Gabapentin in Uremic Pruritus: Clinical Efficacy and Modulation of Interleukin-31 in Hemodialysis Patient

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ABSTRACT

Background: Uremic pruritus (UP), also known as chronic kidney disease-associated pruritus (CKD-aP), is a highly prevalent and distressing complication in patients undergoing hemodialysis. Despite its significant impact on quality of life, sleep, and mental health, the underlying pathophysiology remains multifactorial and incompletely understood. Emerging evidence has highlighted a pivotal role for interleukin-31 (IL-31), a Th2-derived pruritogenic cytokine, in mediating chronic itch in this population. Gabapentin, an anticonvulsant with neuromodulatory effects, has gained increasing attention for its antipruritic properties, although its mechanism of action and impact on immune mediators like IL-31 remain under active investigation. This review aims to comprehensively assess the clinical efficacy of gabapentin in alleviating uremic pruritus among hemodialysis patients, with a particular focus on its potential immunomodulatory effect on IL-31 levels. We also explore the neuroimmune interplay contributing to pruritus in ESRD and evaluate current evidence from clinical trials and observational studies supporting gabapentin's role in symptom control and cytokine modulation.

Conclusion: Gabapentin has demonstrated significant clinical benefit in reducing the severity and frequency of uremic pruritus in hemodialysis patients, often outperforming antihistamines and placebo in randomized trials. Beyond symptomatic relief, preliminary evidence suggests that gabapentin may downregulate IL-31 expression or modulate its downstream signaling pathways, offering a dual neuroimmune mechanism of action. These findings position gabapentin not only as a symptomatic therapy but also as a potential disease-modifying agent in CKD-aP. Further controlled studies are needed to validate its immunological effects and to define optimal dosing regimens tailored to renal function. Integrating gabapentin into a personalized treatment approach may improve patient-centered outcomes in end-stage renal disease and reduce the burden of chronic itch in this vulnerable population.

Keywords: Gabapentin, Uremic Pruritus, Interleukin-31, Hemodialysis Patient

1. INTRODUCTION

Introduction: Chronic Kidney Disease and End-Stage Renal Disease

Chronic kidney disease (CKD) is a progressive condition characterized by a gradual decline in renal function, often leading to end-stage renal disease (ESRD), a state in which the kidneys fail to meet the body's metabolic and fluid regulation needs. Globally, CKD affects approximately 10% of the adult population, and its burden continues to grow due to the rising incidence of diabetes and hypertension—major risk factors for kidney deterioration [1]. As renal function declines, various systemic complications emerge, including cardiovascular diseases, anemia, metabolic acidosis, bone-mineral disorders, and neurologic dysfunction [2].

End-stage renal disease necessitates renal replacement therapies such as hemodialysis, peritoneal dialysis, or kidney transplantation. Hemodialysis remains the most widely used modality, although it does not fully correct the metabolic and immunologic disturbances associated with uremia [3]. Among the less appreciated but highly distressing symptoms encountered in ESRD patients is pruritus, often termed "uremic pruritus." This chronic itch significantly affects sleep, mental health, and overall quality of life [4]. Despite its prevalence and impact, the pathogenesis of uremic pruritus remains poorly understood, though recent insights suggest a complex interplay between systemic inflammation, immune dysregulation, and neurocutaneous signaling [5].

Emerging evidence has implicated interleukin-31 (IL-31), a cytokine associated with pruritic conditions, as a key mediator in the development of uremic pruritus. Gabapentin, an antiepileptic drug with known antipruritic properties, has shown promise in alleviating uremic itch, possibly through its modulatory effects on IL-31 levels [6-9]. This review aims to explore the neuroimmunological underpinnings of uremic pruritus in ESRD, focusing on the role of IL-31 and the therapeutic impact of gabapentin.

IL-31, a cytokine predominantly secreted by activated Th2 cells, has been strongly implicated in the pathogenesis of various pruritic conditions. It binds to a heterodimeric receptor composed of IL-31 receptor A (IL-31RA) and oncostatin M receptor β (OSMRβ), which are expressed on sensory neurons, keratinocytes, and immune cells. Upon activation, IL-31 induces itch by stimulating nerve endings and promoting inflammation. Elevated serum IL-31 levels have been correlated with itch severity in conditions like atopic dermatitis and, increasingly, in CKD-associated pruritus [10-12] .

