When Itch Behaves Like Pain: A Systematic Review of Overlapping Neurobiologic Mechanisms and Implications for Targeted Therapy

Neha Bhupathiraju, BS[1], Nathan Nguyen, BS[2], Jyothika Kumar, BS[2], Mary Cavanagh, MD[3], Ayezel M. Munoz-Gonzalez, MD[3]

[1]Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX; USA, [2]School of Brain and Behavioral Sciences, University of Texas at Dallas, Dallas, TX, USA; [3]Department of Dermatology, The University of Texas Medical Branch, John Sealy School of Medicine, Galveston, TX, USA

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Abstract

Background: Chronic pruritus and neuropathic pain are debilitating somatosensory disorders increasingly recognized to share overlapping mechanisms of neuronal sensitization, maladaptive synaptic plasticity, and impaired inhibitory signaling. Although traditionally conceptualized as distinct sensory modalities, emerging evidence suggests that neuropathic itch may respond to therapies originally developed for neuropathic pain through shared peripheral and central neurobiologic pathways.

Objective: To systematically review overlapping neurobiologic mechanisms between chronic itch and neuropathic pain and evaluate mechanistically targeted pharmacologic therapies for neuropathic itch syndromes.

Methods: A PRISMA 2020–informed systematic review that searched PubMed, Embase, Cochrane Library, and Web of Science for studies published between 2021 and 2026. Eligible studies included randomized controlled trials, cohort studies, translational studies, and case series evaluating pharmacologic treatments for chronic neuropathic itch (≥6 weeks) with mechanistic relevance. Data extraction focused on study design, interventions, clinical outcomes, and underlying neural mechanisms. Due to study heterogeneity, a qualitative synthesis was performed. Of 257 identified records, 16 studies met inclusion criteria. Three independent reviewers screened all records and full-text reports against predefined inclusion and exclusion criteria, with disagreements resolved through consensus discussion; no automation tools were used during study selection.

Results: Sixteen studies met inclusion criteria, including 2 randomized controlled trials, 7 translational studies, 5 case studies, and 2 retrospective cohort studies. Across studies, peripheral sensitization mechanisms included C-fiber hyperactivity, TRPV1/TRPA1 signaling, voltage-

gated calcium channel dysfunction, and neuropeptide-mediated neuroinflammation. Central sensitization mechanisms included dorsal horn hyperexcitability, impaired descending inhibitory pathways, and maladaptive synaptic plasticity. Shared circuitry within dorsal root ganglia and spinothalamic pathways supported mechanistic overlap between itch and pain, although divergence persisted within gastrin-releasing peptide receptor–mediated itch signaling pathways. Gabapentinoids demonstrated the most consistent therapeutic benefit through α2δ subunit modulation of presynaptic voltage-gated calcium channels. Topical anesthetics, sodium channel blockers, TRPV1-targeted therapies, and botulinum toxin A showed benefit predominantly in localized neuropathic itch syndromes associated with peripheral nerve hyperexcitability. Tricyclic antidepressants and NMDA antagonists demonstrated variable efficacy, particularly in centrally mediated or systemic pruritic disorders. Treatment heterogeneity appeared to correlate more strongly with underlying biologic mechanism than with pharmacologic class alone.

Limitations: Included studies were heterogeneous in design, sample size, follow-up duration, and outcome reporting, limiting direct comparison across therapeutic interventions. Most evidence was derived from small observational or translational studies.

Conclusions: Chronic itch and neuropathic pain represent intersecting manifestations of somatosensory dysfunction characterized by shared drivers of neuronal hyperexcitability and sensitization. Therapeutic response patterns support a mechanism-aligned treatment framework in which peripheral nerve–driven disease responds preferentially to calcium and sodium channel–targeting therapies, whereas centrally mediated pruritus demonstrates variable responsiveness. Recognition of biologic heterogeneity may improve treatment selection and guide development of targeted therapies for chronic pruritic disorders.