A systematic review of evidence-based treatments for prurigo nodularis

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Prurigo nodularis is a chronic dermatologic condition involving the development of multiple cutaneous nodules in the setting of intractable pruritus. Given emerging treatment options for this difficult-to-treat condition, a current review of therapeutics is needed. A systematic review was performed for clinical studies investigating prurigo nodularis treatment published from 1990 to present including ≥5 subjects. A total of 35 articles were assigned a level of evidence according to the Oxford Center for Evidence-based Medicine. All 5 studies investigating topical agents, including corticosteroids, calcineurin inhibitors, calcipotriol, and capsaicin, conveyed some beneficial effect with level of evidence 2b or higher. Six of 8 reports investigating photo- and photochemotherapy achieved levels of evidence 2b or greater and showed good partial response rates. Thalidomide was studied by 6 reports providing evidence of good symptom response, only 2 of which were rated level 2b or greater. Cyclosporine and methotrexate have demonstrated benefit in 4 combined studies, albeit with level 4 evidence. Pregabalin, amitriptyline, paroxetine, fluvoxamine, and neurokinin-1 receptor antagonists have demonstrated promising evidence in 5 level 2b studies. Higher-powered studies and additional randomized controlled trials are needed for the evaluation of safe and efficacious systemic treatment options for prurigo nodularis. (J Am Acad Dermatol 2019;80:756-64.)

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

Prurigo nodularis (PN) is a chronic skin condition that is characterized by debilitating paroxysmal pruritus and numerous firm nodules typically localized to extremity extensor surfaces. Nodules may appear flesh-colored, erythematous, or brown-black, and are often found in a linear arrangement, sparing areas such as the upper-middle back that are difficult to reach. Limited evidence suggests that the disease is more frequent, occurs with earlier age of onset, and is more severe in females.[1] Eczemas, psychiatric factors, and underlying systemic disorders, such as malignancy, chronic renal failure, liver failure, and HIV infection, have all shown to be risk factors for PN development.[2,3]

The pathogenesis of PN is largely unknown. Current thinking categorizes PN as a neurodermatitis, resulting in an itch/scratch cycle.[4] A reduction of intraepidermal nerve fiber density in spite of hypertrophy and proliferation of dermal nerves has been noted in PN lesions.[5-7] Scratching likely contributes to the reduced intraepidermal nerve fiber density as opposed to an endogenous neuropathy.[8] Lesional skin nerve fibers are immunoreactive to substance P and calcitonin gene-related peptide (CGRP).[9,10] These and other neuropeptides, along

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Abbreviations used:

CGRP:	calcitonin gene-related peptide
IL:	interleukin
LOE:	level of evidence
MC:	mast cell
MTX:	methotrexate
NRS:	Numerical Rating Scale
PN:	prurigo nodularis
PUVA:	psoralen plus ultraviolet A light phototherapy
RCT:	randomized controlled trial
VAS:	visual analog scale

with histamine from increased mast cells likely contribute to inflammation and itch in PN.[11-14] Interleukin (IL)-31 has also shown to be upregulated in lesional skin of PN in comparison to both nonlesional skin and lesional skin of patients with other chronic inflammatory skin diseases.[15,16]

There is a lack of targeted pharmacologic therapy for PN, and all treatments currently used demonstrate variable success. In addition to identifying and treating the underlying cause when present, a number of topical and systemic therapies are used for PN. This systematic review aims to provide a summary of evidence-based PN treatments with level of evidence (LOE) ratings for each supporting study.

METHODS

A systematic review of the PubMed and Scopus databases was performed for clinical studies regarding PN treatment published between January 1, 1990 and March 22, 2018. A total of 706 unique studies published in English were found using a search strategy developed with the assistance of a research librarian. Only primary clinical studies investigating treatment strategies in PN patients were included. Exclusion criteria comprised studies that did not include outcomes of the treatment implemented. Case reports and series describing <5 patients were also excluded to avoid selection bias. Bibliographies of relevant publications were searched for additional studies meeting the inclusion and exclusion criteria. All articles were screened according to the scheme presented in Fig 1.