Recent studies have demonstrated significantly elevated IL-31 levels in the serum of HD patients with UP compared to those without pruritus and healthy controls. These findings suggest that IL-31 is involved in the inflammatory and neuroimmune dysregulation characteristic of uremic pruritus. Moreover, IL-31 may contribute to peripheral and central sensitization to itch in these patients, potentially making it both a biomarker and a therapeutic target in UP [13-15].

Gabapentin, a γ-aminobutyric acid (GABA) analogue, is commonly used off-label for the treatment of UP. Although it was originally developed as an antiepileptic, gabapentin's antipruritic effect is attributed to its ability to inhibit voltage-gated calcium channels on presynaptic neurons, thereby reducing the release of excitatory neurotransmitters involved in itch transmission. It also modulates neuronal hyperexcitability and can dampen peripheral and central itch pathways [16-20].

While gabapentin's exact interaction with IL-31 is not fully delineated, it may indirectly reduce IL-31-induced pruritus by attenuating the neuronal responsiveness to inflammatory cytokines. Since IL-31 stimulates pruritus through neuronal pathways that involve calcium influx, gabapentin's action on calcium channels may dampen the downstream effects of IL-31 receptor activation, thereby reducing itch intensity [21-24].

A limited number of studies have explored whether gabapentin therapy leads to a measurable reduction in IL-31 levels in HD patients. Some pilot data suggest that patients treated with gabapentin for UP experience both subjective improvement in pruritus and modest reductions in serum IL-31 concentrations, indicating a possible immunomodulatory or indirect anti-inflammatory effect. However, more robust longitudinal studies are needed to confirm this link [25-26].

Gabapentin may influence the neuroimmune interface in UP by modulating microglial and astrocytic activation, which are known to interact with cytokine signaling in chronic itch conditions. This modulation might reduce the central sensitization caused by IL-31 and other pruritogenic cytokines. Therefore, gabapentin's efficacy may not solely be attributed to neural mechanisms but may also involve suppressing the cytokine-induced neuroinflammation that perpetuates pruritus.

It is hypothesized that HD patients with higher baseline IL-31 levels may derive greater benefit from gabapentin therapy, as their pruritus may be more cytokine-driven. Stratifying patients based on IL-31 levels prior to treatment could provide a framework for personalized therapy, where those with cytokine-mediated itch are preferentially treated with gabapentin or related neuromodulators [27].

Compared to antihistamines and topical treatments, gabapentin appears to be more effective in cases where IL-31 is a dominant factor, given its central and peripheral neuromodulatory effects. While agents targeting IL-31 directly (e.g., nemolizumab) are under investigation, gabapentin provides a more accessible and affordable alternative for reducing IL-31-associated itch, especially in resource-limited settings [28].

The potential correlation between gabapentin use and IL-31 modulation opens up promising avenues for biomarker-driven therapy in UP. Future studies should focus on elucidating whether gabapentin directly affects IL-31 expression or receptor signaling and whether IL-31 levels can predict therapeutic response. Combining gabapentin with IL-31-targeted therapies may offer a synergistic approach to managing this complex and burdensome symptom in HD patients [28].

Uremic Pruritus

Uremic pruritus (UP), also known as chronic kidney disease-associated pruritus (CKD-aP), is a distressing and common complication affecting up to 60% of patients undergoing maintenance hemodialysis. Despite improvements in dialysis techniques, UP remains underdiagnosed and undertreated. It significantly impairs quality of life, sleep, and psychological well-being, and has been associated with increased mortality in dialysis patients [28].

The pathophysiology of UP is multifactorial and incompletely understood. It involves an interplay of metabolic disturbances, systemic inflammation, peripheral neuropathy, immune system dysregulation, and opioid imbalance. Elevated serum levels of parathyroid hormone, calcium, phosphate, and inflammatory markers such as C-reactive protein (CRP) have been correlated with UP severity [29]. Additionally, recent studies have implicated specific pruritogenic cytokines—particularly interleukin-31 (IL-31)—as central mediators in the itch pathway [30].

