

## Nocturnal Pruritus: Prevalence, Characteristics, and Impact on ItchyQoL in a Chronic Itch Population

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Chronic pruritus is a distressing condition with a lifetime prevalence of 25.5% (1). Itch is often reported to be especially bothersome during the evening and at night. Nocturnal pruritus (NP) is a reported feature of both dermatologic and systemic conditions and can interfere with the initiation and maintenance of sleep, resulting in deleterious effects on health, functionality, and emotional wellbeing (2, 3). In adults with atopic dermatitis (AD), sleep deficits attributable to NP have been shown to profoundly affect quality of life (QoL), functional ability, and cognition (4). In patients with psoriasis, NP has been implicated as a cause of decreased work productivity (5). Furthermore, in hemodialysis patients, pruritus and related sleep disturbances have been associated with a 17% increased mortality risk (6). However, specific, in-depth studies of NP are lacking. We used validated questionnaires to determine the prevalence, characteristics, severity, and impact on QoL of NP in the chronic itch patient population (7, 8).

### MATERIAL AND METHODS

This study was conducted from April 2015 to March 2016 in the outpatient clinic at Temple Itch Center. All English-speaking individuals between the ages of 10 and 100 with a diagnosis of chronic pruritus were eligible to participate. Chronic pruritus was defined as itch present for  $\geq 6$  weeks (9). Subjects with dementia were excluded from participation. This study was approved by the Temple University Institutional Review Board, and signed informed consent was obtained from each participant.

A total of 160 subjects with a mean  $\pm$  SD age of  $57 \pm 16$  were included in the study. Ninety-seven (60.6%) participants were female, and 63 (39.4%) were male. Subjects were identified as Caucasian (65.6%), African American (23.1%), Hispanic/Latino (5.6%), Asian (1.9%), and other (3.8%).

All participants were asked to complete two validated questionnaires: the itch questionnaire (7) and the itch quality of life survey (ItchyQoL) (8). The itch questionnaire assessed the severity of itch and several associated characteristics, including the presence and severity of NP and the degree of sleep disturbance. Overall itch severity was quantified using an 11-point numeric rating scale (NRS) anchored at 0, representing “no itching,” and 10, representing “worst itch imaginable.” Itch characteristics, including itch severity at different times of day, were measured on a scale anchored at 0 (not at all), 1 (to a minimal extent), 2 (to a mild extent), 3 (to a moderate extent), and 4 (to a great extent).

The ItchyQoL questionnaire contained 21 pruritus-specific items divided into 3 major subscales: Symptoms, Functioning (functional limitations), and Emotions (8). Participants were asked to rate each item on a scale anchored at 1 (never), 2 (rarely), 3 (sometimes), 4

(often), and 5 (all the time). Analysis of the ItchyQoL consisted of individual item scores, subscale scores, and an overall score. Higher scores indicated a lower QoL.

Each participant was examined and diagnosed by an attending physician in the dermatology department. Data pertaining to comorbid conditions were extracted from patient medical records.

### Statistics

All statistical analyses were performed using PASW 18.0 software (SAS, Chicago, IL, USA) with statistical significance set at  $p < 0.05$ . Descriptive statistics for quantitative variables were presented as mean  $\pm$  standard deviation and as percentages for qualitative variables. Differences in quantitative outcomes were assessed using parametric tests when normality and homogeneity assumptions were satisfied; otherwise the equivalent nonparametric tests were used. Correlations were assessed using the nonparametric measure of Spearman’s rank correlation.

