

# Clinical Characteristics and Treatment Outcomes of Prurigo Nodularis: A Retrospective Study

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## Abstract

**Background:** Prurigo nodularis (PN) is a complex chronic skin disease characterized by severe pruritic nodules. PN is often associated with mental health disorders and chronic medical comorbidities. Until recently, PN treatment has been challenging and difficult.

**Objectives:** This study aims to describe the demographic, clinical characteristics, and comorbidities associated with PN. Also, we aim to describe the effectiveness of systemic therapies, including methotrexate, cyclosporine, and narrow band ultraviolet (NB-UVB) in adult patients with PN.

**Methods:** This is a retrospective chart review of adult patients diagnosed with PN at Hamilton Health Science Center and/or McMaster University in Hamilton, Ontario, between 2015 and 2023.

**Results:** The study included 81 patients (57% female). The mean age was 52.8 years, and the mean age of PN diagnosis was 50 years. Reported symptoms included: itching (100%), dry skin (53%), pain (17%), and burning sensation (5%). Lower and upper extremities were the most common areas involved in 93% and 69%, respectively. Mental health disorders were present in 79% of patients, with depression (58%) and anxiety (52%) being the most common. Atopic dermatitis was the most common skin comorbidity noted. Treatments used included cyclosporine, and NB-UVB, and MTX, which resulted in significant improvement of pruritus in 38%, 35%, and 31% of patients, respectively, at week 16.

**Conclusions:** PN is associated with increased risk of mental health disorders and other medical comorbidities. Cyclosporine, methotrexate, and NB-UVB therapy may be effective treatment options, however clinicians must consider the potential short- and long-term adverse effects of these treatments.

## Keywords

prurigo nodularis, pruritus, comorbidities, psychiatric disorders

## Introduction

Prurigo nodularis (PN) is a chronic inflammatory skin disease characterized by hyperkeratotic dome-shaped extremely pruritic papules and nodules that vary from a few millimeters to centimeters in size.<sup>1</sup> The nodules are typically skin coloured, pigmented peripherally, excoriated centrally, and often found symmetrically on the extensor surface of the extremities and upper back.<sup>2</sup> While the exact etiology of PN is unknown, recent research suggests that PN is related to immune dysregulation and neural sensitization in skin.<sup>3</sup> Until recently, there was no valid severity score or classification for PN where itching intensity and physician's judgment were used to assess its severity.

PN is commonly associated with other chronic comorbidities such as atopic dermatitis (AD), type 2 diabetes mellitus (T2DM), hypertension (HTN), chronic kidney disease (CKD), chronic liver disease (CLD), and thyroid disease.<sup>4,5</sup>

PN is also strongly associated with numerous mental health disorders and poses significant physical and psychological harm resulting in poor quality of life (QoL).<sup>6</sup> A study by Whang et al<sup>4</sup> estimated the individual lifetime economic burden of PN to amount to USD \$323,292, and the societal burden to be \$38.8 billion based on data from the 2002-2003 Joint Canada/United States Survey of Health. Therefore, a safe and effective treatment for PN is of utmost importance.

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Treatment of PN is indeed complex and has shown varying success.<sup>7</sup> A wide range of treatments are available, including topical corticosteroids, topical calcineurin inhibitors, systemic therapies such as antidepressants, gabapentinoids, antihistamines, opioid receptor antagonists (naloxone and naltrexone), methotrexate (MTX), cyclosporine, narrow band UV (NB-UVB) therapy, and other forms of phototherapy.<sup>8</sup> However, many of these treatments are based on anecdotal or small retrospective studies. Recently, there have been promising developments with the approval of dupilumab for adult PN patients in Canada and the United States, and the positive results of nemolizumab in phase 3 clinical trials.

To our best of knowledge, this is the first and largest retrospective study to evaluate the demographics, clinical characteristics, and treatment outcomes of patients with PN in a Canadian population. The aim of this study is to describe the demographic, clinical characteristics, and comorbidities of patients with PN in Southwestern Ontario, Canada. Also, we aim to describe the effectiveness of NB-UVB and conventional systemic therapies including MTX and cyclosporine.

