

## ORIGINAL ARTICLE

# Prurigo nodularis: a physician survey to evaluate current perceptions of its classification, clinical experience and unmet need

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## Abstract

**Background** Prurigo nodularis (PN) is a chronic skin condition characterized by intensely pruritic, hyperkeratotic papulonodular lesions that dramatically impairs patients' quality of life. Management of the condition is challenging, and there is no approved therapy in the United States or in Europe.

**Objective** The key aim of this survey was to examine current perceptions of PN diagnosis and management among members of the European Academy of Dermatology and Venereology (EADV).

**Methods** The survey comprised 29 questions, including multiple choice and open responses, and was sent to clinicians via e-mail during December 2016. The survey results were collected and analysed.

**Results** Responses were received from 30 participants from 14 countries, of whom 22 (73.3%) were members of the EADV Task Force Pruritus. The majority (73.3%) considered PN to be a distinct condition, and the preferred description to explain the most common pathogenesis was 'chronic pruritus leading to chronic scratching' (80.0%). Pruritic nodules ( $n = 23/30$ , 76.7%) and scratching ( $n = 12/30$ , 40.0%) were the most common descriptors used to characterize PN. Most respondents (60.0%) reported seeing  $\leq 5$  unique PN patients per month, the majority of whom (68.8%) visited a physician  $\sim 2$ –4 times per year. PN patients reported to the respondents that they experienced persistent, severe pruritus, with a mean  $\pm$  SD numeric rating scale score of  $7.8 \pm 1.2$ , lasting for  $>6$  months in 82.3% of patients and  $>2$  years in 51.0%. The most frequently prescribed therapies by survey respondents for PN symptoms were antihistamines (90.0%), antidepressants (90.0%), gabapentinoids (86.7%) and immunosuppressants (86.7%). Respondents agreed upon the need for new PN therapies (56.7%), revised PN classification and terminology (23.3%) and better understanding of PN pathophysiology (20.0%).

**Conclusion** EADV Task Force Pruritus notes several challenges that must be met to improve symptoms and quality of life for patients with PN.

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## Conflict of Interests

Dr. Pereira declares no conflict of interests. Mr. Basta is Chief Executive Officer at Menlo Therapeutics Inc. Mr. Moore is Director of Life Sciences Strategy at Navigant Life Sciences, which has provided consulting services to Menlo Therapeutics Inc. Dr. Ständer has received grants/research support and honoraria for her role as an investigator and consultant from Menlo Therapeutics Inc, Galderma, Kiniksa Pharmaceuticals, Pierre Fabre Dermo-Cosmetique, Trevi Therapeutics, and Vanda Pharmaceuticals; has received honoraria for participation in advisory boards for Menlo Therapeutics Inc, Beiersdorf AG, Celgene GmbH, Galderma, Kneipp-Werke, NeRRé Therapeutics and Sienna Biopharmaceuticals; and has received patient fees from Menlo Therapeutics Inc, Dermasence, Trevi Therapeutics, and Vanda Pharmaceuticals.

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## Introduction

Prurigo nodularis (PN) is a chronic skin condition characterized by intensely pruritic papulonodular lesions and is the dominant subtype of chronic prurigo.<sup>1</sup> PN is a long-term outcome of scratching by patients with chronic pruritus.<sup>2,3</sup> Lesions can range from a few millimetres up to 2 cm in diameter and are typically distributed symmetrically along the extensor surface of the extremities.<sup>3–5</sup> The incidence and prevalence of PN are largely unknown, although small epidemiologic studies suggest that it is most common in women and older adults.<sup>2,4,6</sup> PN has a significant impact on patient quality of life, with studies finding an association between PN and depression and anxiety.<sup>7,8</sup> The pruritus associated with PN is difficult to treat, and there is a significant unmet need for a safe and effective pruritus therapy.<sup>4,8,9</sup>

