiology, patient demographics, physical examination findings, and symptoms to aid in the timely recognition and diagnosis of prurigo nodularis. (J Am Acad Dermatol 2020;83:1567-75.)

Key words: antipruritic; clinical features; itch; management; pathogenesis; prurigo nodularis; pruritus; therapeutics.

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Funding sources: Dr Kwatra received grant funding from the Skin of Color Society and is a recipient of the Dermatology Foundation Medical Dermatology Career Development Award.
Conflicts of interest: Dr Kwatra is an advisory board member for Pfizer Inc, Regeneron Pharmaceuticals, and Menlo Therapeutics and has received grant funding from Pfizer and Kiniksa Pharmaceuticals. The other authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).
Accepted for publication April 23, 2020.
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0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.04.182

Date of release: December 2020.
Expiration date: December 2023.

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PATHOGENESIS OF PRURIGO NODULARIS

Key points

- Immune and neural dysregulation are implicated in the pathogenesis of prurigo nodularis
- Immune cells and neuropeptides play an important role in cutaneous inflammation and altered neural circuitry that drives pruritus associated with prurigo nodularis

Prurigo nodularis (PN) is a chronic, inflammatory skin condition characterized by severely pruritic nodules that cause a profound negative impact on quality of life.[1] The pathogenesis of PN is thought to be a cutaneous reaction pattern caused by vicious cycles of chronic itch followed by repeated scratching.[1,2] The exact pathogenesis of PN remains unknown. However, previous studies show that significant interaction and dysregulation between immune cells and neuronal circuitry play important roles in the pathogenesis of PN.

Immune dysregulation

Histopathologic studies show dense dermal, interstitial, and perivascular infiltrates in the dermis of PN lesions, primarily consisting of increased numbers of T lymphocytes, mast cells, and eosinophilic granulocytes.[3,4] Immune cells in the skin generate a robust inflammatory response and intense itch by releasing mediators such as interleukin (IL)-31, tryptase, eosinophil cationic protein, histamine, prostaglandins, and neuropeptides.[3,4] This immune response is central to the pathogenesis of PN.

Eosinophils play a role in the cutaneous inflammation and pruritus associated with PN. There is an accumulation of eosinophils in the dermis of PN lesional skin. Granules released by eosinophils include neuropeptides and eosinophil cationic protein, eosinophil-derived neurotoxin, eosinophil protein X, and major basic protein.[5-7] Eosinophil cationic protein and eosinophil-derived neurotoxin are of particular interest because they have a neurotoxic effect and are both significantly increased in the skin of patients with PN.[5,6,8]

T cells and their cytokines, particularly IL-31, are also involved in the pathogenesis of PN. Messenger RNA for the T cell–derived cytokine IL-31 is more abundant in PN lesional skin when compared with healthy skin.[4,9] IL-31 propagates itch via binding to the heterodimeric IL-31A and oncostatin M receptor.[4,5] This mechanism is supported by transgenic mouse studies showing that IL-31 expression was associated with significant skin inflammation and severe itch, while the use of anti–IL-31 monoclonal antibodies led to a significant reduction in scratch activity.[5,10,11] Finally, subsets of T_H2 cytokines such as IL-4 have also been found to be increased in prurigo-like skin lesions.

Neural dysregulation

Multiple studies have investigated the architecture and distribution of nerve fibers in the lesional and nonlesional dermis of patients with PN.[5] In 1934, Pautrier described neuronal hyperplasia (Pautrier neuroma) within the dermis of a patient with PN.[4,12] Several studies have verified this by staining for the panneuronal marker protein gene product-9.5 and nerve growth factor receptor within lesional PN skin.[6] One study showed that the nerve growth factor receptor– and protein gene product–immunoreactive structures in the dermis of PN patients are present at a significantly greater density compared with healthy control subjects. In contrast, the epidermis of patients with PN lack nerve growth factor receptor–immunoreactive nerve fibers and far fewer PGP-9.5$^+$ nerve fibers.[6] Despite this difference in nerve fiber density between the dermis and epidermis, a functional small fiber neuropathy in patients with PN has not been identified.[4,13] This finding argues against intrinsic neuropathy as the cause of reduced intraepidermal nerve fiber density in patients with PN, which may be secondary to repeated mechanical scratching. However, increased dermal nerve fiber density seen in patients with PN and its association with peripheral neuropathies warrants further investigation.[14]

Dysregulation of several neuropeptides, particularly calcitonin gene-related peptide and substance P (SP) have been implicated in the pathogenesis of PN. SP is a neurotransmitter secreted by neurons that binds to the neurokinin-1 receptor in the skin and in the central nervous system.[3,4] One study found an increased number of SP$^+$ nerve fibers and increased expression of SP in dermal PN skin.[4,5,15] Calcitonin gene-related peptide is another neuropeptide with a similar mechanism to SP that is also upregulated in PN and may contribute to disease pathogenesis. Calcitonin gene-related peptide can be secreted into cutaneous tissue via nerve fibers causing neurogenic inflammation through the regulation of eosinophils and mast cells.[4,6] CGPR can also affect endorphin levels and cause dysregulated expression of mu and kappa opioid receptors, both of which may contribute to pruritus in PN.