## Patients and Methods

The study was approved by the Hamilton Research Ethics Board (16274). A retrospective chart review was conducted for adult patients diagnosed with PN. Data was collected from the Dermatology Clinics at Hamilton Health Science Center and/or McMaster University in Hamilton, Ontario, spanning the period from January 2015 to June 2023. Electronic medical records were searched using the terms “prurigo nodularis” or “nodular prurigo.” Inclusion criteria for eligible participants required them to be adults (aged 18 years and above) and have a clinical diagnosis of PN. Potential subjects were excluded if they had a questionable diagnosis or if the necessary data required for the study was not available.

Demographic data including sex, current age, age at PN diagnosis was collected. Data on symptoms (presence of itching, pain, xerosis, burning sensation), location of lesions, presence of comorbid diseases T2DM, thyroid disease, HTN, CKD, CLD, human immunodeficiency virus (HIV), hepatitis B or C, mental health conditions (anxiety, depression, bipolar disorder, personality trait disorder, other mental health conditions), and malignancy was extracted. Additionally, data on type of treatment and outcomes was collected. Calculations were performed to derive mean, standard deviation (SD), and range values for each metric item. In the case of categorical data, frequencies and percentages were determined. When available, the severity of the disease was assessed by the intensity of pruritus measured by a simple mono-dimensional scale that is routinely used in clinical care. Patients were asked to rate their peak itching from 0 (no itch) to 10 (worst imaginable itch) with the numerical rating

scale. Scores 0 to 3 is considered mild, scores 4 to 6 is considered moderate, and 7 to 10 considered severe.

## Results

Supplementary Table S1 summarizes demographic and clinical characteristics of patients. The study included 81 patients, 46 (57%) of which were female. The mean age of the study population was 52.8 years (range: 30–77 years, SD: 11.2 years). The mean age of male and female patients was 54.2 and 51.8 years, respectively. The mean age of patients at the time of PN diagnosis was 50 years (SD: 10.8). The mean age at time of PN diagnosis specifically for males and females was 51.6 and 48.8 years, respectively. All patients (100%) experienced itching, 43 (53%) experienced dry skin and xerosis, 14 (17%) experienced pain, and 4 patients (5%) experienced burning sensation. When available, all patients described their itching at baseline as severe (ranging from 8–10 out of 10). The most common areas involved were lower extremities (93%), upper extremities (69%), upper back (33%), lower abdomen (22%), lower back (17%), and face (5%). No data was available on the exact count of the lesions.

Skin biopsy was available for 26 patients (32%). Skin biopsies were completed for all patients aged 65 and above ( $n=8$ ) at onset of diagnosis to confirm the PN diagnosis and to rule out pemphigoid nodularis (PN-like bullous pemphigoid). Supplementary Table S2 summarizes histopathological findings.

AD was the most common skin comorbidity noted in this population (22%). Other skin comorbidities included psoriasis (5%), lichen planus (4%), pityriasis lichenoides chronica (1%), and vitiligo (1%).

Supplementary Table S3 summarizes the mental and physical health comorbidities of patients. Mental health disorders were present in 64 patients (79%). Depression was the most common mental health disorder in 47 (58%) patients. Other mental health disorders were anxiety (52%), substance use disorder (14%), personality trait disorder (7%), bipolar disorder (5%), post-traumatic stress disorder (5%), childhood or adult onset attention-deficit and hyperactivity disorder (ADHD) in 4 (5%) of patients, eating disorder (2%), and schizophrenia (1%).

Other comorbid medical conditions were: HTN (35%), T2DM (12%), thyroid disease (9%), CKD (11%), CLD (4%), fibromyalgia (10%), rheumatoid or other inflammatory arthritis (11%), irritable bowel syndrome (IBS) (11%), coronary artery disease (2%), osteoporosis (6%), hepatitis C (1%), and HIV (1%). Malignancy, including non-melanoma skin cancer, was seen in 27% of patients.

Out of 81 patients, 69 (85%) received NB-UVB (thrice weekly), 26 (32%) received MTX (15–25 mg weekly), and 16 (20%) received cyclosporine (2.5–5 mg/kg/day). All patients received potent topical corticosteroids. Among those treated with NB-UVB, MTX, and cyclosporine, 35%, 31%,

and 38% respectively showed significant improvement at week 16, defined as a numerical rating scale 0 to 3 or no/mild itching. However, there was insufficient data available on the long-term outcome or effects of these treatments.