Articles providing evidence to support the implementation of an intervention were assigned a LOE according to an adaptation of the Oxford Center for Evidence-based Medicine LOE.[17] Articles were assessed for quality evidence according to the following scheme: 1a, systematic review of randomized controlled trials (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; and 5, case reports or expert opinion.

RESULTS

A total of 35 original reports meeting the inclusion and exclusion criteria were found, including 15 prospective cohort studies, 11 retrospective reviews, 8 RCTs, and a single case series. Only 3 of the 8 RCTs included samples of >22 patients with PN (Table I).

Topical agents: Corticosteroids, calcineurin inhibitors, calcipotriol, and capsaicin

Topical treatment regimens studied include 50 μg/g calcipotriol ointment, 0.025% to 0.3% topical capsaicin, 1% pimecrolimus cream, 0.1% tacrolimus ointment, and 0.1% betamethasone valerate tape.[18-22] Corticosteroids likely work through immunomodulatory effects on T cells and cytokines, thereby influencing neuropeptides, such as substance P and CGRP.[21] Calcineurin inhibitors and capsaicin likely cause neural modulation of itch through influence on vanilloid receptor 1.[20,23-25] Calcipotriol, or vitamin D_3, may alter itch sensation through its inhibition of tumor necrosis factor−α expression or an altered distribution pattern of Langerhans cells.[26] All 5 studies included in this category were rated LOE 2b or higher.[18,21,22]

Wong and Goh[18] carried out a RCT to compare the efficacy of calcipotriol ointment 50 μg/g to betamethasone valerate ointment 0.1% twice daily in 10 patients with PN using internalized controls. The results conveyed a significantly reduced number and size of nodules on the region treated with calcipotriol compared with the betamethasone-treated region at 4 and 8 weeks ($P < .05$ for all).[18]

Saraceno et al[21] carried out a pilot study in 12 patients with severe PN to compare the efficacy of betamethasone valerate 0.1% tape versus an Aveeno moisturizing antipruritic cream with feverfew, a medicinal herb. Implementing an internalized control study design, the once daily−applied betamethasone tape contributed to greater mean pruritus visual analog scale (VAS) score improvements from baseline (4.85 points, $P < .005$ from baseline) compared with the region treated with antipruritic cream twice daily for 4 weeks (3.15 points, $P < .005$ from baseline, not significant for comparison to the other group). Overall, subjects were satisfied with cosmetic results, tolerated treatment well, and preferred the tape because of a