Clinically, UP often presents as a bilateral, symmetrical itch predominantly affecting the back, face, arms, and abdomen. It may be intermittent or continuous and tends to worsen at night or post-dialysis. The skin may appear normal, xerotic, or excoriated due to intense scratching. Importantly, the pruritus is not typically linked to primary dermatologic conditions [31].

Assessment tools such as the Visual Analog Scale (VAS), Numeric Rating Scale (NRS), and the 5-D itch scale are used to quantify the severity and impact of UP. However, due to the subjective nature of itching, patient-reported outcomes remain critical in guiding therapy [32].

Effective management of UP requires a multidisciplinary approach including optimization of dialysis adequacy, correction of mineral bone disorder, skin hydration, and targeted pharmacologic therapies. Increasing attention has been directed toward neuromodulators like gabapentin, which appear to mitigate neuropathic itch and modulate central sensitization [33].

Clinical Presentation of Uremic Pruritus

The clinical manifestation of uremic pruritus (UP) is characteristically diverse, yet certain features are consistently observed among hemodialysis patients. Pruritus in this population is typically bilateral, symmetrical, and predominantly non-dermatomal, with frequent involvement of the trunk, arms, scalp, and face. Itching may be generalized or localized, and it often worsens at night, interfering with sleep and leading to chronic fatigue and psychological distress [34].

Unlike allergic or dermatologic pruritus, UP often occurs in the absence of primary skin lesions. However, secondary skin changes such as excoriations, lichenification, xerosis, and prurigo nodularis may develop due to persistent scratching [35]. The absence of visible inflammation with intense itching should alert clinicians to a systemic etiology like uremia.

In terms of onset and course, UP usually develops gradually in patients undergoing maintenance dialysis and tends to persist or fluctuate over time. Some patients report post-dialysis worsening, possibly due to skin dryness or shifting of metabolic solutes. UP can occur independently of dialysis

modality, though some studies suggest slightly higher prevalence in hemodialysis compared to peritoneal dialysis [36].

The intensity of pruritus varies widely among individuals and is typically evaluated using subjective scoring systems. These include the Visual Analog Scale (VAS), Numeric Rating Scale (NRS), 5-D Itch Scale, and Itch Severity Scale. These tools assess severity, duration, degree of distress, impact on sleep, and overall quality of life [37].

Clinicians should maintain a high index of suspicion for UP in dialysis patients presenting with unexplained itching and should evaluate associated factors such as dry skin, dialysis adequacy, mineral bone disorder, and inflammatory markers. Early recognition and comprehensive management of UP are essential for improving patient comfort and reducing morbidity [38].

Specific Antipruritic Therapy in Uremic Pruritus

Managing uremic pruritus (UP) requires a multifaceted approach tailored to the underlying pathophysiology and severity of symptoms. Despite its high prevalence and impact, UP remains undertreated due to the lack of FDA-approved therapies, complex etiology, and variable response to interventions [39].

1. Topical therapies are often the first-line treatments. Emollients, especially those containing urea, menthol, or structured lipids, help alleviate xerosis, a major contributing factor to UP [40]. Capsaicin creams and pramoxine-containing formulations have shown limited benefits but may be tried for localized itching [41].

2. Phototherapy, particularly narrowband UVB (NB-UVB), has shown efficacy in patients with refractory UP. Its antipruritic effect is believed to involve modulation of cutaneous immune responses and nerve fiber density. However, accessibility and long-term safety remain concerns [42].

3. Systemic therapies include antihistamines, which are widely used but generally ineffective in UP due to the non-histaminergic nature of the itch. Nonetheless, sedating antihistamines may help improve sleep quality in select patients [43]. Antidepressants like sertraline and mirtazapine, and thalidomide, an immunomodulator, have shown some benefit in small studies but carry risks of side effects [44].

4. Opioid pathway modulators have emerged as effective options. Kappa-opioid receptor agonists like nalfurafine and difelikefalin have shown promise in reducing itch intensity by modulating the central and peripheral itch pathways [45]. Difelikefalin was recently approved for UP in hemodialysis patients in several countries, showing statistically significant improvements in VAS scores and quality of life [46].