Opinion varies in the medical literature concerning several issues associated with PN, including whether PN is a separate disease entity or merely a sign of another underlying condition, the exact pathogenesis of PN and the optimal management strategy for patients.<sup>2,4–6,8,10</sup> The pathology associated with PN includes neurologic changes such as dermal nerve hypertrophy and proliferation, and marked increases in populations of calcitonin gene-related peptide (CGRP)- and substance P (SP)-immunoreactive nerves compared to individuals without PN. It is hypothesized that these neuropeptides may mediate the cutaneous neurogenic inflammation and pruritus in PN.<sup>5</sup> Although a variety of systemic and atopy-related conditions has been associated with PN, the aetiology is unknown in many cases,<sup>3,8</sup> often rendering it impossible to treat the underlying cause. In several cases, treatment of the underlying cause does not resolve PN, and symptomatic relief is needed for many patients.<sup>3,4</sup>

The European Academy of Dermatology and Venereology (EADV) recently established a Task Force Pruritus, with members from multiple European countries, to initiate projects of scientific or educational relevance.<sup>11,12</sup> The aims of this task force are to conduct projects and surveys related to symptom prevalence and patient care, to extend knowledge and to fill educational gaps in this area of patient treatment.<sup>12</sup> The first-year focus of the Task Force Pruritus included expanding the validation of pruritus tools (PruNet<sup>13</sup>) throughout Europe, updating the EADV/EDF (European Dermatology Forum) European Guideline on pruritus, achieving a consensus on the definition, diagnostic criteria and terminology of PN<sup>1</sup> and creating a pan-European registry for PN. Here, we present the results of a survey that was conducted to characterize perceptions of PN held by members of the EADV and Task Force Pruritus, to assess the current state of alignment among physicians regarding PN diagnosis and management and to improve the diagnosis and management of PN and PN-related pruritus.

## Methods

The survey was designed in collaboration with experts of the EADV Task Force Pruritus steering committee (M. Augustin, C.

Forner, F. Legat, M. Pereira, C. Riepe, S. Ständer, S. Steinke, J. Szepletowski, J. Wallengren, E. Weisshaar, C. Zeidler) and staff at Navigant Life Sciences (San Francisco, CA, USA). The survey was programmed and hosted online by Navigant Life Sciences and comprised 29 questions, including multiple choice and open responses (Table S1). It was sent via e-mail to select clinicians who were members of the EADV Task Force Pruritus and/or were associated colleagues of the Task Force members as of December 2016. The initial list of potential respondents was assembled by the Task Force steering committee. All survey results were collected and analysed by staff at Navigant Life Sciences.

## Results

### Respondents

Responses were received from 30 participants in 14 countries, of whom almost three quarters ( $n = 22$ , 73.3%) were members of EADV Task Force Pruritus. Most participants ( $n = 25$ , 83.3%) were from European countries (Austria, Finland, France, Germany, Italy, Norway, Poland, Portugal, Spain, Sweden, UK); the remaining five (16.7%) were from India, Russia and Turkey.

### Definition and terminology

Most respondents (73.3%) considered PN to be a distinct condition. When asked to select a concept to explain the most common pathogenesis, there was overwhelming support from all respondents (80.0%) for 'chronic pruritus leading to chronic scratching'. A total of 10.0% preferred 'subtype of atopic dermatitis', and 10.0% supported 'idiopathic chronic scratching'. There was no support for PN as a psychiatric disease or a subtype of perforating collagenosis.

When asked to describe PN in their own words, respondents commonly mentioned itchy/pruritic nodules ( $n = 23/30$ , 76.7%), scratching ( $n = 12/30$ , 40.0%), excoriation ( $n = 8/30$ , 26.7%), chronic pruritus ( $n = 6/30$ , 20.0%), atopic background ( $n = 5/30$ , 16.7%) and hyperpigmentation ( $n = 3/30$ , 10.0%). Four (13.3%) respondents indicated that PN nodules should have a standard definition, variously suggesting a minimum diameter of  $\geq 1$  cm,  $>1$  cm or  $>0.5$  cm for a PN nodule.

