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Have We Just Scratched the Surface? A Narrative Review of Uremic Pruritus in 2020

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Abstract

Purpose of review: Uremic pruritus is a highly prevalent and debilitating symptom in patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD). The purpose of this review is to examine current evidence on the mechanisms and treatments of pruritus in CKD and highlight promising areas for future research.

Sources of information: Published literature, including randomized controlled trials, cohort studies, case reports, and review articles, was searched for evidence pertaining to the pathophysiology and treatment of uremic pruritus.

Methods: A comprehensive narrative review was conducted to explore the molecular mechanisms underlying uremic pruritus, as well as the evidence (or lack thereof) supporting pharmacological and nonpharmacological treatments for uremic pruritus. The potential role of patient sex in the pathophysiology and management of uremic pruritus is also discussed.

Key findings: The pathophysiology of uremic pruritus involves a complex interplay of uremic toxins, systemic inflammation, mast cell activation, and imbalance of opioid receptors. Classic treatment strategies for uremic pruritus include optimization of dialysis parameters, amelioration of CKD-related mineral and bone disease, topical emollients and analgesics, antihistamines, the anticonvulsant medications gabapentin and pregabalin, and ultraviolet light B (UV-B) phototherapy. Strong data to support many of these classical treatments for uremic pruritus are limited. Newly evolving treatment approaches for uremic pruritus include opioid receptor modulators, neurokinin-1 inhibitors, and cannabinoids. Further studies regarding their efficacy, pharmacodynamics, and safety in the CKD and ESKD population are needed before these agents are accepted into widespread use. Additional nonpharmacological strategies aimed at treating uremic pruritus include psychotherapy, acupuncture, omega-3 fatty acids, and exercise. Finally, sex differences may exist regarding uremic pruritus, but studies directly addressing sex-specific mechanisms of uremic pruritus remain absent.

Limitations: High-quality evidence in the management of uremic pruritus remains lacking. Most recommendations are based on expert opinion or studies involving small numbers of patients. In addition, our understanding of the pathophysiological mechanisms behind uremic pruritus is incomplete and continues to evolve over time.

Implications: Uremic pruritus is a common symptom which reduces quality of life in CKD and ESKD. The identification of novel targeted treatment approaches may ease the burden of uremic pruritus in the future.

Abrégé

Justification: Le prurit urémique est un syndrome débilitant très prévalent chez les patients atteints d'insuffisance rénale chronique (IRC) et terminale (IRT). Cette revue examine les données probantes actuelles sur les mécanismes et le traitement de cette affection en contexte de néphropathie, et met en évidence les axes de recherche prometteurs.

Sources: La littérature publiée, soit les essais contrôlés à répartition aléatoire, les études de cohorte, les rapports de cas et les articles de synthèse, a été consultée afin de répertorier les données probantes relatives à la physiopathologie et au traitement du prurit urémique.

Méthodologie: Une revue narrative complète a été menée afin d'explorer les mécanismes moléculaires sous-tendant le prurit urémique et les données probantes (ou leur absence) appuyant ses traitements pharmacologiques et non pharmacologiques. Le rôle potentiellement joué par le sexe du patient dans la physiopathologie et la gestion de la maladie a également été discuté.

Principaux résultats: La physiopathologie du prurit urémique implique l'interaction complexe des toxines urémiques, d'une inflammation systémique, de l'activation des mastocytes et d'un déséquilibre des récepteurs opioïdes. Les stratégies classiques de traitement comprennent l'optimisation des paramètres de dialyse, l'apaisement des troubles minéraux osseux

liés à l'IRC, les émollients et analgésiques topiques, les antihistaminiques, les anticonvulsivants gabapentine et prégabaline et la photothérapie par UV-B. Les données robustes appuyant ces traitements classiques sont cependant limitées. Parmi les nouvelles approches de traitement, on compte les modulateurs de récepteurs opioïdes, les inhibiteurs de NK-1 et les cannabinoïdes. Des études supplémentaires se penchant sur leur efficacité, leur pharmacodynamie et leur innocuité chez les populations de patients atteints d'IRC et d'IRT sont toutefois nécessaires avant que ces agents ne soient approuvés pour un usage répandu. Les stratégies non pharmacologiques comptent la psychothérapie, l'acupuncture, la prise d'acides gras oméga 3 et l'exercice physique. Enfin, des différences liées au sexe du patient pourraient exister, mais les études portant directement sur les mécanismes sexospécifiques du prurit urémique manquent toujours.