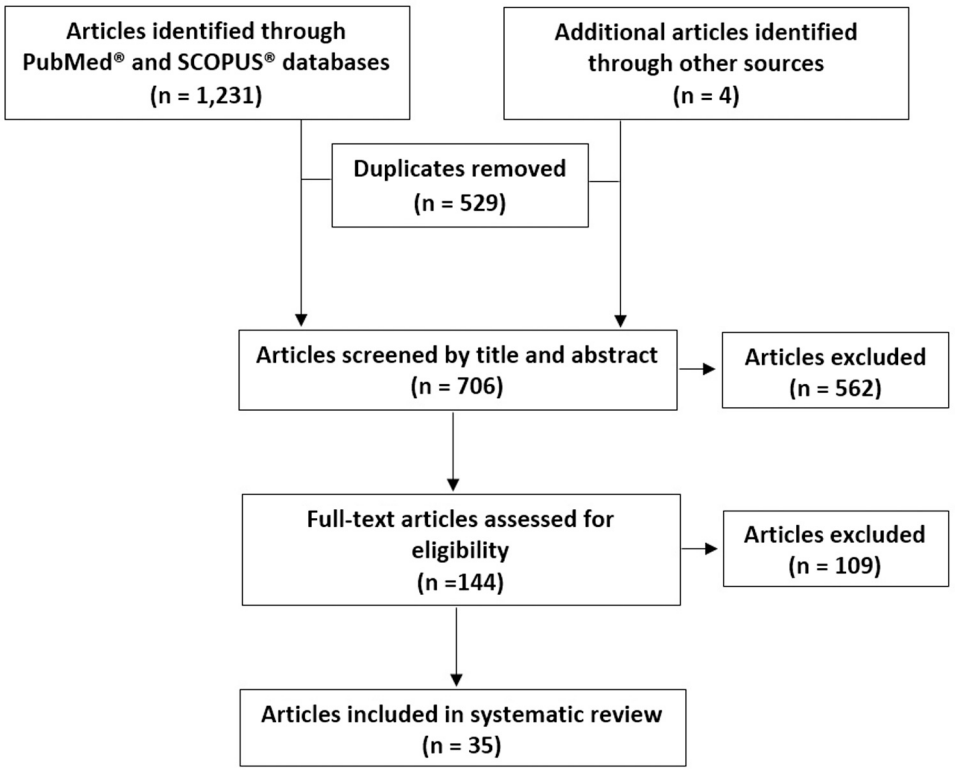

Fig 1. Literature review screening scheme for articles included in a systematic review of treatments for prurigo nodularis.

diminished ability to scratch. Many patients, however, noted a loss of adhesion within a day.[21]

Siepmann et al[22] carried out a RCT comparing 1% pimecrolimus cream to 1% hydrocortisone cream, each applied twice daily for 8 weeks in 30 patients with PN. The investigators found that skin regions treated with both agents yielded similar mean reductions in VAS compared with baseline (a 2.7-point reduction for pimecrolimus and a 2.8-point reduction for hydrocortisone, $P < .001$ from baseline for both treated regions). Both agents also contributed to significantly improved prurigo lesions at 10 days, 4 weeks, and 8 weeks.[22]

Topical agents represent a commonly used first-line treatment for PN. Studies to date have demonstrated promising results implementing a heterogeneity of treatment agents and regimens.

Phototherapy and photochemotherapy

Numerous studies have described the efficacy of ultraviolet (UV) treatment in PN, including psoralen plus ultraviolet A light phototherapy (PUVA), ultraviolet A (UVA) light alone, and ultraviolet B light (UVB) alone.[27-34] Six of 8 studies in this category were rated LOE 2b or higher. The antipruritic effects of UVB treatment are likely caused by both induction of T-regulatory cells and the inhibition of mast cell granule release.[27,35] UVA offers the benefit of deeper UV penetration, while PUVA has been shown to downregulate CGRP.[9,32,36]

Brenninkmeijer et al[28] studied the utility of 308-nm excimer light weekly in comparison to an internal control intervention of 0.05% clobetasol propionate ointment once daily for 10 weeks in 13 patients with PN. Evaluation at week 34 demonstrated that more excimer-treated sites (8) showed ≥40% improvement in the Physician Assessment of Individual Signs (an outcome encompassing nodule number and appearance, along with pruritus) in comparison to clobetasol-treated sites (3, *P* value not presented). In addition, excimer-treated sites resulted in 63% improvement in VAS at week 34 compared with only 49% improvement with clobetasol-treated sites (*P* value not presented).[28]

Hammes et al[27] carried out a RCT studying UVB 308-nm excimer light with bath PUVA compared with PUVA alone in 22 patients with recalcitrant PN. Combination treatment resulted in complete remission in 7 of 10 patients after a mean of just 9.8 treatments compared with 6 patients with complete remission after a mean of 20.4 treatments in the

Table I. Randomized controlled trials for prurigo nodularis treatment with published results[18,21,22,27,28,56,57,72]