Descriptions of PN focused mainly on itch ( $n = 12/30$ , 40.0%) and scratch-related papules/nodules/lesions ( $n = 13/30$ , 43.3%). When respondents were asked to describe lichen simplex chronicus (LSC), another cutaneous condition associated with scratching,<sup>14</sup> the terminology that was used was somewhat different, with respondents mentioning lichenification ( $n = 13/30$ , 43.3%), plaques ( $n = 12/30$ , 40.0%), thickened skin ( $n = 6/30$ , 20.0%) and localization ( $n = 10/30$ , 33.3%), as well as itch ( $n = 11/30$ , 36.7%), hyperpigmentation ( $n = 4/30$ , 13.3%) and scratching ( $n = 15/30$ , 50.0%).

The respondents considered that, in current clinical practice and teaching, 'prurigo nodularis' (100.0%) and 'prurigo'

(73.3%) are the most regularly used diagnostic terms for PN. Overall, respondents indicated a marked preference for using either the general term 'prurigo' (30.0%), or terminology related to the clinical appearance of the disease (e.g. 'prurigo nodularis', 'papular prurigo' or 'plaque prurigo'; 40.0%). There was little support for terminology related to the comorbidity (e.g. 'atopic prurigo', 'diabetic prurigo'; 13.3%).

### Prevalence of PN

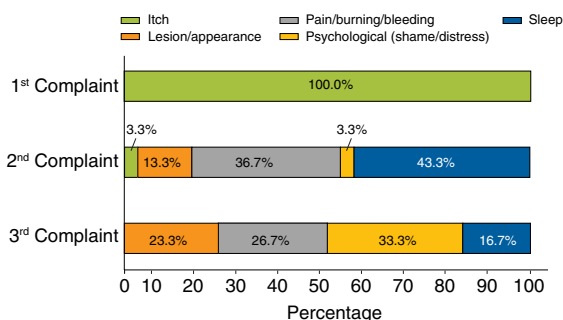
Most respondents (60.0%) reported seeing  $\leq 5$  unique PN patients per month; however, 30.0% of respondents saw  $>10$  unique PN patients per month.

### Patient demographics and disease burden

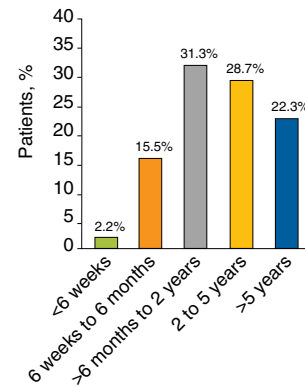
In line with the published finding that PN affects mostly older adults,<sup>6</sup> most of the respondents' PN patients were aged  $\geq 40$  years (78.6%); most were in the 40–60 years (38.4%) and 60–80 years (29.9%) age groups. Conversely, only 4.4% of patients were in the  $<20$  years age group.

Physicians estimated that they see the majority of their PN patients (68.8%) every 3–6 months, resulting in  $\sim 2$ –4 visits per year: 13.5% of PN patients visited their physician every month. When queried about their PN patients' three most common complaints, all respondents (100%) stated that itch is the number one symptom reported; followed by sleep disturbance (43.3%), pain/burning/bleeding (36.7%) and psychological distress/shame (33.3%) (Fig. 1).

Based on responding physicians' estimates, patients with PN reported experiencing pruritus of high severity, with a mean  $\pm$  SD score on a numeric rating scale of 0–10 (where 0 is no itch and 10 is the worst itch imaginable) of  $7.8 \pm 1.2$ . PN-associated pruritus was persistent, lasting for  $>6$  months in most patients (82.3%) and  $>2$  years in more than half (51.0%) (Fig. 2).



**Figure 1** Top three complaints reported by patients with prurigo nodularis to physicians ( $N = 30$ ).



**Figure 2** Duration of time patients with prurigo nodularis experienced pruritus ( $N = 30$ ).

### Diagnosis

Overall, the survey responses indicated that most patients with PN are diagnosed by clinical evaluation only (57.8%), while 40.4% are diagnosed by a combination of clinical and histological evaluation. Very few patients (1.8%) are diagnosed solely based on histology. According to the survey respondents, most PN patients present with  $\geq 20$  lesions (74.3%); almost one-third (29.2%) are affected in  $\geq 5$  areas (trunk and each extremity) at presentation, and nearly half (49.0%) have three or four affected areas.

