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*Letter to Editor*

# Therapeutic unresponsiveness of gabapentin and hydroxyzine combination in moderate-severe chronic prurigo nodularis of Hyde

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Dear Editor,

Prurigo nodularis of Hyde (PNH) is a type of neurodermatitis characterized by an intensely itchy, chronic, idiopathic skin condition that usually manifests as multiple, excoriated, dome-shaped, hyperkeratotic papules and nodules with hyperpigmented borders, typically located on the extensor surfaces of the extremities in a symmetrical distribution.[1] PNH is otherwise known as chronic nodular prurigo (CNPG), which is defined by the European Academy of Dermatology and Venereology's European Prurigo project.[2] It is mostly diagnosed as a clinical entity in routine practice; however, dermoscopy and histopathology aid in the diagnosis.

Although multiple modalities of treatments are available, control of the itch in these cases is a challenge to dermatologists. The addition of gabapentin to first-generation sedative antihistaminics has been reported to be an effective treatment option in cases of CNPG. Patients in our case series had already been treated with various therapeutic modalities without significant improvement. Therefore, in view of the chronicity and recalcitrant nature of CNPG, we considered combining two different groups of drugs, such as hydroxyzine and gabapentin, for rapid relief from the itch-scratch cycle. We included 6 males and 4 females, clinically diagnosed patients with chronic moderate-to-severe CNPG (without any underlying atopy or any systemic conditions such as chronic kidney disease and chronic liver disease); the mean age was 42 ± 6 years, and the duration ranged from 8 months to 2 years. The clinical diagnosis was corroborated by dermoscopy to rule out other differential diagnoses such as lichen planus hypertrophicus and perforating disorders, and histopathology was not considered as all the patients had already previously been treated with many medications. However, none had received oral or topical corticosteroids or any other immunosuppressant drugs for a minimum of 2 weeks before the baseline visit. The patients were recruited after written consent for a prospective interventional single-arm study and all were prescribed oral hydroxyzine (25 mg) and gabapentin (300 mg) combination along with urea-based emollient. The doses of gabapentin were upgraded every 4 weeks up to the maximum permissible dose (maximum dose of 1200 mg) as per the patient's requirement and safety profile. However, the dose of hydroxyzine remained constant (a single dose of 25 mg). The response was evaluated at the end of 4 weeks, 8 weeks, and 12 weeks in terms of both subjective parameters, such as the Visual Analog Scale, Pittsburgh Sleep Quality Index (PSQI), and objective parameters, such as 12-item Pruritus Severity Scale (12-PSS), Dermatology Life Quality Index (DLQI), Investigator Global Assessment (IGA) of CNPG which showed minimal response in controlling the itch and lesional improvement as is depicted in Table 1. Further, all patients had sleep disturbance, having PSQI >5. During up dosing of gabapentin, only transient dizziness was noticed as an adverse effect in 3 (30%) cases that resolved on further continuation of the drug. Although in their suggested therapeutic ladder, Ständer *et al.*[3] include both the drugs as first-line and third-line systemic modalities for the management of PNH, in our limited patient experience of 10 patients, we did not see significant results among the cases treated with gabapentin and hydroxyzine combination even when given for 12 weeks at the maximum permissible dose (percentage improvement 2.01–8.57% [Figures 1 and 2]). CNPG is an inflammatory reaction to repeated scratching due to multiple dermatological, systemic, infectious, and psychiatric issues.[4] The itch-scratch cycle strictly correlates to the persistence and the progression of skin lesions presenting predominantly over the accessible sites. It may lead to significant physical and psychological morbidity and is often refractory to conventional treatments.[5]

Ständer *et al.*[3] suggested a therapeutic ladder for the management of CNPG, which is depicted in Box 1.