Limites: Les données probantes concernant la gestion du prurit urémique manquent toujours. La plupart des recommandations sont fondées sur l'avis d'experts ou sur des études portant sur de faibles échantillons. De plus, notre compréhension des mécanismes physiopathologiques causant le prurit urémique est incomplète et en constante évolution.

Conclusion: Le prurit urémique est un symptôme courant chez les patients atteints d'IRC et d'IRT, dont il réduit la qualité de vie. L'identification de nouvelles approches de traitement ciblées pourrait alléger le fardeau associé au prurit urémique.

Keywords

pruritus, quality of life, sex hormone

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Why is this review important?

Uremic pruritus is a common symptom of chronic kidney disease (CKD) that negatively affects quality of life and is a top research priority of patients. This review summarizes current evidence on the mechanisms and treatments for uremic pruritus and highlights promising areas for future research in this field.

What are the key messages?

A number of treatment strategies for uremic pruritus exist (eg, optimization of dialysis parameters, topical emollients and analgesics, antihistamines, ultraviolet light B [UV-B] phototherapy), although the evidence behind their efficacy is limited. Additional exploratory treatment approaches such as opioid receptor modulators, neurokinin-1 inhibitors, cannabinoids, psychotherapy, and exercise are promising avenues for future investigation, as is the role of sex in uremic pruritus.

Introduction

Pruritus refers to an unpleasant itch sensation on the skin that provokes the desire to scratch.[1] It results from a systemic condition in which the cross talk between keratinocytes, immune cells, and neurons is perturbed.[2] In patients with chronic kidney disease (CKD) and, particularly, patients with end-stage kidney disease (ESKD), uremic pruritis is one of the most common and bothersome manifestations of uremia that signals the ensuing need for renal replacement therapy.[3] The Dialysis Outcomes and Practice Patterns Study (DOPPS) of more than 6000 hemodialysis patients across 17 countries from 2012 to 2015 found that 18% of patients reported being very much or extremely bothered by itching.[4] Among those patients very much or extremely bothered by itching, 58% reported being depressed about the itching, 45% reported the itching made it hard to work, and 35% reported the itching reduced their desire to be with other people.[4] Yet, despite the significant impact on work and social life, 18% of patients very much or extremely bothered by itching reported taking no medication to relieve their symptoms.[4]

Uremic pruritus therapies remain an unmet clinical need, ranking among patients' top research priorities. Its molecular underpinnings, however, remain largely unknown. A lack of animal models in which pruritus can be studied in the context of CKD and/or dialysis has limited our capacity to understand and treat this condition.[5] Recent advancements in our comprehension of related pruritic diseases (eg, cholestatic pruritus) have translated into novel strategies for pruritus management, some of which have the potential to become effective treatments for uremic pruritus.[6,7] However, a clear void remains in bridging the basic understanding of its

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pathogenesis at the bench with effective therapies that offer relief to patients with CKD at the bedside. In this review, we summarize insights into the pathophysiology of uremic pruritus and provide a comprehensive description of the current and emerging pharmacological and nonpharmacological treatment options. We suggest feasible and innovative means to address related research in a more specific, patient-oriented fashion. Finally, we rationalize patient sex as an overlooked biological variable in uremic pruritus and propose that its consideration in future studies may contribute to more tailored management.

Methods

A comprehensive narrative review was conducted to explore the molecular mechanisms underlying uremic pruritus, as well as the evidence supporting pharmacological and nonpharmacological treatments for uremic pruritus. We used PubMed searches of English, peer-reviewed articles using keywords "uremic pruritus" and "pruritus" and searched for nephrology-related studies of itch. Additional subsearches related to the influence of sex on pruritus were also performed, and a data table was generated. Information was amalgamated into a narrative review, which was internally peer reviewed as part of the Kidney Research Scientist Core Education and National Training (KRESCENT) program prior to external peer review.