5. Gabapentinoids, especially gabapentin and pregabalin, are now widely recognized for their antipruritic and neuromodulatory properties in UP. These agents reduce peripheral and central sensitization by acting on voltage-gated calcium channels—a topic that will be discussed in depth in the following sections [47].

Overall, treatment should be individualized, with consideration of pruritus severity, comorbidities, and tolerance to therapy. A stepwise escalation of therapy, starting with skin care and progressing to systemic agents, remains the cornerstone of UP management [48].

Gabapentin: Mechanism of Action and Clinical Relevance

Gabapentin is a structural analog of gamma-aminobutyric acid (GABA), originally developed as an anticonvulsant. Despite its chemical similarity to GABA, it does not bind to GABA receptors but rather to the α2δ subunit of voltage-gated calcium channels in the central nervous system. This binding reduces calcium influx into neurons, thereby inhibiting the release of excitatory neurotransmitters, such as glutamate and substance P, which are implicated in neuropathic pain and pruritus pathways [49,50].

The role of gabapentin in modulating neuronal hyperexcitability and central sensitization has made it a promising therapeutic option beyond epilepsy. It is now widely used for neuropathic pain, restless leg syndrome, fibromyalgia, and chronic itch syndromes, including uremic pruritus [51]. Gabapentin also exerts indirect effects on pruritus by enhancing GABAergic inhibition and modulating itch signaling in the dorsal horn of the spinal cord [52].

Pharmacokinetically, gabapentin is not metabolized by the liver, and it is excreted unchanged via the kidneys, making dose adjustment crucial in patients with chronic kidney disease. Its relatively favorable side-effect profile, particularly at lower doses, has encouraged its off-label use in pruritus management [53].

Recent research has highlighted gabapentin's role in regulating IL-31, a cytokine increasingly recognized in pruritic conditions. Although not fully elucidated, gabapentin's effect on neuroimmune signaling pathways may contribute to its ability to lower IL-31 expression or its downstream signaling, potentially alleviating inflammatory-driven itch sensations [54].

Overall, gabapentin’s unique neuromodulatory profile, ease of oral administration, and tolerability make it a clinically relevant option for managing pruritus, particularly when conventional antipruritic therapies fail or are contraindicated.

Pregabalin: Mechanism of Action and Clinical Utility in Pruritus

Pregabalin, like gabapentin, is a structural analog of GABA, but it exerts its effects through high-affinity binding to the α2δ subunit of voltage-gated calcium channels in the central nervous system. This interaction leads to inhibition of calcium influx, which in turn suppresses the release of neurotransmitters such as glutamate, noradrenaline, and substance P, all of which are involved in nociceptive and pruritic transmission [55,56].

Although originally approved for neuropathic pain and epilepsy, pregabalin has gained attention for its antipruritic properties, particularly in refractory cases of chronic pruritus, including that related to uremia. Several mechanisms may underlie its antipruritic effects, including central desensitization, reduction in hyperexcitability of spinal neurons, and indirect modulation of pruritogenic cytokines, such as interleukin-31 (IL-31) [57].

Pregabalin is more bioavailable than gabapentin and exhibits linear pharmacokinetics, which allows for more predictable dosing. However, its renal excretion also necessitates dose adjustments in patients with chronic kidney disease (CKD) or those undergoing dialysis to prevent accumulation and adverse effects [58].

Clinical studies have demonstrated beneficial effects of pregabalin in reducing itch intensity and improving sleep and quality of life in patients with uremic pruritus [59]. A comparative trial also suggested that pregabalin may be as effective as gabapentin, with similar safety profiles, although more robust head-to-head trials are needed to confirm this [60].

Interleukin-31: Pathophysiological Role and Relevance to Pruritus

Interleukin-31 (IL-31) is a cytokine produced mainly by activated Th2 cells, and it has emerged as a key mediator of chronic pruritus across various dermatologic and systemic diseases [61]. IL-31 exerts its effects by binding to a heterodimeric receptor composed of IL-31 receptor A (IL-31RA) and oncostatin M receptor β (OSMRβ), which are expressed in keratinocytes, sensory neurons, eosinophils, basophils, and other immune cells [62,63].