Studied intervention	Control group intervention	N	Key findings	Side effects
Betamethasone valerate 0.1% tape once daily[21]	Moisturizing itch-relief cream twice daily	11/12 subjects completed treatment course	Betamethasone-treated side with better clinical response at week 4 compared with Aveeno-treated side (mean VAS reductions from baseline of 4.85 and 3.15 points, respectively)	None reported
Calcipotriol 50 μg/g ointment twice daily[18]	Betamethasone valerate 0.1% ointment twice daily	10	Number and size of nodules decreased 49% and 56%, respectively, in calcipotriol group and 18% and 25%, respectively, in betamethasone group after 8 weeks	Self-resolving mild perilesional skin irritation with calcipotriol
Pimecrolimus 1% cream twice daily[22]	Hydrocortisone 1% cream twice daily	30	Significant mean VAS reduction from baseline with both pimecrolimus (2.7 points) and hydrocortisone (2.8 points) treatments at day 10, along with significantly improved prurigo lesions for both treatments at 10 days, 4 weeks, and 8 weeks	Progression, suspected contact allergy to wound dressing
308-nm excimer weekly[28]	Clobetasol 0.05% ointment once daily	13	PAIS with $\geq$40% improvement in 8 excimer-treated sites at week 34 compared with 3 clobetasol-treated sites, VAS with 63% improvement with excimer treatment at week 34 compared with 49% improvement with clobetasol treatment, and PGA with 6 excimer-treated sites were mild-almost clear at week 34 compared with 2 clobetasol-treated sites	Hyperpigmentation, erythema, burning, vesicles, and blistering
PUVA plus 308-nm excimer twice weekly[27]	PUVA alone 4 times weekly	21	6/11 patients receiving PUVA alone with complete remission, 7/10 patients receiving combination therapy with complete remission	PUVA alone; moderate erythema Combination therapy; erythema, vesicles and edema
Aprepitant 10 mg/g gel twice daily[56]	Vehicle gel twice daily	6 subjects with PN (19 total)	Presented for all patients combined and not PN patients alone; no significant difference in pruritus or lesion appearance improvement between groups (however, both groups with >50% reduction in VAS)	Pain at administration site, cutaneous reactions
Oral serlopitant 5 mg daily[57]	Placebo daily	127	Significantly improved VAS reduction in serlopitant group (-3.6 cm) compared with the placebo group (-1.9 cm) at 8 weeks from baseline, 54.4% of serlopitant patients with $\geq$4 cm VAS response by week 8 compared with only 25.0% of placebo patients	Well-tolerated, only mild-moderate adverse events

Continued

Table I. Cont'd

Studied intervention	Control group intervention	N	Key findings	Side effects
Oral ketotifen 1 mg daily plus topical antibiotic 3 times daily (with halobetasol ointment daily plus oral hydroxyzine 25 mg as needed)[72]	Halobetasol ointment daily plus oral hydroxyzine 25 mg as needed alone	27	9/14 patients in the ketotifen group had complete resolution of pruritus by the end of week 1, which was maintained until the end of week 4 (overall, 10/14 patients with complete resolution by the end of week 4 compared with 0/13 patients in the control group)	Many subjects with sedation and drowsiness at varying points throughout treatment

PAIS, Physician Assessment of Individual Signs; *PGA*, Physician Global Assessment; *PN*, prurigo nodularis; *PUVA*, psoralen plus ultraviolet A light phototherapy; *VAS*, visual analog score.

control group ($P < .02$ for number of treatments). In turn, patients receiving combination treatment required a significantly lower cumulative dose of PUVA (16.9 J/cm^2) compared with patients receiving PUVA alone (23.7 J/cm^2, $P < .05$).[27]

Photo- and photochemotherapy have demonstrated moderate efficacy in treating PN. Mild side effects have been noted overall, including erythema, hyperpigmentation, vesicles, or edema in 45 of 117 patients (38%) in the included reports.[27-29,31]

Thalidomide

Thalidomide, which likely counters pruritus by way of a multimodal approach involving central neural mediation and immunomodulation, is known to have a poor safety profile, limiting its use.[37-40] However, there is substantial evidence regarding the efficacy of thalidomide in treating the symptoms of PN.[37,41-43] Only 2 of 6 studies reviewed achieved LOE 2b or higher.