MANAGEMENT OF PRURIGO NODULARIS

Key points

- The diagnostic workup for prurigo nodularis includes a complete blood cell count with differential, liver and renal function tests, and a thorough

review of systems to guide evaluation for associated systemic diseases
- Obtaining a skin biopsy specimen is indicated in subsets of patients
- Treatment for prurigo nodularis is centered on topical, intralesional, and systemic neuroimmune modulatory therapies to break a short-circuited itch–scratch cycle
- There are currently no therapies for prurigo nodularis approved by the US Food and Drug Administration, which leads to highly variable practices in the prescription of off-label therapies and highlights the need for a multimodal approach to therapeutics

History and physical examination

PN is a clinical diagnosis, and therefore a thorough history and physical examination are essential for diagnosis. Patients with PN will endorse intense pruritus present for ≥6 weeks that can be constant, intermittent, or paroxysmal in nature, and is sometimes also accompanied by burning or stinging sensations.[16] A complete history should be obtained, including a careful review of medications and supplements. In addition, a thorough history of all medical problems, including psychiatric history, can also be helpful in diagnosing conditions associated with PN.

On physical examination, patients with PN typically display clustered nodules located on ≥2 different extensor surfaces and may also involve the trunk. Though many patients with PN may also have associated dermatoses, such as atopic dermatitis, these hyperkeratotic and sometimes excoriated nodules are specific to PN. A more detailed discussion of the clinical features of PN can be found in the first article in this continuing medical education series.

Laboratory workup

As described in the first article in this series, there are several comorbid conditions associated with PN. It is important to identify underlying systemic diseases that may be contributing to PN. Focused laboratory work-up for a systemic etiology is especially important for patients without a history of underlying dermatoses, such as atopic dermatitis.[16,17] The recommended laboratory work-up for patients with PN includes a complete blood cell count with a differential as well as liver and renal function tests. Additional testing for thyroid function testing, hemoglobin A1c/diabetes screening, HIV serology, and hepatitis B and C serologies is suggested based on the presence of risk factors, review of systems, and clinical examination.[16,18] Other laboratory tests to consider based on clinical history and review of systems are serum immunofixation, serum and urine protein electrophoresis, urinalysis, chest radiograph, stool examination for ova and parasites, and iron studies.[16,17] Patients should also be up to date with age-appropriate malignancy screening. There should be greater concern for underlying associated malignancy in patients with PN with acute rather than chronic onset of pruritus (<1 year).

Additional testing may be warranted for subsets of patients. Although PN is a clinical diagnosis, obtaining a skin biopsy specimen may be indicated for atypical clinical presentations. Skin biopsy procedures, though not routine, can provide useful information in the work-up of PN, particularly when considering primary dermatoses as the cause of PN.[16,19] On review of the biopsy specimen, the lesions of PN typically display orthohyperkeratosis, irregular epidermal hyperplasia, hypergranulosis, and an increased number of fibroblasts and capillaries.[16,20] These changes correlate with scratch-induced injury and hyperkeratosis. As discussed earlier, cutaneous nerve studies have shown a decrease in epidermal nerve fiber density and an increase in dermal nerve fiber density within lesional PN skin. When accompanied by urticaria and in the elderly population, direct immunofluorescence studies can identify an underlying autoimmune blistering disorder, such as bullous pemphigoid.[16,20]

Treatment approaches

PN remains a difficult condition to treat because there are currently no targeted treatments approved by the US Food and Drug Administration (FDA). Therefore, providers often prescribe off-label therapies with a high degree of variability among treatment regimens used.[21] The overall goal in treating PN is to break the itch–scratch cycle and reduce pruritus to heal nodules.[1] To adequately treat PN, treatment regimens need to address both the neural and immunologic components of the disease. An individualized treatment plan, based on the patient's age, comorbidities, disease severity, and side effect profile of treatments is needed to personalize treatment. This is often best achieved by using a multimodal regimen including systemic and topical therapies.[22] Current and emerging therapies for PN are shown in Table I, and a theraputic ladder is shown in Figure 1.

Topical treatment. Topical therapies for PN that have been examined in randomized clinical trials include corticosteroids, pimecrolimus, and calcipotriol. The limited efficacy of these treatments