The binding of IL-31 to its receptor activates the JAK/STAT, MAPK, and PI3K/AKT pathways, leading to downstream inflammatory signaling and neuronal sensitization. This promotes epidermal barrier dysfunction, immune cell infiltration, and pruritogenic signaling, contributing to a cycle of inflammation and itch [64].

IL-31 is also known to stimulate outgrowth of sensory nerve fibers, enhancing the skin's neuronal network density, which is strongly associated with itch severity [65]. In animal models, intradermal IL-31 administration triggers intense scratching behavior, providing functional evidence for its direct pruritogenic role [66].

Elevated serum and cutaneous levels of IL-31 have been documented in several pruritic conditions, including atopic dermatitis, psoriasis, cutaneous T-cell lymphoma, and most notably, uremic pruritus in patients with end-stage renal disease (ESRD) [67,68]. Its levels correlate with pruritus severity and duration, underscoring its potential as a biomarker and therapeutic target in chronic itch syndromes.

Neutralization of IL-31 signaling using monoclonal antibodies (e.g., nemolizumab) has shown promising results in clinical trials for atopic dermatitis and other pruritic diseases, indicating the therapeutic potential of targeting IL-31 in uremic pruritus as well [69].

Interleukin-31 and Uremic Pruritus

Interleukin-31 (IL-31) has been increasingly recognized as a pivotal cytokine in the pathogenesis of uremic pruritus, a common and distressing symptom in patients with end-stage renal disease (ESRD) undergoing hemodialysis. IL-31 exerts pruritogenic effects through its interaction with IL-31RA/OSMRβ receptors expressed on cutaneous nerves, immune cells, and keratinocytes, triggering a cascade of itch-associated signaling pathways [70].

Several clinical studies have demonstrated significantly elevated serum levels of IL-31 in hemodialysis patients suffering from uremic pruritus compared to asymptomatic counterparts. Ko et al. reported that IL-31 levels were positively correlated with pruritus severity in this population, suggesting a pathophysiological role of IL-31 in mediating itch perception [71]. Similarly, Oweis et al. and Abd El-Aziz et al. found that IL-31 concentrations were markedly increased in pruritic hemodialysis patients and were associated with disease severity and decreased quality of life [72,73].

Moreover, a potential mechanistic link has been proposed between uremia-induced immune dysregulation and the upregulation of IL-31. Chronic systemic inflammation, altered T-helper cell profiles, and persistent immune activation in ESRD could contribute to enhanced IL-31 production, thereby amplifying the pruritic response [74].

The presence of IL-31 receptors in dorsal root ganglia and cutaneous nerve fibers supports its direct action on sensory neurons, enhancing neuronal excitability and itch signaling [75]. This neuroimmune interaction underlines the complex interplay between the immune system and peripheral nerves in uremic pruritus.

Given its central role, IL-31 is being investigated as a potential therapeutic target. Antibodies blocking IL-31 or its receptor have shown promise in other chronic itch conditions and may offer new treatment avenues for patients with uremic pruritus refractory to conventional therapy [76].

Gabapentin

Gabapentin, a structural analogue of gamma-aminobutyric acid (GABA), is widely used as an antiepileptic and for neuropathic pain syndromes. Over the past two decades, its off-label use has expanded to include the treatment of chronic pruritus, including uremic pruritus (UP), due to its modulatory effects on neuronal excitability and central sensitization [77].

Gabapentin binds to the α2δ subunit of voltage-gated calcium channels in the central nervous system, reducing excitatory neurotransmitter release and neuronal firing in the dorsal horn of the spinal cord [78]. In the context of pruritus, this results in dampened transmission of itch signals from peripheral to central neurons, thereby alleviating symptoms. Additionally, gabapentin is known to enhance GABAergic inhibitory signaling, contributing to its antipruritic effect [79].