Atopic predisposition (44.9%) and dry skin (31.6%) were cited by respondents as the most common dermatologic findings in patients with PN. Atopic dermatitis (AD) is the most common underlying atopic condition and is diagnosed as the only atopic condition in approximately half of PN patients with atopic predisposition (51.5%), whereas 25.5% of PN patients with atopic predisposition have a combination of AD plus asthma and/or allergic rhinitis.

### Treatment

When respondents were asked to indicate all systemic therapies they are using to treat PN, most respondents reported prescribing antihistamines (90.0%), antidepressants (90.0%), gabapentinoids (86.7%) and immunosuppressants (86.7%) (Fig. 3a). Despite unanimous agreement among respondents that antihistamines are generally ineffective for PN-associated pruritus, they were prescribed for the majority of their PN patients irrespective of symptom severity (73.0% for mild and moderate pruritus; 51.5% for severe pruritus) (Fig. 3b). The majority of respondents indicated that immunosuppressants and gabapentinoids are the most effective systemic treatments for PN (26.7% and 16.7%, respectively; Fig. 3a).

The most frequently used supportive therapy for PN-associated pruritus are emollients (93.3%), followed by

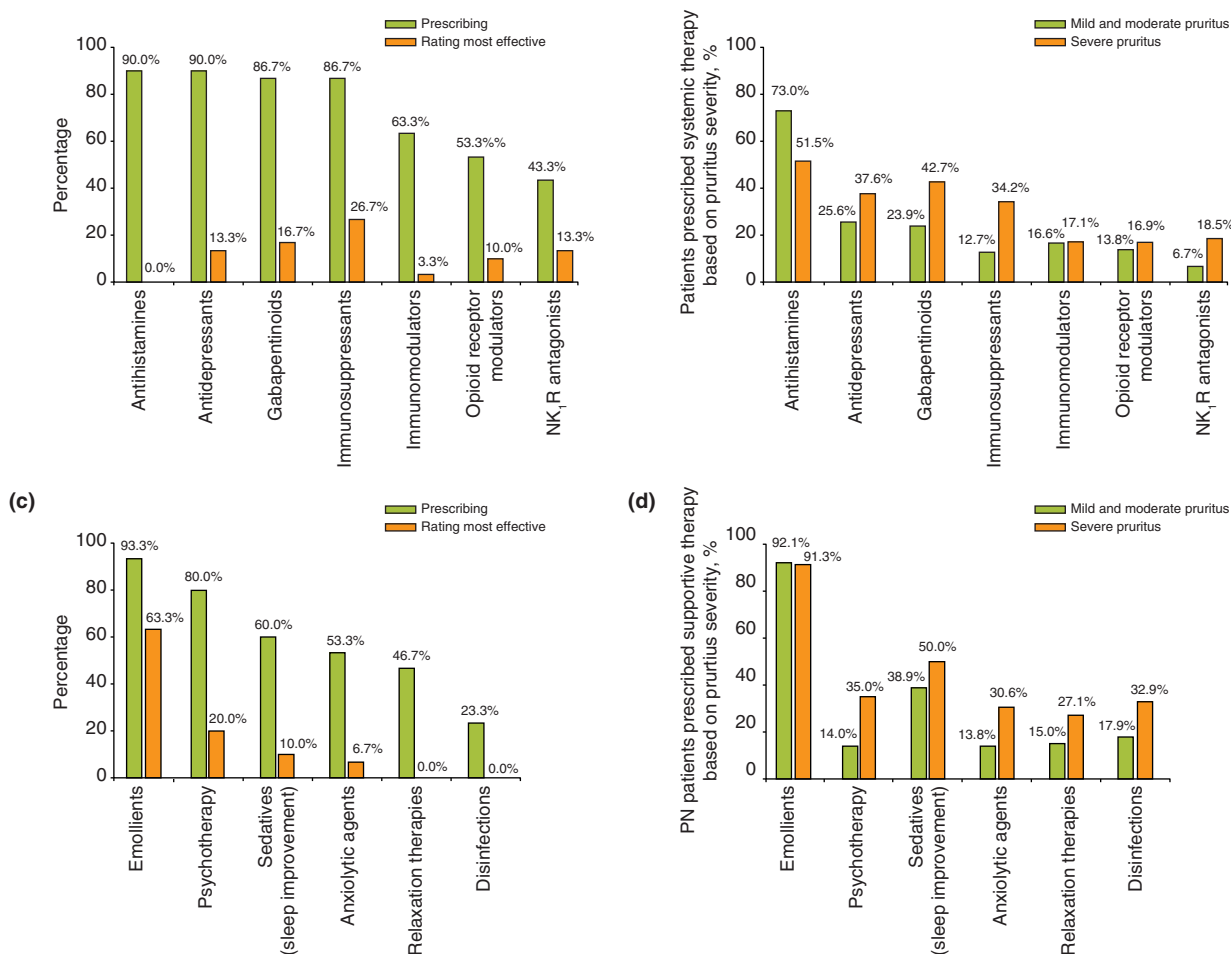
psychotherapy (80.0%) and sedatives (60.0%) (Fig. 3c). Emollients were almost universally used as supportive therapy for pruritus in patients with PN (92.1% of patients with mild or moderate pruritus and 91.3% of those with severe pruritus); sedatives to help improve sleep were the second choice (38.9% and 50.0%) (Fig. 3d). Respondents reported prescribing all other supportive therapies (e.g. psychotherapy, anxiolytic agents, relaxation therapies and disinfectants) at similar rates based on pruritus severity (i.e. 13.8–17.9% for mild/moderate pruritus and 27.1–35.0% for severe pruritus).