Table I. Current and emerging therapies for the treatment of prurigo nodularis

Locally acting agents	Phototherapy	Systemic neuromodulating agents	Systemic immunomodulating agents	Emerging therapies and therapeutic targets
Topical steroids/ flurandrenolide tape	NBUVB (2-3 times/week)	Gabapentin (100-3600 mg/day)	Methotrexate (15-25 mg/ week)	Anti—IL-31: nemolizumab
Topical anesthetics	PUVA (2-3 times/week)	Pregabalin (75-600 mg/ day)	Cyclosporine (2.5-5 mg/ kg/day)	Anti-OSM beta receptor: KPL-716
Topical calcineurin inhibitors		Aprepitant (80 mg/day)	Mycophenolate mofetil (500-3000 mg/day)	Mu and kappa opioid receptors modulation: nalbuphine
Topical calcipotriene		Naltrexone (25-50 mg/ day)	Azathioprine (50-150 mg/day)	NK1R inhibitor serlopitant
Topical capsaicin (0.025-0.3% cream 4-6 times/ day)		Butorphanol (1 mg intranasally every 4 hours as needed)	Dupilumab* (600 mg induction followed by 300 mg every 2 weeks)	
Intralesional corticosteroids (10 mg/mL)		Duloxetine (20-60 mg/ day)		
		Paroxetine (10 mg/day for 3 days followed by maintenance 30-60 mg/day)		
		Fluvoxamine (25 mg/day for 3 days followed by maintenance 50-150 mg/day)		
		Thalidomide (50-150 mg/ day)		

NBUVB, Narrowband ultraviolet B light; *NK1R*, neurokinin-1 receptor; *OSM*, oncostatin M; *PUVA*, psoralen plus ultraviolet A light phototherapy.

highlights the need for continued research to develop more targeted topical therapies for PN.

The first-line topical therapy for PN remains high-potency topical corticosteroids. Betamethasone valerate 0.1% tape reduced pruritus and flattened nodules in patients with PN compared with moisturizing itch relief cream alone.[23] Flurandrenolide tape, a medicated occlusive skin barrier that can be occluded to specific nodules while sparing surrounding skin, can also be an effective treatment for patients with PN. Because flurandrenolide tape can be expensive, patients may also be offered alternatives such as high-potency topical steroids under occlusion with an Unna boot. In addition to enhancing the effect of the medication, treatments involving occlusion also act as a physical aversion to scratching the skin. In additional to topical agents, intralesional injections of corticosteroid can be effective in alleviating pruritus and flattening PN lesions. Intralesional injections of triamcinolone acetonide, usually started at 10 mg/mL, can demonstrate clinical improvement in PN.

Topical anesthetics are another alternative antipruritic treatment option for patients with chronic pruritus and that can provide modest itch relief in patients with mild PN. Over the counter 1% pramoxine lotion, lidocaine spray, and compounded topical anesthetic creams may be used.

Other nonsteroid topical agents have also been studied for the treatment of PN, including topical calcineurin inhibitors (ie, pimecrolimus), vitamin D derivatives, and capsaicin. A previous study found that 1% pimecrolimus cream is helpful in treating itch in patients with PN with reductions in visual analog scale from 7.1 to 4.4.[24]

Finally, capsaicin has been tried in PN to disrupt pain and pruritus via the depletion of neuropeptides in small sensory cutaneous nerve fibers.[25] One study of patients with PN showed remission of itching and healing of nodules with topical capsaicin 0.025% to 0.3% 4 to 6 times a day.[25] The study also showed depletion of neuropeptides in PN skin after treatment with capsaicin.[25] In the authors' experience, capsaicin has limited practical efficacy in PN because of the high frequency of application required, significant associated irritation, and minimal efficacy.

Phototherapy. Ultraviolet light therapy reduces pruritus in many skin conditions, including PN, through its antiinflammatory effects.[26] This is a particularly useful option in medically complex