In hemodialysis patients, gabapentin has been investigated extensively for its efficacy in uremic pruritus. Randomized controlled trials (RCTs) have shown significant reductions in pruritus intensity scores in patients treated with gabapentin compared to placebo or antihistamines [80,81]. Nofal et al.

reported marked improvement in Visual Analog Scale (VAS) and sleep disturbance scores after 4 weeks of gabapentin therapy [82].

Moreover, gabapentin's beneficial effects are not merely symptomatic; they may also attenuate central sensitization and hyperexcitability that underlie chronic itch. However, dose adjustments are essential in ESRD due to renal excretion of the drug, with 100–300 mg doses post-dialysis typically recommended to minimize toxicity [83].

Gabapentin is generally well-tolerated, although dizziness, somnolence, and fatigue are common side effects. It should be used cautiously in the elderly and those at risk of falls or respiratory depression [84].

Gabapentin in Uremic Pruritus

Gabapentin has gained widespread attention as a targeted pharmacological agent for managing uremic pruritus (UP), particularly in patients undergoing hemodialysis. UP remains a complex, multifactorial condition that is often refractory to conventional therapies such as antihistamines and emollients. The introduction of gabapentin has provided a novel and effective treatment modality due to its action on neuropathic itch pathways [85].

Several randomized controlled trials (RCTs) and observational studies have demonstrated the clinical benefits of gabapentin in alleviating UP symptoms. In a placebo-controlled trial by Gunal et al., a significant proportion of patients reported complete resolution or substantial reduction in itching after administration of gabapentin post-dialysis sessions [86]. Nofal and colleagues also confirmed these findings, showing significant improvement in VAS scores and sleep quality among patients treated with gabapentin versus placebo [87].

The mechanism by which gabapentin alleviates UP is believed to involve the inhibition of neuronal hyperexcitability via calcium channel modulation and enhancement of GABAergic inhibitory neurotransmission, which collectively reduce the peripheral and central sensitization associated with chronic itch [88,89]. This distinguishes it from traditional antipruritic drugs that primarily target histamine pathways, which are often ineffective in UP due to its non-histaminergic nature.

Dosing strategies vary but are generally titrated based on tolerability and renal function. A common regimen involves administering 100–300 mg after each dialysis session, which has shown optimal efficacy with minimal adverse effects in most studies [90]. Reported side effects include dizziness, somnolence, and fatigue, emphasizing the need for individualized dosing and cautious use in elderly or frail patients [91].

In addition to symptom control, gabapentin may improve the overall quality of life and sleep in hemodialysis patients, which is critically important given the chronic nature and psychological burden of UP [92].

Conclusion

Uremic pruritus remains a distressing and prevalent complication in patients undergoing hemodialysis, significantly impairing their quality of life and psychological well-being. While the exact mechanisms are multifactorial, emerging evidence has highlighted the role of interleukin-31 (IL-31) as a key neuroimmune mediator linking immune dysregulation to the pathogenesis of itch in chronic kidney disease. Elevated serum levels of IL-31 have been consistently associated with the severity of pruritus in dialysis patients, supporting its role as both a biomarker and a potential therapeutic target.

Gabapentin, initially developed as an antiepileptic agent, has demonstrated promising efficacy in alleviating uremic pruritus. Its mechanism of action involves modulation of neuronal excitability and enhancement of inhibitory GABAergic neurotransmission, thereby dampening central and peripheral pruritic pathways. Moreover, recent studies suggest that gabapentin may exert immunomodulatory effects, including potential downregulation of IL-31 expression, though this relationship warrants further investigation.

Integrating IL-31 pathway understanding into clinical practice may pave the way for more targeted and effective management strategies for uremic pruritus. The therapeutic benefit of gabapentin in this context not only offers symptom relief but may also provide insights into the neuroimmune interactions underlying pruritus in ESRD. Future research should focus on validating IL-31 as a therapeutic biomarker and elucidating the long-term safety and efficacy of gabapentin, particularly in vulnerable dialysis populations.

In conclusion, gabapentin represents a valuable option in the management of uremic pruritus, potentially acting through both neurophysiological and immunological pathways, including modulation of IL-31. Personalized approaches incorporating cytokine profiling could enhance treatment precision and improve outcomes for patients suffering from this challenging condition.

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