## Discussion

To the best of our knowledge this is the first report on patients with PN in Canada with a comprehensive description of the demographic, clinical characteristics, and outcomes of different treatments used for PN.

The demographic data of our patient cohort aligns with existing literature, revealing a higher prevalence of PN among females, with a peak occurrence between ages 50 and 59 years. In our study, the mean age was approximately 54 for males and 52 for females. In a retrospective study of 37 PN patients, the mean age of PN patients was 45 with average of 51 for men and a lower mean of 39 for women.<sup>9</sup> PN is found to be more common, intense, and occur at an earlier age of onset in females, and the overall peak prevalence is at 50 to 59 years of age.<sup>5</sup> Our study was also consistent with existing literature confirming that itching is the most common symptom. Additionally, our results are in keeping with literature with lower and upper extremities, and the upper back being the most common areas affected by PN. In our study, lower extremities, upper extremities, and back were affected in 93%, 69%, and 50% of cases, respectively. Similarly, a study by Tey and Tan<sup>9</sup> found lower extremity, upper extremity, and back involvement in 97%, 62%, and 50% of patients, respectively. While exact lesion counts are not available in our study, previous reports showed that female patients displayed more lesions and experienced greater detriments to their QoL compared to male patients.<sup>6</sup>

In our study, PN was associated with mental health disorders in over half of the patients, with depression and anxiety being the most prevalent. In a large retrospective cohort study of 288 patients with PN, Han et al<sup>6</sup> found at least 1 psychiatric comorbidity in approximately 44% of patients, with mood (74.8%) and anxiety (63%) having the highest prevalence. Jørgensen et al<sup>10</sup> also found significant correlations between PN, and depression and anxiety.<sup>10</sup> Personality disorders, schizophrenia, substance use, and ADHD were also other mental disorders reported in our patients. There is less data regarding the relationship between PN and other psychiatric disorders; however, one study showed that the risk of self-harm, ADHD, eating disorders, and schizophrenia are higher among PN patients.<sup>11</sup> Other studies have shown that PN patients are significantly more likely to have a psychiatric disorder compared to age-matched controls.<sup>10</sup> While it is not possible to determine causation from this study, there may be a bidirectional relationship where PN contributes to poor mental health and vice versa. A relationship has been previously established between emotional dysregulation and PN type of dermatoses, where psychological distress has resulted in increased release of inflammatory cytokines resulting in

worse pruritus and scratching, poor wound healing, and subsequently exacerbation of mental health disorders.<sup>12</sup> To illustrate, a correlation has been observed between severity of depression and higher intensity of pruritus.<sup>6</sup> Additionally, PN patients with neuropsychiatric associations often have a more prolonged disease course, characterized by frequent recurrences and diminished treatment responses.<sup>12</sup> Importantly, PN patients are more likely to be diagnosed with depression than those with other chronic pruritic conditions.<sup>6</sup> Further research is warranted to investigate this relationship and how both psychiatric and psychological treatment, in addition to pharmacological interventions targeting skin inflammation, may improve outcomes. Overall, addressing the psychological aspects associated with PN is critical to improving care and long-term outcomes for patients with PN.

PN was associated with several other inflammatory skin conditions, most frequently AD, which was present in 22% of our cohort. Similarities among AD and PN include intensely pruritic lesions, cutaneous type 2 inflammatory response as well as the common occurrence of itch-scratch cycle. A study by Tanaka et al indicates that 50% of PN patients exhibit an atopic predisposition.<sup>13</sup> Furthermore, in a study of 31 PN patients, 65% also had AD.<sup>13</sup> In both PN and AD, there is dysregulated Th2-based immune response, as seen through the overexpression of multiple type 2 cytokines, such as IL-4, IL-13, and IL-31 in the skin and peripheral blood. Furthermore, dupilumab, a monoclonal antibody that binds interleukin 4 receptor  $\alpha$  (IL-4R $\alpha$ ) and inhibits signaling of both IL-4 and IL-13, has shown excellent results and is currently approved for both AD and PN.<sup>14</sup>