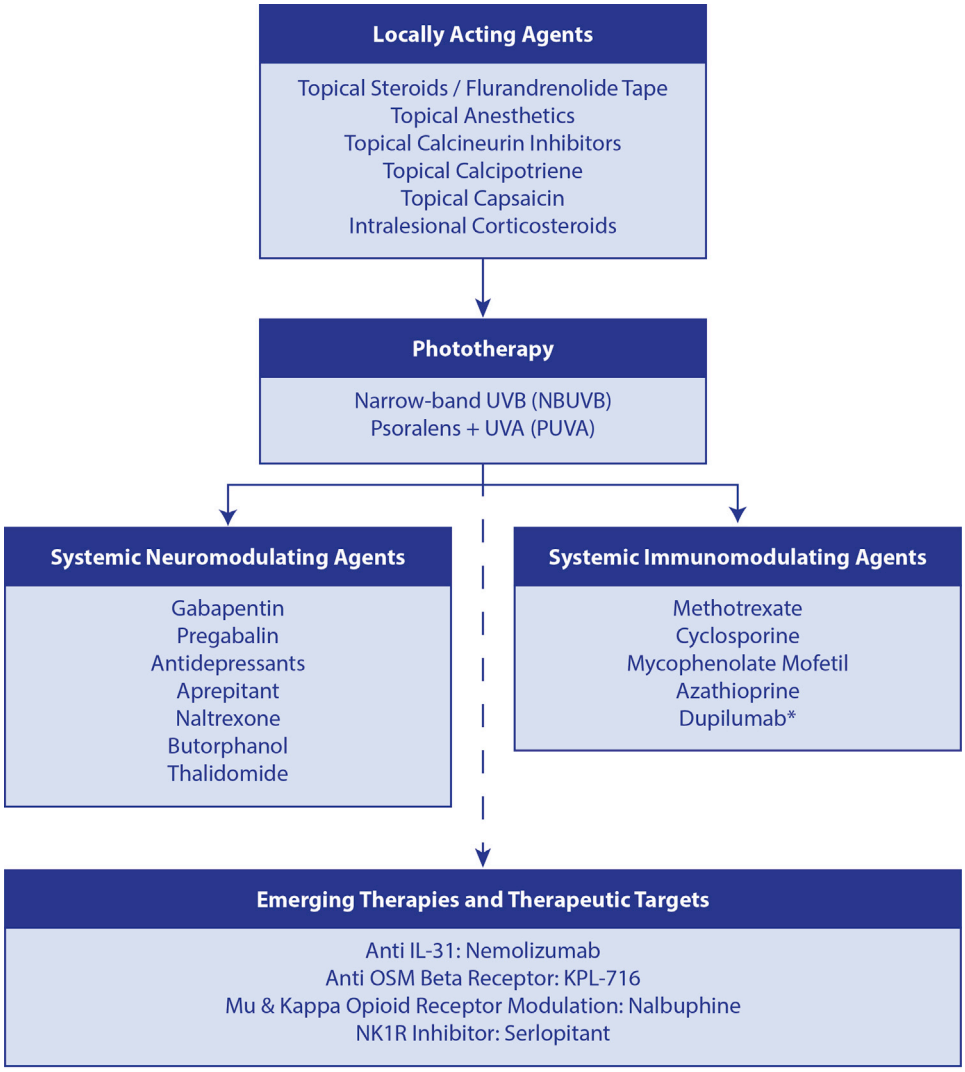

Fig 1. Prurigo nodularis (PN) therapeutic ladder. We recommend a multimodal approach to therapeutics for patients with PN involving topical, intralesional, phototherapy, and systemic agents tailored to patient comorbidities and severity of clinical presentation. Several emerging targeted antipruritic therapeutics are under development for use in PN. *Dupilumab has been approved by the US Food and Drug Administration for the treatment of atopic dermatitis and is undergoing trials for PN with published case reports indicating efficacy in PN. *IL-31*, Interleukin-31; *NK1R*, neurokinin-1 receptor; *OSM*, oncostatin M.

patients whose treatment options may be limited by comorbidities and drug interactions with other medications.[22]

Of the available ultraviolet light therapies, narrow-band ultraviolet B light therapy 2 to 3 times weekly is considered to be first-line therapy for patients with PN. Ultraviolet A light, psoralen plus ultraviolet A light phototherapy, and ultraviolet B light have all shown some efficacy in treating PN.[22] In addition, the efficacy of a modified Goeckerman regimen for pruritus has also been shown. However, because the Goeckerman regimen consists of daily broad-band ultraviolet B light therapy followed by the application of crude coal tar and topical corticosteroids under occlusion for 4 hours each day, it should be used with caution to minimize carcinogenic side effects.[27] Phototherapy along with topical therapy will only be sufficient treatment for a minority of patients with PN. Most patients with PN will require adjunctive systemic therapy as outlined below.

Systemic therapy. Patients with PN usually require treatment with systemic therapies because many patients are refractory to the treatments described above. Systemic options for the treatment of PN include immunosuppressants, gabapentinoids, antidepressants, and mu-opioid receptor