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**Table 1:** Comparison of the parameters at baseline and follow-up visits.

| Parameters | Baseline | 4 weeks | 8 weeks | 12 weeks | Percentage Improvement (at the end of 12 weeks) (%) |
|---|---|---|---|---|---|
| VAS | 0.72–0.96 | 0.70–0.87 | 0.63–0.79 | 0.78–0.92 | 2.12 |
| 12-PSS | 12–19 | 13–17 | 9–14 | 11–16 | 8.57 |
| DLQI | 15–18 | 14–17 | 10–13 | 14–19 | 5.26 |
| IGA-CNPG | 52–73 | 48–64 | 42–59 | 54–76 | 2.01 |

VAS: Visual analog scale, 12-PSS: 12-Pruritus severity scale, DLQI: Dermatological life quality index, IGA-CNPG: Investigator global assessment of chronic nodular prurigo, PSQI: Pittsburgh sleep quality index, wks: Weeks

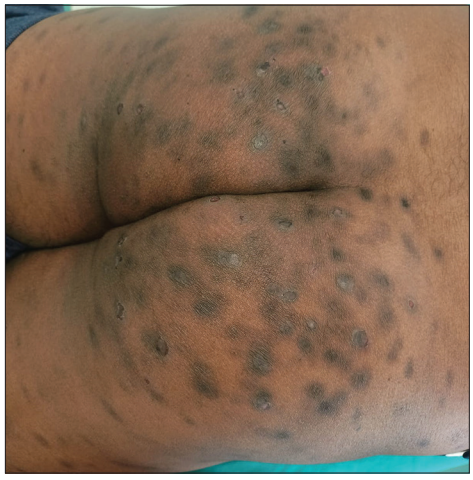

**Figure 1:** Multiple prurigo nodularis lesions over buttock before treatment.

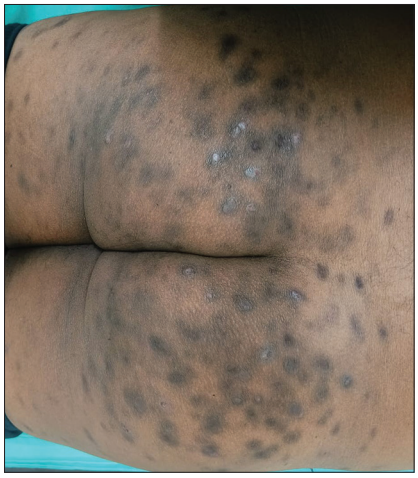

**Figure 2:** No remarkable change after 12 weeks of therapy with hydroxyzine and gabapentin combination therapy.

Gabapentin is known to increase the threshold of nociception, which plays an important role in controlling pruritus. Its primary mechanism may also be due to an increase in the concentration of the excitatory neurotransmitter gamma-aminobutyric acid (GABA), as in pain syndromes. Gabapentin blocks the calcium channels located in the spinal cord and inhibits the release of GABA as well as increasing the synthesis of GABA by altering the activity of glutamic acid decarboxylase.[6] Itch follows similar neural pathways to pain from the skin to the sensory cortex, therefore suggesting the use of gabapentin for CNPG. Dereli *et al*. reported a patient with PN treated successfully with gabapentin.[7] Randomized controlled trials (RCTs) have shown that gabapentinoids can successfully treat both neuropathic pain and chronic pruritus of different origins.[8] The successful use of gabapentinoids in nodular prurigo has previously been reported only in case series.[9] However, it is recommended as a treatment option.

Antihistamines are utilized in CNPG therapy given an increased number of mast cells detected in CNPG lesions.[10] First-generation antihistaminics are also known to act on a psychocutaneous axis that may play a role in arresting pruritus. However, the role of antihistaminics alone in nodular prurigo is also debatable. The addition of the above two separate groups of drugs having different mechanisms of action in CNPG may increase the effectiveness of individual drugs over the disease. Remarkably, in our study, this combination showed limited efficacy, which is under-reported in the literature. The cause of treatment failure may be hypothesized to be due to the different pathomechanisms related to the disease process. As both the neural and immunologic components of pruritus are involved in the causation of PN, the action of gabapentin may rely on arresting the neuronal component of itch, but the immunological inflammation may be overactive that further requires other immunosuppressives such as methotrexate, cyclosporine, tofacitinib, or the newer approved biologics such as dupilumab. Treatment goals are to reduce pruritus, interrupt the itch-scratch cycle, and completely heal CNPG lesions. Most of the treatments used are off-label, with high variability in treatment selection and a lack of consensus on dosing regimens. Dupilimab was the first biologic that was approved by the US Food and Drug Administration on September 28, 2022, for CNPG.[11]