Most respondents indicated that the treatments that they prescribe for both PN overall (84.6%) and PN-associated pruritus (70.0%) in patients with atopic predisposition and dry skin as underlying conditions are similar to the treatments that they

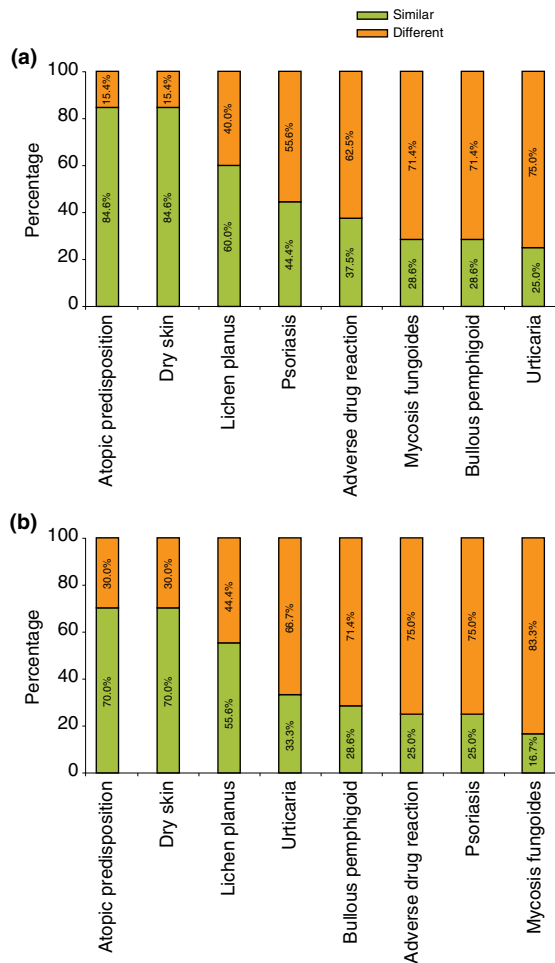
prescribe for patients who do not have one of the underlying conditions listed in the survey (Fig. 4a and b). For certain rarer underlying conditions in PN (e.g. bullous pemphigoid, mycosis fungoides), respondents may use specific treatments (Fig. 4a and b), if available.

### Unmet need

Respondents agreed that several key topics in PN need to be addressed, including a need for new therapies (56.7%), revised classification and terminology (23.3%) and better understanding of the pathophysiology of this condition (20.0%). Respondents commented that the first step towards addressing these unmet needs should be to clarify and unify the nomenclature, and once achieved, this should render the



**Figure 3** The most commonly used therapies for prurigo nodularis. (a) Systemic therapies: prescription frequency and efficacy rating. (b) Systemic therapies: use according to condition severity. (c) Supportive therapies: prescription and efficacy rating. (d) Supportive therapies: use according to condition severity.