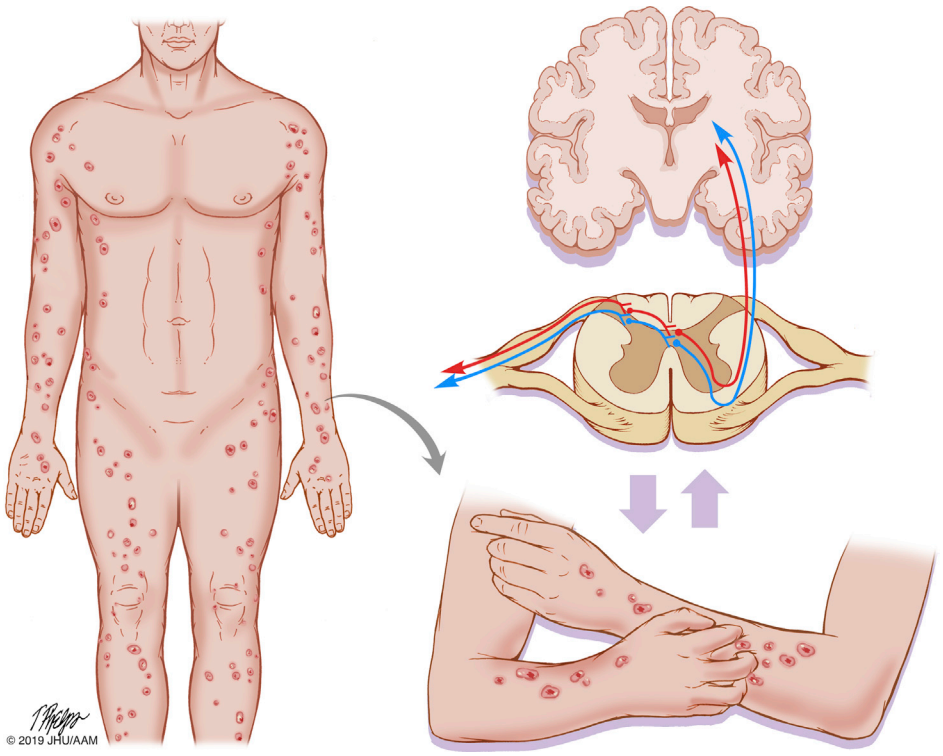

Fig 2. Prurigo nodularis itch neural transmission pathway. The itch transmission pathway is a bidirectional signaling process spanning from cutaneous nerve fibers in the skin to the dorsal root ganglion, spinal cord, and brain. A multimodal approach to therapy targets the itch signaling cascade at multiple points in the itch pathway.

antagonists.[21,22] PN is a nonhistaminergic itch condition, and therapy with antihistaminergic agents is generally ineffective aside from its sedative properties and not recommended unless a comorbid histamine-mediated condition is suspected.[22,28]

Given the important role of immune dysregulation in the pathogenesis of PN, systemic immunosuppressants are a commonly used medication class. Immunosuppressants that have been used to treat PN with evidence in retrospective studies include methotrexate and cyclosporine.[29] Two retrospective studies of methotrexate as treatment for PN showed significant relief from pruritus and healing of lesions in these patients.[30,31] Given its favorable side effect profile, methotrexate is commonly used in the Johns Hopkins Itch Clinic as frontline immunosuppressive therapy starting at around 15 to 20 mg weekly along with topical therapy. For more severe cases on presentation, cyclosporine may also be used. Several reports show that cyclosporine 2 to 5 mg/kg/day provided improvement of PN symptoms and resolution of nodules.[32,33] A drawback to treatment with cyclosporine is its significant side effect profile, requiring patients to have regular monitoring of blood pressure, renal function, hepatic function, and complete blood cell counts.[32,33]

PN treatment also includes several agents specifically targeting the neural pathogenesis of itch transmission, which spans from neural innervation in the skin to the dorsal root ganglion, traversing through the spinal cord to the brain (Fig 2). Gabapentinoids are commonly prescribed, including gabapentin and pregabalin. These agents are thought to reduce itch via inhibition of calcium signaling.[34] Elderly patients are usually started at low doses (100 mg nightly) and gradually titrated up to higher doses given the risk of significant sedation. Younger patients may be started at 300 mg nightly and titrated upwards to ≤3600 mg daily (divided into thrice daily dosing). Pregabalin has a similar mechanism of action and is gradually titrated upwards with doses ranging from 75 to 600 mg daily. While these agents may be effective in subsets of patients because higher doses are often needed to reduce itch intensity, sedation often becomes an important side effect and is a top reason for treatment discontinuation.

Another drug class that has shown some efficacy in targeting the neural pathogenesis of itch are neurokinin-1 receptor antagonists, which are believed to reduce itch by blocking SP.[35,36] One agent in this class, aprepitant, is approved by the FDA for chemotherapy-associated nausea and vomiting.

When used off-label for treatment of chronic pruritus, the dose can vary depending on the underlying disease but has been prescribed at 80 mg daily.[35,37] An open-label study suggested that aprepitant may be effective in reducing itch associated with PN, but a randomized phase II trial failed to show efficacy of aprepitant in reducing itch severity in PN.[37] Similarly, serlopitant is another neurokinin-1 receptor antagonist that had promising phase II data only to fall short of its primary endpoint in 2 phase III trials.[38]

Thalidomide is another neuroactive medication that can be used for patients with PN who are recalcitrant to treatment, often dosed between 50 and 150 mg daily.[39-41] However, it requires use with extreme caution because of its known neurotoxic and teratogenic effects, including an increased risk of peripheral neuropathy and birth defects in pregnant women.[39] For these reasons, thalidomide should be reserved for patients who have failed to improve on traditional therapeutic agents.

Imbalances between the mu- and kappa-opioid systems may also play a role in the development of pruritus.[42] Several studies have examined the efficacy of opioid receptor—modulating drugs as therapies for chronic pruritus, with mixed kappa-opioid agonist/mu-opioid antagonists nalbuphine and butorphanol both showing promise.[42-45] In particular, intranasal butorphanol 1 mg as needed has been used in PN and is also used in the Johns Hopkins Itch Clinic for recalcitrant cases to attempt to break the itch—scratch cycle.[42] Lastly, the opioid antagonist naltrexone (50 mg) has also shown antipruritic effects in subsets of patients with PN.[43]

Finally, antidepressants such as paroxetine, fluvoxamine, duloxetine, and amitriptyline can provide mild to moderate relief of pruritus.[46-50] Paroxetine (10 mg daily for 3 days followed by maintenance dosing at 20-60 mg daily) or fluvoxamine (25 mg daily for 3 days followed by maintenance dosing at 50-150 mg daily) can reduce itch in patients with PN. Duloxetine 20 to 60 mg daily is an antidepressant approved for neuropathic pain that also may help with treating itch associated with PN.[47] Finally, several patients with PN responded to amitriptyline in a pilot study with an initial dosage of 60 mg daily for 3 weeks, followed by 30 mg daily for 2 weeks and 10 mg daily for 1 week.