CNPG is a chronic condition, typically preceded by an underlying cause of pruritus. The treatment of CNPG is a challenge to the clinician due to the lack of sufficient RCTs.

| **Box 1:** Therapeutic ladder for chronic prurigo nodularis. |
|---|
| First line – Topical corticosteroids, topical calcineurin inhibitors, H1 antihistamines<br>Second line – Topical capsaicin, intralesional corticosteroid, UV phototherapy<br>Third line – Gabapentin, pregabalin, antidepressant, cyclosporine, methotrexate<br>Fourth line – Neurokinin-1 receptor antagonist, μ opioid receptor antagonist, thalidomide, dupilumab, nemolizumab |
| UV: Ultraviolet |

The combination therapy of drugs such as gabapentin and hydroxyzine also has limited therapeutic effects. Further trials, including larger study samples, may be conducted for evaluation of better treatment outcomes in this field.

### Limitations

The sample size was small. No objective scoring was done for assessment and histopathological study was not performed.

### Ethical approval

Institutional Review Board approval is not required.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

## REFERENCES

1. Zeidler C, Tsianakas A, Pereira M, Ständer H, Yosipovitch G, Ständer S. Chronic prurigo of nodular type: A review. Acta Derm Venereol 2018;98:173-9.
2. Pereira MP, Steinke S, Zeidler C, Forner C, Riepe C, Augustin M, *et al*. European academy of dermatology and venereology European prurigo project: Expert consensus on the definition, classification and terminology of chronic prurigo. J Eur Acad Dermatol Venereol 2018;32:1059-65.
3. Ständer HF, Elmariah S, Zeidler C, Spellman M, Ständer S. Diagnostic and treatment algorithm for chronic nodular prurigo. J Am Acad Dermatol 2020;82:460-8.
4. Iking A, Grundmann S, Chatzigeorgakidis E, Phan NQ, Klein D, Ständer S. Prurigo as a symptom of atopic and non-atopic diseases: Aetiological survey in a consecutive cohort of 108 patients. J Eur Acad Dermatol Venereol 2013;27:550-7.
5. Harbaoui S, Litaiem N. Acquired perforating dermatosis. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2023.
6. Gencoglan G, Inanir I, Gunduz K. Therapeutic hotline: Treatment of prurigo nodularis and lichen simplex chronicus with gabapentin. Dermatol Ther 2010;23:194-8.
7. Dereli T, Karaca N, I ̇nanır I, Öztürk G. Gabapentin for the treatment of recalcitrant chronic prurigo. Eur J Dermatol 2008;18:85-6.
8. Matsuda KM, Sharma D, Schonfeld AR, Kwatra SG. Gabapentin and pregabalin for the treatment of chronic pruritus. J Am Acad Dermatol 2016;75:619-25.e6.
9. Fostini AC, Girolomoni G, Tessari G. Prurigo nodularis: An update on etiopathogenesis and therapy. J Dermatolog Treat 2013;24:458-62.
10. Kowalski EH, Kneiber D, Valdebran M, Patel U, Amber KT. Treatment-resistant prurigo nodularis: Challenges and solutions. Clin Cosmet Investig Dermatol 2019;12:163-72.
11. Müller S, Zeidler C, Ständer S. Chronic prurigo including prurigo nodularis: New insights and treatments. Am J Clin Dermatol 2024;25:15-33.

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