**Figure 4** Physicians who reported treating patients similarly or differently, according to the underlying disease. (a) Treatment of prurigo nodularis. (b) Treatment of prurigo nodularis-associated pruritus.

development of consensus algorithms for diagnosis and management easier and enable the design of robust clinical trials to test therapeutic agents.

## Discussion

One of the aims of EADV Task Force Pruritus is to improve knowledge about PN,<sup>12</sup> and the aim of the present survey was to examine current perceptions of and experiences managing PN among EADV members. Although opinion varies in the medical literature regarding whether PN is a distinct condition – because it evolves from a subset of patients with chronic pruritus – or a sign of an underlying condition,<sup>5,6,8,10</sup> nearly three quarters (73.3%) of our survey respondents considered PN to be a distinct condition.

As expected, respondents agreed that there are several critical areas of uncertainty in PN that should be addressed, including terminology, pathophysiology and treatment. In particular, respondents indicated that the most urgent topics in PN are the need for consensus regarding the classification and terminology of the condition, and new therapies. New terminology would be welcome, as it would better enable physicians to construct diagnosis and treatment algorithms as well as aid in the development and testing of new therapeutic options. Recently, the EADV published an expert consensus document on the definition, classification and terminology of chronic prurigo.<sup>1</sup>

The results of this survey also support the established finding that PN confers a heavy burden on patients and that these patients likely require more frequent use of healthcare resources.<sup>2,15,16</sup> In this survey, the primary complaint among all respondents' patients was pruritus, which was also likely responsible for the second most common complaint, sleep disturbance. Sleep disturbance has been demonstrated to have serious consequences, including poor health, missed workdays and doctor visits owing to other skin conditions.<sup>17</sup> For many patients with PN, the most important symptom to treat is often pruritus because of its impact on quality of life;<sup>16,18–23</sup> however, pruritus is difficult to treat.<sup>4,8,9</sup>

Treatment for PN is commonly standardized, and the goal of therapy is often to manage pruritus. Most of the respondents' patients with PN are prescribed systemic treatments and supportive therapy. In most cases, the therapies used to treat PN are relatively ineffective,<sup>8,24</sup> as evidenced in this study by the far higher rates of therapy prescription compared with the respective rates of effectiveness. An exception would be emollients, which are prescribed in the vast majority of cases and were found to be most effective as supportive agents. Despite the consensus among the respondents that antihistamines are not particularly effective for PN, they remain commonly prescribed. In line with what is reported in the literature,<sup>8,25,26</sup> respondents rated immunosuppressants and gabapentinoids as the most effective systemic treatments for pruritus in PN. However, the evidence base for many of the prescribed treatments is not from randomized controlled trials.<sup>8</sup> The success of agents such as gabapentin and pregabalin may be attributable to the potentially neuropathic basis of PN-associated itch.<sup>2,25–29</sup> Of particular note is the use of antidepressants.<sup>30</sup>

PN is a chronic skin condition with a significant impact on patient quality of life;<sup>19</sup> however, there are currently no approved therapies. Treatments that are used for patients with PN often have inadequate efficacy, and some are associated with side-effects that may limit their use.<sup>4,8</sup> Thus, there is a significant unmet need for effective treatment options for patients with PN.

## Conclusion

The results of this clinician survey largely concur with what is known about PN and PN-associated pruritus and its treatment:

prurigo nodularis is a distressing chronic condition of often unknown aetiology and ambiguous pathogenesis that impacts patient mental health and quality of life, and for which there is a dearth of epidemiologic data, no currently approved treatment and little clinical trial evidence. The findings emphasize the need for a clear consensus on the definition and terminology for PN, and for well-powered, randomized controlled trials to establish the best treatment for PN and PN-associated pruritus, as well as specific therapies for PN or the associated pruritus of PN. EADV Task Force Pruritus has identified several challenges that must be met to improve the symptoms and quality of life of patients with PN.

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### Supporting information

Additional Supporting Information may be found online in the Supporting Information section at the end of the article:

**Table S1.** Survey Questions for the EADV and Task Force Pruritus.