Andersen and Fogh[37] found that 32 of 42 patients with PN retrospectively reviewed experienced slight improvement or better after treatment with thalidomide. Patients studied in this sample were on an average of 100 mg daily of thalidomide daily for an average of 105 weeks.[37] Peripheral neuropathy, however, was a reason for cessation of therapy in an overwhelming 25 patients.[37] Other side effects occurring in ≥3 patients included sedation, dizziness, rash, depression, and nausea. Thalidomide treatment also carries risk of thromboembolism and teratogenicity.[44] There is, however, limited evidence supporting efficacy with fewer side effects with a 50- to 100-mg daily dose of thalidomide.[42,45,46]

Systemic immunomodulatory drugs: Methotrexate and cyclosporine

Four studies included in the present review investigate systemic immunomodulatory agents in patients with PN, and were all rated a LOE of 4.[47-50] These studies focus on cyclosporine, a calcineurin inhibitor that likely affects itch by way of IL-2 signaling modulation, and methotrexate (MTX), a folic acid antagonist with immunomodulatory properties influencing pruritus via an poorly understood mechanism.[47,49]

Multiple retrospective reviews have demonstrated the utility of MTX in PN treatment.[47,48] Spring et al[47] conducted a retrospective review of 13 patients with resistant PN receiving 7.5 to 20 g MTX administered subcutaneously weekly for at least 6 months. Investigators noted a ≥75% decrease in the Prurigo Nodularis Area and Severity Index and or the Pruritus Numeric Rating Scale in 10 of 13 patients. Only 1

patient developed fatigue, nausea, and transaminitis. Several patients developed typical nausea at the beginning of the treatment.[47] A recent report of 39 patients receiving MTX 5 to 25 mg weekly conveyed disease response rates of 91% and 94% at 3 and 6 months, respectively.[48] Common side effects included nausea, transaminitis, and gastrointestinal symptoms.[48]

Cyclosporine at doses of 3 to 5 mg/kg has been investigated in multiple small studies as well, demonstrating therapeutic effect after about 3 weeks, with a maximal effect after a mean of 2 to 3 months.[49,50] Clinical improvement has been noted in 19 of 22 patients included in these 2 samples. Side effects are prevalent and include hypertension, gastrointestinal upset/nausea, hypercholesterolemia, elevated creatinine, and gingival hyperplasia.[49,50]

Antiepileptics and antidepressants

Antiepileptics and antidepressants, including pregabalin and amitriptyline, have been studied in a combined 97 patients from the 3 level 2b studies included. Pregabalin modulates neural γ-aminobutyric acid signaling, while antidepressants, including selective serotonin reuptake inhibitors, act by an unclear mechanism to modulate itch.[51,52] Pregabalin 75 mg daily contributed to complete response in 23 of 30 patients after just 3 months of treatment in 1 cohort.[53] Side effects were noted in 6 patients and caused treatment discontinuation in only 2 patients from sedation and headache.[53] Zalaudek et al[54] demonstrated the beneficial effect of amitriptyline contributing to clinical improvement in 17 PN patients treated with doses of 10 to 60 mg for 6 weeks. Ständer et al[51] studied the antipruritic effects of paroxetine 10 to 60 mg or fluvoxamine 25 to 150 mg, with results showing partial lesion clearing in 17 of 31 patients, and complete lesion healing in 14 of 31 patients. Central nervous system, gastrointestinal, and cardiovascular side effects were prevalent.[51]