Emerging therapies

New potential targets that are currently under investigation for itch pathogenesis in PN include IL-31, oncostatin m (OSM) beta receptor, and the IL-4 receptor.

With the recent discovery of elevated levels of IL-31 in patients with PN, IL-31 may be a new target for therapy. A phase II clinical trial by Ruzicka et al[51] on subcutaneous nemolizumab, a humanized antibody against IL-31 receptor A, reported significant improvement of pruritus in patients with atopic dermatitis.[52] In addition, the FDA recently gave nemolizumab breakthrough therapy status for PN based on its phase II trial efficacy in reducing pruritus in these patients.[53] In this trial, a subcutaneous nemolizumab dose of 0.5 mg/kg of body weight showed dramatic improvement in peak pruritus of patients with PN in the treatment group compared with placebo.[54]

OSM beta receptor is another novel target for combating itch in PN. As a proinflammatory signaling molecule similar to IL-6 cytokine family, OSM is activated by monocytes and T-lymphocytes to stimulate collagen production in dermal fibroblasts. KPL-716 is an OSM beta receptor monoclonal antibody that has been tried for itch in atopic dermatitis and is undergoing further study in the treatment of chronic pruritus in PN.

Finally, several case series have reported effective reduction in pruritus of PN with IL-4 receptor antagonists and both topical and oral cannabinoids.[55-60] Dupilumab, a monoclonal antibody antagonist of the IL-4 receptor, has already been approved by the FDA for the treatment for atopic dermatitis.[56] Given its specificity for the IL-4 pathway and inhibition of itch-specific neural pathways, dupilumab has also been explored for PN treatment, with preliminary case reports showing promising results.[56-60]

With regard to cannabinoids, cannabinoid receptors 1 and 2 expressed on cutaneous nerve fibers are also thought to contribute to itch.[55] A systematic review study has shown significant symptom relief in patients with chronic pruritus who were treated with cannabinoids and who were refractory to first-line treatment.[55] However, larger studies with appropriate control groups are needed to better study the efficacy and safety of cannabinoids in the treatment of PN.

With novel therapeutics on the horizon for PN, it is important for clinicians to better understand the pathogenesis and current management of PN. We continue to learn about the etiology of this disease and identify new targets for effective therapies for this chronic, recalcitrant condition.

REFERENCES

1. Kwatra SG. Breaking the itch—scratch cycle in prurigo nodularis. *N Engl J Med*. 2020;382:757-758.
2. Schuhknecht B, Marziniak M, Wissel A, et al. Reduced intraepidermal nerve fibre density in lesional and nonlesional prurigo nodularis skin as a potential sign of subclinical cutaneous neuropathy. *Br J Dermatol*. 2011;165:85-91.