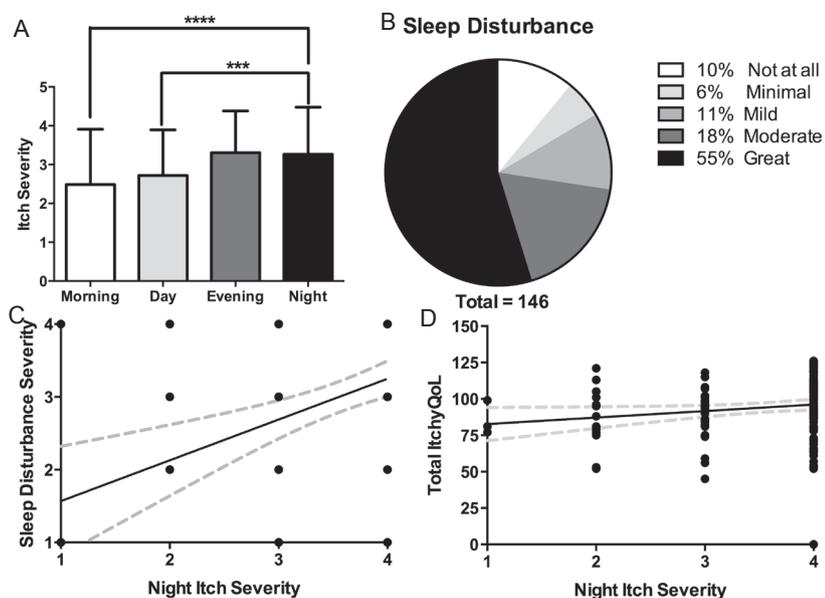
### RESULTS

NP was present in 146 (91.3%) of the 160 subjects. The mean  $\pm$  SD overall itch severity among subjects with NP ( $8.2 \pm 2.1$ ) was not significantly different from that of subjects without NP ( $6.8 \pm 2.6$ ). The prevalence and severity of NP were similar among different dermatologic conditions (Table S1<sup>1</sup>). NP was not found to be significantly associated with age, sex, ethnicity, or the presence of comorbid conditions such as depression.

The severity of NP was significantly correlated with overall itch severity ( $r = 0.22$ ,  $p = 0.006$ ). On average, subjects reported significantly higher itch severity at night compared to morning or day ( $p < 0.0001$ , Fig. 1A). 69 (47.3%) subjects with NP experienced itch constantly throughout the night. Of the 146 subjects with NP, 90% reported sleep disturbance, with 55% “to a great extent” (Fig. 1B). Furthermore, for subjects with NP, the severity of itch at night was significantly correlated with the severity of sleep disturbance ( $r = 0.35$ ,  $p < 0.0001$ , Fig. 1C). In turn, the severity of sleep disturbance was correlated with feelings of anger and irritability ( $r = 0.32$ ,  $p = 0.0001$ ) as well as depression and sadness ( $r = 0.19$ ,  $p = 0.03$ ).

The severity of NP was significantly correlated with total ItchyQoL score ( $r = 0.22$ ,  $p = 0.006$ , Fig. 1D), indicating that NP was associated with an overall reduced

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**Fig. 1. Characteristics of nocturnal pruritus (NP) and its correlation to sleep disturbance.** A) Temporal variation in itch severity, \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$ . B) Degree of sleep disturbance reported by subjects with NP. C) Correlation between sleep disturbance severity and NP severity, rated as 0 (not at all), 1 (to a minimal extent), 2 (to a mild extent), 3 (to a moderate extent), or 4 (to a great extent). D) Correlation of NP severity and overall ItchyQoL score.

QoL. Specifically, the severity of NP was correlated with Functioning ( $r=0.29$ ,  $p=0.0004$ ) and Emotions ( $r=0.18$ ,  $p=0.03$ ), but not Symptoms ( $r=0.15$ ,  $p=0.08$ ) subscales.

## DISCUSSION

This study demonstrates that NP is highly prevalent within a wide range of pruritic conditions. Our results corroborate previous reports that have highlighted the significance of NP in atopic dermatitis and psoriasis (4, 5). We additionally found that NP was prevalent in patients with brachioradial pruritus, prurigo nodularis, and chronic spontaneous urticaria (10). Almost all subjects with NP reported some degree of sleep disturbance, and this sleep disturbance was correlated with negative emotional states. The impact of NP on QoL highlights the need for targeted clinical intervention.