Review

Differential Diagnosis of Pruritus in Patients With CKD/ESKD

While uremic pruritus affects a large number of patients with CKD and ESKD, clinicians must consider nonuremic causes of pruritus among this population. Nonuremic causes of pruritus include hypersensitivity reactions (eg, contact dermatitis), primary dermatological conditions (eg, atopic dermatitis, psoriasis), infections (eg, tinea corporis, postherpetic neuralgia), infestations (eg, lice, scabies, bed bugs), cholestatic conditions (eg, viral hepatitis, primary biliary cholangitis), and hematological malignancies (eg, Hodgkin lymphoma, cutaneous T-cell lymphoma). Clinical clues into these nonuremic causes include systemic symptoms, appearance of the skin, itch that is new or suddenly worsening, or itch that is refractory to therapy.

Pathophysiology of Uremic Pruritus

Several clinical factors have been associated with uremic pruritus, including hyperparathyroidism, allergic sensitization, neuropathy, and abnormal levels of magnesium, calcium, iron, bile acids, nitric oxide, vitamin A, and parathyroid hormone.[8] The development of itch has largely been attributed to systemic immune responses to hemodialysis, leading to nociceptive responses. Uremic toxins and increased serum levels of C-reactive protein, interleukin (IL)-6, and IL-31 in patients on hemodialysis with pruritus support the inflammatory nature of the disease.[9-12] Proliferation, degranulation, and histamine release by mast cells are considered key events triggering the itch response.[13,14] Interestingly, dialysis membranes may also stress blood cells and induce the release of pruritogenic cytokines,[15] further contributing to this condition.

In pruritus, stimulation of dermal itch receptors or peripheral nerve endings generates impulses that are transmitted centrally via C-fibers.[16,17] Endogenous opioids activate mast cells, promoting histamine release and undesirable effects such as urticaria and tachycardia.[13] An imbalance in the levels and activation of opioid receptors in dermal cells, lymphocytes, peripheral nerves, and brain accentuates itch and predisposes patients to scratch.[18] Antihistamine medications often fail to attenuate itch, suggesting a role of histamine-independent mechanisms in uremic pruritus.[17,19] In this regard, receptors for morphine, endothelin-1, chloroquine, and IL-13/31 may mediate the itch sensation.[9,13]

The precise molecular underpinnings that drive the pathophysiology of uremic pruritus remain unclear. The lack of reliable experimental models has resulted in a paucity of research studies investigating the cross talk between mast cells, keratinocytes, and neurons in a more physiological "uremic-like" setting. Thus, it is not currently possible to investigate uremic-specific mechanisms in the laboratory and to differentiate them from mechanisms more generally involved in other itch-related disorders. Encouragingly, some of the "anti-itch" pharmacological and nonpharmacological therapeutic approaches that are described in the following section have shown promising effects in patients with uremic disease. The optimization of dialysis conditions and CKD-related mineral and bone disease (CKD-MBD) parameters is currently the only treatment that directly targets itch pathogenesis. Most of these promising strategies focus on the consequence rather than the cause of uremic pruritus and aim to target the nociceptive phase of the disease. None have shown the capacity to fully ameliorate inflammation, which is likely the trigger to the perpetuation of itch. A better understanding of the current therapeutic approaches to uremic pruritus at the bedside, and the molecular mechanisms targeted by these strategies, is required to identify the key mechanisms and cell types warranting further investigation at the bench.

Therapies for Uremic Pruritus and Their Molecular Mechanisms

High-quality evidence in the management of uremic pruritus remains lacking, with many recommendations based on expert opinion or studies involving small numbers of patients. Here, we aim to summarize the evidence of classic and emerging pharmacological treatments, their molecular bases where available, and contraindications to their current use in the clinic (summarized jointly in Table 1 and Figure 1) to provide insight into their suitability for patients with CKD and areas warranting further investigation.

Table 1. Treatment Options for Uremic Pruritus.