Emerging treatment approaches

Recent studies have investigated the utility of neurokinin-1 receptor antagonists, including aprepitant and serlopitant, in treating PN.[55-57] The neurokinin-1 receptor is a target of substance P, a mediator of itch and a probable pathogenic agent in PN.[55] Binding by these agents likely disrupt substance P signaling, thereby halting PN pathogenesis.[55] Aprepitant has shown potential benefit with systemic administration, but equivocal evidence when applied topically.[55,56] Ständer et al[57] carried out a RCT comparing the effect of serlopitant 5 mg daily versus placebo daily for 8 weeks in 127 patients with PN patients. The evidence demonstrated a significant difference in VAS reduction from baseline to 8 weeks in the serlopitant group (3.6 cm) versus the placebo group (1.9 cm, $P = .0005$).[57] Treatment was well-tolerated.[57]

A recent retrospective review investigated the efficacy of compounded topical ketamine (5-10%), amitriptyline (5%), and lidocaine (5%) in a lipoderm cream used up to 3 times daily.[58] A significant mean improvement in the Pruritus Numeric Rating Scale was noted (5.22, $P < .001$) in 18 patients with PN.[58] The antipruritic effects of this compound are likely achieved through modulation of N-methyl-D-aspartate glutamate receptors and sodium channels.[59]

DISCUSSION

Many treatments for PN have a limited capacity for clinical application because of their low efficacy or a high frequency of side effects. Furthermore, of the 35 studies included, only 8 were RCTs, and only 9 reports included ≥25 patients. The lack of success with existing treatments for PN is likely related to the hetergeneous nature of the etiology of chronic pruritus. In addition to cutaneous origins, a variety of systemic conditions, as well as neurologic, psychiatric, and somatoform factors may contribute to the onset of pruritus.[60] Careful patient-directed therapeutic selection plays a pivotal role in disease management.

Thalidomide use in PN is limited because of its poor safety profile.[37] Its analog, lenalidomide, has been introduced with the hope of achieving similar clinical efficacy with a better safety profile. Such efficacy is supported by several recent case reports.[61-63] In 1 reported case, however, treatment was terminated out of concern for possible drug-induced neuropathy or myopathy.[62] Increased thromboembolic risk, myelosuppression, and Stevens–Johnson syndrome have also been associated with lenalidomide use.[64,65] Current studies investigating lenalidomide for PN did not reach sufficient power for inclusion into the present review.[61-63]

Systemic immunomodulatory agents, including MTX and cyclosporine, demonstrate successful treatment of PN at the cost of poor safety profiles.[37,47-50] Antieptileptics and antidepressants, however, show promise as treatment options in PN with diminished side effects. Gabapentin, which functions similarly to pregabalin by acting on calcium channels to modulate γ-aminobutyric acid neurotransmitter signaling, is used in chronic pruritus and has been supported by anecdotal successful reports in patients with PN.[52,66-68]

However, reports detailing the efficacy of gabapentin in treating PN lack sufficient power for inclusion in the present article.[67,68]

In addition to neurokinin-1 receptor antagonists, promising newer therapeutic approaches for PN include targeting of IL-31 signaling and opioid receptor modulation.[69-71] Nemolizumab, an IL-31 receptor A antagonist, is currently undergoing phase II study in patients with PN (NCT03181503).[70] Nalbuphine, an opioid κ-receptor agonist and μ-receptor antagonist, has demonstrated beneficial effects for patients with PN in a recent multicenter, double-blind, RCT with results released but not yet published (NCT02174419).[71] Findings from this 62-patient sample suggest trends for efficacy of nalbuphine extended release 180 mg twice daily compared with placebo.[71] No serious drug-attributed adverse events were noted.[71]

This summary provides evidence-based guidance for practitioners while helping researchers to identify gaps in PN treatment development and study. In addition to direct treatment of comorbidities, patients with PN would benefit from safer and more effective systemic therapies. Neurokinin-1 receptor antagonists, κ-opioid receptor modulators, and IL-31 receptor antibodies under recent investigation all show promise in achieving this goal. In addition, the genetic underpinning of disease warrants further investigation for possible development of targeted and personalized therapies. As new reports emerge, the variety of options in the practitioner's toolbox will grow to meet the needs of an equally diverse population of patients with PN.

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