Available therapeutic options for the treatment of NP remain limited. First generation antihistamines are commonly used to provide sedation, but otherwise have little ability to relieve chronic itch. Medications with dual antipruritic and soporific effects, including mirtazapine, GABAergics (gabapentin and pregabalin), and kappa opioid agonists (butorphanol) may be able to simultaneously target both itch and sleep impairment (11, 12). We found a correlation between overall itch severity and NP severity, which suggests that using antipruritic agents to treat itch generally should impact NP as well. However, some antipruritic drugs may cause side effects that disturb sleep. For instance, nalfurafine, which is licensed in Japan to treat pruritus associated with chronic kidney

disease, has been shown to reduce NP, but may also cause insomnia (13).

There are a number of limitations to our study. Notably, our subjects were recruited from a specialized itch center within a dermatology clinic and may therefore represent more severe cases of chronic pruritus than would routinely be seen in other settings. Additionally, some dermatological pruritic conditions were not well represented within our sample, and we did not investigate the role of NP in the context of pruritic systemic conditions, such as chronic kidney disease and cholestasis.

Despite these limitations, this study shows the important role of NP in QoL for the general chronic itch population. Our results confirm those of previous studies that show itch is usually more severe at night than during the day. The reasons behind this effect are still unclear. Further studies are needed to determine the underlying pathophysiology and central mechanisms that mediate nocturnal itch, with the ultimate goal of ushering in novel targeted therapies.

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## REFERENCES

- Matterne U, Apfelbacher CJ, Vogelgsang L, Loerbroks A, Weisshaar E. Incidence and determinants of chronic pruritus: a population-based cohort study. *Acta Derm Venereol* 2013; 93: 532–537.
- Dinges DF, Pack F, Williams K, Gillen KA, Powell JW, Ott GE, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep* 1997; 20: 267–277.
- Daley M, Morin CM, LeBlanc M, Gregoire JP, Savard J, Bailargeon L. Insomnia and its relationship to health-care utilization, work absenteeism, productivity and accidents. *Sleep Med* 2009; 10: 427–438.
- Silverberg JI, Garg NK, Paller AS, Fishbein AB, Zee PC. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. *J Invest Dermatol* 2015; 135: 56–66.
- Kimball AB, Edson-Heredia E, Zhu B, Guo J, Maeda-Chubachi T, Shen W, et al. Understanding the relationship between pruritus severity and work productivity in patients with moderate-to-severe psoriasis: sleep problems are a mediating factor. *J Drugs Dermatol* 2016; 15: 183–188.
- Pisoni RL, Wikstrom B, Elder SJ, Akizawa T, Asano Y, Keen ML, et al. Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2006; 21: 3495–3505.

7. Dawn A, Papoiu AD, Chan YH, Rapp SR, Rasette N, Yosipovitch G. Itch characteristics in atopic dermatitis: results of a web-based questionnaire. *Br J Dermatol* 2009; 160: 642–644.
8. Desai NS, Poindexter GB, Monthrope YM, Bendeck SE, Swerlick RA, Chen SC. A pilot quality-of-life instrument for pruritus. *J Am Acad Dermatol* 2008; 59: 234–244.
9. Ständer S, Weisshaar E, Mettang T, Szepietowski JC, Carstens E, Ikoma A, et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. *Acta Derm Venereol* 2007; 87: 291–294.
10. Moolani Y, Lynde C, Sussman G. Advances in Understanding and Managing Chronic Urticaria. *F1000Research* 2016; 5(F1000 Faculty Rev): 177.
11. Hundley JL, Yosipovitch G. Mirtazapine for reducing nocturnal itch in patients with chronic pruritus: a pilot study. *J Am Acad Dermatol* 2004; 50: 889–891.
12. Lavery MJ, Stull C, Kinney MO, Yosipovitch G. Nocturnal Pruritus: The Battle for a Peaceful Night's Sleep. *Int J Mol Sci* 2016; 17: 425.
13. Inui S. Nalfurafine hydrochloride to treat pruritus: a review. *Clin Cosmet Investig Dermatol* 2015; 8: 249–255.