## Title

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# Treating Chronic Pruritus: Are We at the Threshold of a Breakthrough?

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## Abstract

Chronic pruritis, characterized by persistent itchiness lasting more than six weeks, affects up to 15% of the population, significantly impairing quality of life. Despite its prevalence and impact, there is an absence of FDA-approved medications specifically for the treatment of chronic pruritus, highlighting a significant unmet need in dermatology. Advancements in dermatologic medications, however, including the development of biologics and Janus kinase (JAK) inhibitors, signal potential breakthroughs in pruritus management through a radically different mechanism of action that focuses on their effect on the nervous system. Currently, the most commonly utilized treatments for pruritis are sedating antihistamines, which have been largely ineffective for non-histamine-induced itch, underscoring the necessity for novel approaches. This editorial reviews key studies and clinical trials with a particular focus on cases of prurigo nodularis, where itch serves as the primary pathology rather than just a symptom. The effectiveness of dupilumab in phase III trials for treating prurigo nodularis, independent of its effects on dermatitis or atopic background, alongside the success of JAK inhibitors in managing chronic idiopathic pruritus, indicates a shift towards therapies that directly and specifically target itch nerve pathways instead of indirectly via immune system modulation or sedation. These developments suggest that significant progress may be on the horizon for treating chronic itch, providing hope for those suffering from pruritis, the number one cause of misery in dermatology.

Chronic pruritis is a condition that manifests as persistent itchiness for more than six weeks. It affects up to 15% of the population and severely impacts quality of life.[1–3] Pruritus is the most common and distressing cutaneous symptom in dermatology, yet, remarkably, there is no medication currently explicitly FDA-approved for its treatment.[4] This represents a significant unmet need within the field. However, recent advancements in biologics and Janus kinase (JAK) inhibitors are showing promise, potentially heralding a new era in the effective management of pruritus.

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The treatment landscape for chronic itch in dermatology has evolved over the years. Traditionally, sedating antihistamines like hydroxyzine and diphenhydramine were the go-to medications for itch management.[4] The introduction of nonsedating antihistamines initially raised hope for a more effective treatment for pruritic conditions like psoriasis and eczema. However, Sam Schuster et al. conducted a study utilizing limb meters (devices adapted from self-winding watches to quantify nocturnal scratching), which revealed that nonsedating antihistamines were ineffective for pruritus not triggered by histamine release.[5] The study found that sedating antihistamines and benzodiazepines had comparable efficacy for treating pruritis, suggesting it was a sedative effect rather than innate anti-itch properties responsible for the efficacy of sedating antihistamines. This realization led to the abandonment of nonsedating antihistamines for treating non-histamine-induced pruritic conditions like psoriasis.[5] This study underscored an important concept in dermatology: while not all cases of pruritis are mediated by histamine, the involvement of nervous system pathways is a constant feature in all pruritic conditions.

One of the most intensely pruritic and burdensome dermatologic conditions is prurigo nodularis (PN).[6] The pathogenesis of PN begins with an itch sensation. Subsequently, patients develop fibrotic papulonodular lesions. This makes PN unique from conditions such as AD, where visible skin inflammation exists. However, between 18.7% and 46.3% of adult patients with PN have a history of atopy or current atopic comorbidity, in which cases the intense pruritus from these conditions leads to the development of secondary PN.[7]

In 2019, two key phase III PN clinical trials focused on adults with prurigo nodularis who continued to experience severe itch that could not be managed with topical treatments. These studies randomly assigned participants to receive either 300mg of subcutaneous dupilumab or a placebo bi-weekly over 24 weeks. The primary measure of effectiveness was the proportion of patients achieving at least a 4-point decrease on the Worst Itch Numeric Rating Scale (WI-NRS).[7]

The findings from these trials indicated that dupilumab treatment led to significant improvements in both itch intensity and skin lesions when compared to the placebo group. However, the most remarkable and almost unexpected finding was that dupilumab worked well in over half (57%) of the study participants deliberately selected to have no visible rash or inflammation and no current or past history of any condition associated with atopy. Only 4% of the subjects were allowed to have mild AD, and individuals with moderate-to-severe AD were excluded from the study. Therefore, the efficacy of dupilumab did not depend on whether the patient did or did not have visible inflammation or an atopic background.[7]

Interestingly, animal studies have demonstrated the presence of IL-4 and IL-13 receptors on the dorsal root ganglion, which can be blocked by an agent such as dupilumab. Moreover, the work of Brian Kim et al. has demonstrated in the murine model that directly blocking IL-4 on the nervous system is likely to normalize the pathology that leads to the initiation of the “itch-scratch cycle.” This critical pathology appears to result from the hyperactive and hypersensitive sensory nervous system, which, with the presence of excessive IL-4 (and possibly IL-13 and IL-31), is locked into sending itch signals excessively and incessantly. Brian Kim and his colleagues demonstrated how this hyperexcitable sensory nervous system

can be downregulated and normalized by actively blocking excessive IL-4, which makes the nervous system hyperexcitable in the first place.[8] IL-4Ra or JAK inhibitors likely disrupt sensory nerve signals directly, suggesting that these treatments could also effectively address chronic itch in non-inflammatory skin conditions, such as chronic idiopathic pruritus (CIP).

Supporting this notion, a 2017 study demonstrated significant improvement in individuals with CIP without a visible rash treated with tofacitinib, a JAK inhibitor initially approved for rheumatoid arthritis, after other anti-inflammatory medications, including cyclosporine, failed to relieve pruritis. All participants reported substantial itch alleviation within a month of commencing tofacitinib therapy.[8]

In summary, medications like dupilumab and JAK inhibitors represent promising advances in chronic itch treatment, possibly by targeting the neural pathways, which is an effect above and beyond their immunomodulatory effects. Not all itch is mediated by histamine, but no itch can exist without the nervous system. These recent developments suggest that neurons could be a novel and more universally impactful target for itch therapies, offering hope based on an entirely different nervous system-oriented approach, which may work better than the traditional approaches with antihistamines or sedative agents.

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