3. Almeida TA, Rojo J, Nieto PM, et al. Tachykinins and tachykinin receptors: structure and activity relationships. *Curr Med Chem*. 2012;11:2045-2081.
4. Zeidler C, Yosipovitch G, Ständer S. Prurigo nodularis and its management. *Dermatol Clin*. 2018;36:189-197.
5. Raap U, Günther C. Pathogenese der prurigo nodularis. *Hautarzt*. 2014;65:691-696.
6. Johansson O, Liang Y, Marcusson JA, Reimert CM. Eosinophil cationic protein- and eosinophil-derived neurotoxin/eosinophil protein X-immunoreactive eosinophils in prurigo nodularis. *Arch Dermatol Res*. 2000;292:371-378.
7. Lee MR, Shumack S. Prurigo nodularis: a review. *Australas J Dermatol*. 2005;46:211-220.
8. Liang Y, Marcusson JA, Jacobi HH, Haak-Frendscho M, Johansson O. Histamine-containing mast cells and their relationship to NGFr-immunoreactive nerves in prurigo nodularis: a reappraisal. *J Cutan Pathol*. 1998;25:189-198.
9. Sonkoly E, Muller A, Lauerma AI, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol*. 2006;117:411-417.
10. Dillon SR, Sprecher C, Hammond A, et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol*. 2004;5:752-760.
11. Grimstad Ø, Sawanobori Y, Vestergaard C, et al. Anti-interleukin-31-antibodies ameliorate scratching behaviour in NC/Nga mice: a model of atopic dermatitis. *Exp Dermatol*. 2009;18:35-43.
12. Pautrier LM. Le névrome de la lichénification circonscrite nodulaire chronique (lichen ruber obtusus corné, prurigo nodularis). *Ann Dermatol Syphil*. 1934;41:897-919.
13. Pereira MP, Pogatzki-Zahn E, Snels C, et al. There is no functional small-fibre neuropathy in prurigo nodularis despite neuroanatomical alterations. *Exp Dermatol*. 2017;26:969-971.
14. Hughes J-DM, Woo TE, Belzberg M, et al. Association between prurigo nodularis and etiologies of peripheral neuropathy: suggesting a role for neural dysregulation in pathogenesis. *Medicines (Basel)*. 2020;7:4.
15. Haas S, Capellino S, Phan NQ, et al. Low density of sympathetic nerve fibers relative to substance P-positive nerve fibers in lesional skin of chronic pruritus and prurigo nodularis. *J Dermatol Sci*. 2010;58:193-197.
16. Kwon CD, Khanna R, Williams KA, Kwatra MM, Kwatra SG. Diagnostic workup and evaluation of patients with prurigo nodularis. *Medicines (Basel)*. 2019;6:97.
17. Saco M, Cohen G. Prurigo nodularis: picking the right treatment. *J Fam Pract*. 2015;64:221-225.
18. Ständer HF, Elmariah S, Zeidler C, Spellman M, Ständer S. Diagnostic and treatment algorithm for chronic nodular prurigo. *J Am Acad Dermatol*. 2020;82:460-468.
19. Elmariah SB. Diagnostic work-up of the itchy patient. *Dermatol Clin*. 2018;36:179-188.
20. Weigelt N, Metze D, Stander S. Prurigo nodularis: systematic analysis of 58 histological criteria in 136 patients. *J Cutan Pathol*. 2010;37:578-586.
21. Huang AH, Canner JK, Kang S, Kwatra SG. Analysis of real-world treatment patterns in patients with prurigo nodularis. *J Am Acad Dermatol*. 2020;82:34-36.
22. Zeidler C, Tsianakas A, Pereira M, Ständer H, Yosipovitch G, Ständer S. Chronic prurigo of nodular type: a review. *Acta Derm Venereol*. 2018;98:173-179.
23. Saraceno R, Chiricozzi A, Nistic SP, Tiberti S, Chimenti S. An occlusive dressing containing betamethasone valerate 0.1% for the treatment of prurigo nodularis. *J Dermatolog Treat*. 2010;21:363-366.
24. Siepmann D, Lotts T, Blome C, et al. Evaluation of the antipruritic effects of topical pimecrolimus in non-atopic prurigo nodularis: results of a randomized, hydrocortisone- controlled, double-blind phase II trial. *Dermatology*. 2014;227:353-360.
25. Ständer S, Luger T, Metze D. Treatment of prurigo nodularis with topical capsaicin. *J Am Acad Dermatol*. 2001;44:471-478.
26. Hammes S, Hermann J, Roos S, Ockenfels HM. UVB 308-nm excimer light and bath PUVA: combination therapy is very effective in the treatment of prurigo nodularis. *J Eur Acad Dermatol Venereol*. 2011;25:799-803.
27. Sorenson E, Levin E, Koo J, Berger TG. Successful use of a modified Goeckerman regimen in the treatment of generalized prurigo nodularis. *J Am Acad Dermatol*. 2015;72:e40-e42.
28. Fostini AC, Girolomoni G, Tessari G. Prurigo nodularis: an update on etiopathogenesis and therapy. *J Dermatolog Treat*. 2013;24:458-462.
29. Pereira MP, Ständer S. Novel drugs for the treatment of chronic pruritus. *Expert Opin Investig Drugs*. 2018;27:981-988.
30. Spring P, Gschwind I, Gilliet M. Prurigo nodularis: retrospective study of 13 cases managed with methotrexate. *Clin Exp Dermatol*. 2014;39:468-473.
31. Klejtman T, Beylot-Barry M, Joly P, et al. Treatment of prurigo with methotrexate: a multicentre retrospective study of 39 cases. *J Eur Acad Dermatol Venereol*. 2018;32:437-440.
32. Siepmann D, Luger TA, Ständer S. Antipruritic effect of cyclosporine microemulsion in prurigo nodularis: results of a case series [in German]. *JDDG*. 2008;6:941-946.
33. Wiznia LE, Callahan SW, Cohen DE, Orlow SJ. Rapid improvement of prurigo nodularis with cyclosporine treatment. *J Am Acad Dermatol*. 2018;78:1209-1211.
34. Matsuda KM, Sharma D, Schonfeld AR, Kwatra SG. Gabapentin and pregabalin for the treatment of chronic pruritus. *J Am Acad Dermatol*. 2016;75:619-625.e6.
35. He A, Alhariri JM, Sweren RJ, Kwatra MM, Kwatra SG. Aprepitant for the treatment of chronic refractory pruritus. *Biomed Res Int*. 2017;2017:4790810.
36. Ständer S, Kwon P, Hirman J, et al. Serlopitant reduced pruritus in patients with prurigo nodularis in a phase 2, randomized, placebo-controlled trial. *J Am Acad Dermatol*. 2019;80:1395-1402.
37. Ständer S, Siepmann D, Herrgott I, Sunderkötter C, Luger TA. Targeting the neurokinin receptor 1 with aprepitant: a novel antipruritic strategy. *PLoS One*. 2010;5:e10968.
38. Terry M. Menlo's serlopitant for prurigo nodularis itching flunks two phase III trials. Available at: https://www.biospace.com/article/menlo-s-serlopitant-for-prurigo-nodularis-itching-flunked-2-phase-iii-trials/. Accessed April 16, 2020.
39. Sharma D, Kwatra SG. Thalidomide for the treatment of chronic refractory pruritus. *J Am Acad Dermatol*. 2016;74:363-369.
40. Taefehnorooz H, Truchetet F, Barbaud A, Schmutz JL, Bursztejn AC. Efficacy of thalidomide in the treatment of prurigo nodularis. *Acta Derm Venereol*. 2011;91:344-345.
41. Andersen TP, Fogh K. Thalidomide in 42 patients with prurigo nodularis hyde. *Dermatology*. 2011;223:107-112.
42. Dawn AG, Yosipovitch G. Butorphanol for treatment of intractable pruritus. *J Am Acad Dermatol*. 2006;54:527-531.
43. Metze D, Reimann S, Beissert S, Luger T. Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. *J Am Acad Dermatol*. 1999;41:533-539.
44. Lee J, Shin JU, Noh S, Park CO, Lee KH. Clinical efficacy and safety of naltrexone combination therapy in older patients with severe pruritus. *Ann Dermatol*. 2016;28:159-162.