Our findings indicate numerous comorbidities are associated with PN including HTN, T2DM, thyroid disease, CKD, CLD, fibromyalgia, IBS, HIV, and hepatitis C. Importantly, it has been shown that the systemic comorbidities associated with PN add burden to patients with PN.<sup>11</sup> Kim et al<sup>15</sup> found that patients receiving dialysis have higher incidence of PN, suggesting patients with CKD may have a higher risk of developing PN. A nationwide cohort study in Korea showed that CKD, as measured by estimated glomerular filtration rate and proteinuria, increases the risk for PN.<sup>15</sup> Therefore, preservation of renal function may be an important factor in reducing PN incidence in patients with kidney diseases.<sup>15</sup> PN has been also associated with HIV, with a study from United States indicating 2.68 higher odds of HIV infection in PN patients.<sup>11</sup> Interestingly, only 1 patient had concomitant HIV in our study. This discrepancy may be due to small sample size and/or the characteristics of an Ontario patient population, but further research is needed to explore HIV in PN patients in Canada.

Recently dupilumab has been approved for the treatment of PN.<sup>14</sup> Prior to this approval, treating PN posed a challenge for clinicians, given the limited availability of randomized controlled trials outlining therapy options. Our study evaluated NB-UVB, MTX, and cyclosporine for treatment of patients with PN. MTX has previously been shown to be an effective

monotherapy for PN in case series and retrospective studies. This is in accordance with our results showing MTX improved PN symptoms in 8 of 26 patients (31%). A study by Klejtman et al<sup>16</sup> showed that 91% of 39 patients with PN who received MTX up to 25 mg weekly, experienced improvements in their lesions, and 89% of the patients experienced decreased pruritus. Furthermore, in a retrospective review, 10 of 13 treatment-resistant PN patients were treated with 7.5 to 20 mg of MTX weekly for 6 months, had a  $\geq 75\%$  decrease in PN lesions count and reduced pruritus.<sup>17</sup> However, long-term data on efficacy and safety of MTX for PN is not available. Furthermore, MTX can be associated with adverse effects like nausea, fatigue, cytopenia, hepatotoxicity, and rare cases of pneumonitis.<sup>14</sup>

Cyclosporine may be another effective treatment for PN, as 38% of our patients exhibited significant improvement in itching after 16 weeks of treatment with cyclosporine. In a clinical trial evaluating 14 patients with PN who received oral cyclosporine at a dose of 2 to 5 mg/kg/day, 93% of the patients demonstrated significantly improved pruritus symptoms.<sup>18</sup> Currently, cyclosporine is commonly used as first-line systemic treatment for severe, chronic, and refractory PN in the absence of contraindications.<sup>14</sup> This is in accordance with our results showing cyclosporine had slightly higher treatment success compared to MTX and NB-UVB therapy. However, it is important to note that prolonged use of cyclosporine is not recommended due to potential adverse effects particularly nephrotoxicity, HTN, immunosuppression, and increased risk of malignancy.<sup>14</sup>

Our study also showed that NB-UVB therapy can be used for treatment of PN. Arrieta et al<sup>12</sup> found that phototherapy, including UVB and PUVA modalities, is a suitable monotherapy or combination treatment in a considerable proportion of PN patients. An observational study of 44 patients treated with phototherapy, most commonly NB-UVB, found that treatment resulted in at least a 75% reduction in lesions and symptoms in over half of the patients.<sup>12</sup> UV therapy exhibits excellent anti-inflammatory properties on the skin and induces immunosuppression with UV-induced regulatory T-cells playing a significant role in this process. Additionally, expression of key cytokines, particularly IL-4 and IL-13, was found to be significantly reduced after treatment with various forms of phototherapy.<sup>19</sup> While emerging therapies may offer greater superiority in treating PN, NB-UVB remains a valid treatment option primarily due to its established high safety profile especially for patients with PN and complex medical comorbidities.<sup>12</sup>

Overall, our study provides comprehensive analysis of demographic, clinical characteristics, and treatment outcomes for patients with PN in a Canadian population. Limitations include the retrospective study design, and the relatively small sample size.

In conclusion, PN is a complex, chronic, and severely pruritic skin disease, which poses substantial impact on patient QoL. PN is associated with mental health disorders and other comorbidities such as AD, HTN, and T2DM. Cyclosporine, MTX, and NB-UVB therapy may improve itching and other

symptoms in PN patients. However, considering their potential long-term adverse effects and the emergence of more effective agents like dupilumab and nemolizumab, these treatments may become less favourable options in the future. Our findings will help guide clinicians with managing PN in real life practice.

### Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: DT and IS declare no conflicts of interest. MA received honoraria, served as a speaker and/or advisor for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Galderma, Janssen, Leo, Lilly, L'Oreal, Medexus, Novartis, Pfizer, Sanofi, Sun Pharma.

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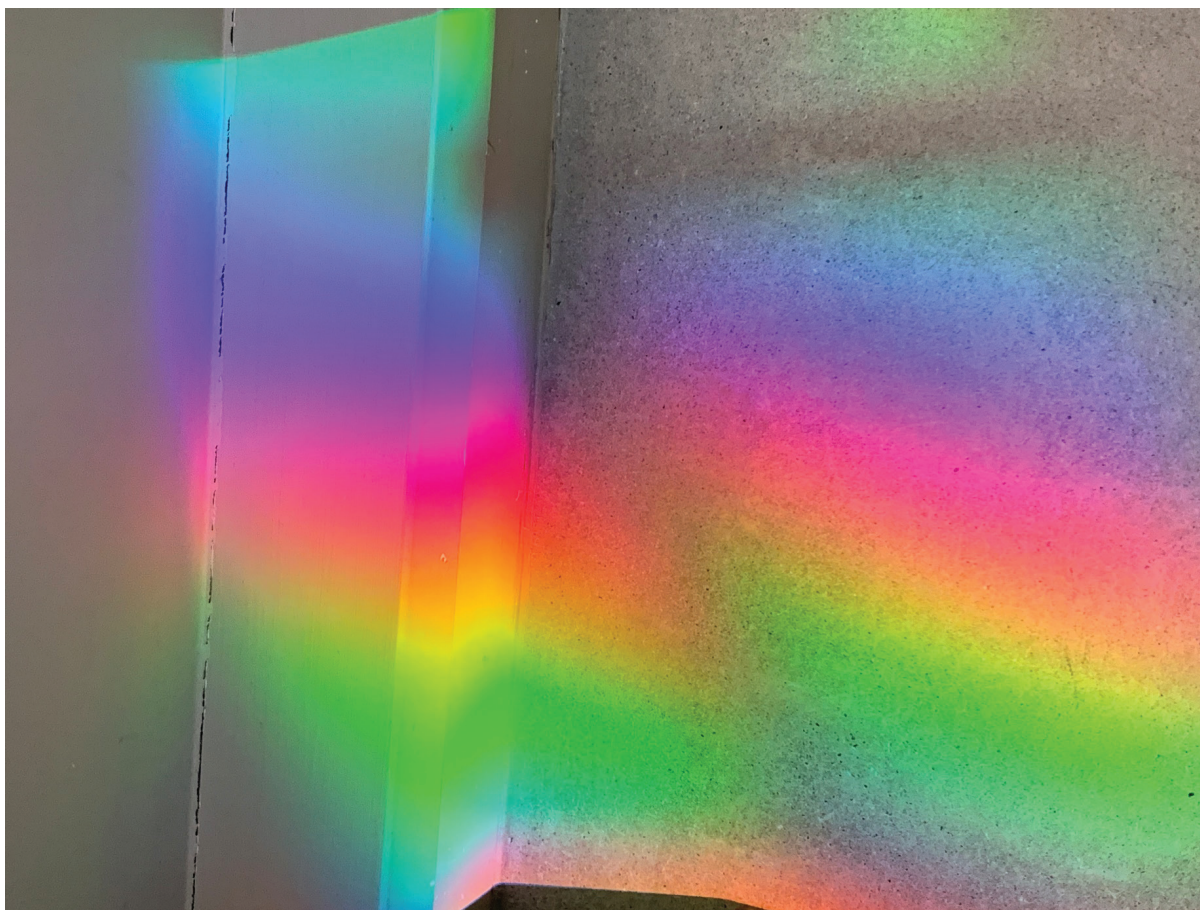
### Supplemental Material

Supplemental material for this article is available online.

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The End of the Rainbow

Photo by Ronald Vender