45. Hawi A, Alcorn H, Berg J, Hines C, Hait H, Sciascia T. Pharmacokinetics of nalbuphine hydrochloride extended release tablets in hemodialysis patients with exploratory effect on pruritus. *BMC Nephrol*. 2015;16:47.
46. Ständer S, Böckenholt B, Schürmeyer-Horst F, et al. Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof-of-concept study. *Acta Derm Venereol*. 2009;89:45-51.
47. Hashimoto T, Satoh T, Yokozeki H. Prurigo successfully treated with duloxetine hydrochloride. *Australas J Dermatol*. 2019;60:237-239.
48. Griffin JR, Davis MDP. Amitriptyline/ketamine as therapy for neuropathic pruritus and pain secondary to herpes zoster. *J Drugs Dermatol*. 2015;14:115-118.
49. Zalaudek I, Petrillo G, Baldassarre MA, et al. Amitriptyline as therapeutic and not symptomatic approach in the treatment of prurigo nodularis: a pilot study. *G Ital Dermatol Venereol*. 2006;141:433-437.
50. Boozalis E, Khanna R, Zampella JG, Kwatra SG. Tricyclic antidepressants for the treatment of chronic pruritus [e-pub ahead of print]. *J Dermatolog Treat*; 2019. https://doi.org/10.1080/09546634.2019.1623369. Accessed August 14, 2020.
51. Ruzicka T, Hanifin JM, Furue M, et al. Anti-interleukin-31 receptor a antibody for atopic dermatitis. *N Engl J Med*. 2017;376:826-835.
52. Schneider LC. Ditching the itch with anti-type 2 cytokine therapies for atopic dermatitis. *N Engl J Med*. 2017;376:878-879.
53. Park B. Nemolizumab gets breakthrough therapy status for prurigo nodularis. Available at: https://www.empr.com/home/news/nemolizumab-gets-breakthrough-therapy-status-for-prurigo-nodularis/. Accessed February 23, 2020.
54. Ständer S, Yosipovitch G, Legat FJ, et al. Trial of nemolizumab in moderate-to-severe prurigo nodularis. *N Engl J Med*. 2020;382:706-716.
55. Khanna R, Khanna R, Denny G, Kwatra SG. Cannabinoids for the treatment of chronic refractory pruritus [e-pub ahead of print]. *J Dermatolog Treat*; 2019. https://doi.org/10.1080/09546634.2019.1639603. Accessed August 14, 2020.
56. Zhai LL, Savage KT, Qiu CC, Jin A, Valdes-Rodriguez R, Mollanazar NK. Chronic pruritus responding to dupilumab—a case series. *Medicines (Basel)*. 2019;6:72.
57. Mollanazar NK, Elgash M, Weaver L, Valdes-Rodriguez R, Hsu S. Reduced itch associated with dupilumab treatment in 4 patients with prurigo nodularis. *JAMA Dermatol*. 2019;155:121-122.
58. Beck KM, Yang EJ, Sekhon S, Bhutani T, Liao W. Dupilumab treatment for generalized prurigo nodularis. *JAMA Dermatol*. 2019;155:118-120.
59. Napolitano M, Fabbrocini G, Scalvenzi M, Nisticò SP, Dastoli S, Patruno C. Effectiveness of dupilumab for the treatment of generalized prurigo nodularis phenotype of adult atopic dermatitis. *Dermatitis*. 2020;31:81-84.
60. Rambhia PH, Levitt JO. Recalcitrant prurigo nodularis treated successfully with dupilumab. *JAAD Case Rep*. 2019;5:471-473.

Answers to CME examination

Identification No. JB1220

December 2020 issue of the Journal of the American Academy of Dermatology.

Williams KA, Huang AH, Belzberg M, Kwatra SG. J Am Acad Dermatol 2020;83:1567-75.

1. b
2. a
3. c
4. b