Treatment	Mechanism of action	Limitations/drawbacks
Dialysis optimization		
↑ Dialysis dose (↑ Kt/V)	↑ Clearance of uremic toxins[20-23]	
High flux dialyzer	↑ Clearance of uremic toxins[24]	
Optimization of CKD-MBD parameters		
Parathyroidectomy	Reduction in parathyroid hormone and calcium-phosphate product; mechanism remains unclear[25,26]	
Topical therapies		
Emollients	Reduce xerosis	
Analgesics (eg, Capsaicin, Pramoxine)	Analgesia	Insufficient evidence of efficacy of Capsaicin in CKD/ESKD patients[27]
Immunosuppressant (eg, Tacrolimus)	Suppression of immune-mediated exacerbation of dry skin, inflammation, and pruritus	Evidence indicates Tacrolimus is ineffective in CKD/ESKD patients[28] FDA warning (risk of dermatological malignancies)
Cannabinoids (THC, CBD)	Analgesia, ↓ histamine-independent inflammation; exert effects on ionotropic TRPV1-4, TRPA1, and TRPM8 channels[29]	Insufficient evidence of efficacy in CKD/ESKD patients[30,31] Inconsistent CBD/THC content pharmacokinetics not well understood
Systemic pharmacological interventions		
Antihistamines	Block effects of histamine, reducing its contribution to itch	Evidence indicates ineffective in CKD/ESKD patients[32,33]
Anticonvulsants (Gabapentin, Pregabalin)	Negatively modulate voltage-gated calcium channels and calcitonin gene–related peptide release[34]; possible modulation of μ-opioid receptors[35]	Neurological side effects such as dizziness and somnolence reported[36]
Opioid receptor modulators		
μ-antagonist (Naltrexone, Naloxone)	Inhibits μ-opioid receptor, a mediator of itch	Effective in a subset of patients[37] Sedation, gastrointestinal complications, among other side effects Dependency risk
Selective κ-agonist (Nalfurafine)	Selective central activation of the κ-receptor,[38] which contributes to anti-itch sensation (research underway to determine mechanism of this biased agonism[39,40])	Only approved in Japan,[6,41,42] US randomized controlled trial terminated due to insufficient enrollment[43]
Peripheral κ-agonist (Difelikefalin)	Activation of peripheral κ-receptors (does not penetrate the blood-brain barrier)[7]	Increased diarrhea, dizziness, vomiting No independent trials, not FDA approved
Dual κ-agonist/μ-antagonist (Nalbuphine, Butorphanol)	Dual targeting reduces adverse dysphoria that κ-agonism can contribute to or the sedation associated with μ-antagonism	Absent or limited number of controlled, randomized, placebo-controlled trials[44-46]
Neurokinin-1 inhibitors (Aprepitant, Serlopitant)	Blocks substance P-mediated itch sensation in histamine-independent pruritus[47]	Interactions of Aprepitant with other medications restrict use in some patients[48,49] Limited number of studies in uremic pruritus patients

Note. CKD = chronic kidney disease; MBD = mineral and bone disorder; ESKD = end-stage kidney disease; FDA = Federal Drug Agency; THC = tetrahydrocannabinol; CBD = cannabidiol; TRP = transient receptor potential.

Dialysis optimization. As it is likely that uremic toxins considerably contribute to the development of uremic pruritus, ensuring that patients are adequately dialyzed often leads to a modest improvement in symptoms. For patients who have progressed to ESKD requiring dialysis, increasing the dose of hemo- or peritoneal dialysis may reduce itch.[20-22] For instance, a prospective study among 111 patients on maintenance hemodialysis showed that achieving a Kt/V ≥ 1.5 was associated with a reduction in pruritus intensity compared with a Kt/V < 1.5.[22] The use of high-flux versus low-flux dialyzers can further alleviate symptoms.[23] Finally, the use of bioincompatible hemodialysis membranes may contribute to uremic pruritus in some patients. In these instances, transition to a biocompatible membrane (eg, polymethylmetacrylate) may reduce its severity.[24]

Optimization of CKD-MBD parameters. Several small studies have suggested that an elevated calcium-phosphate product and secondary/tertiary hyperparathyroidism contribute to uremic itch.[25,26] The largest study included a relatively small

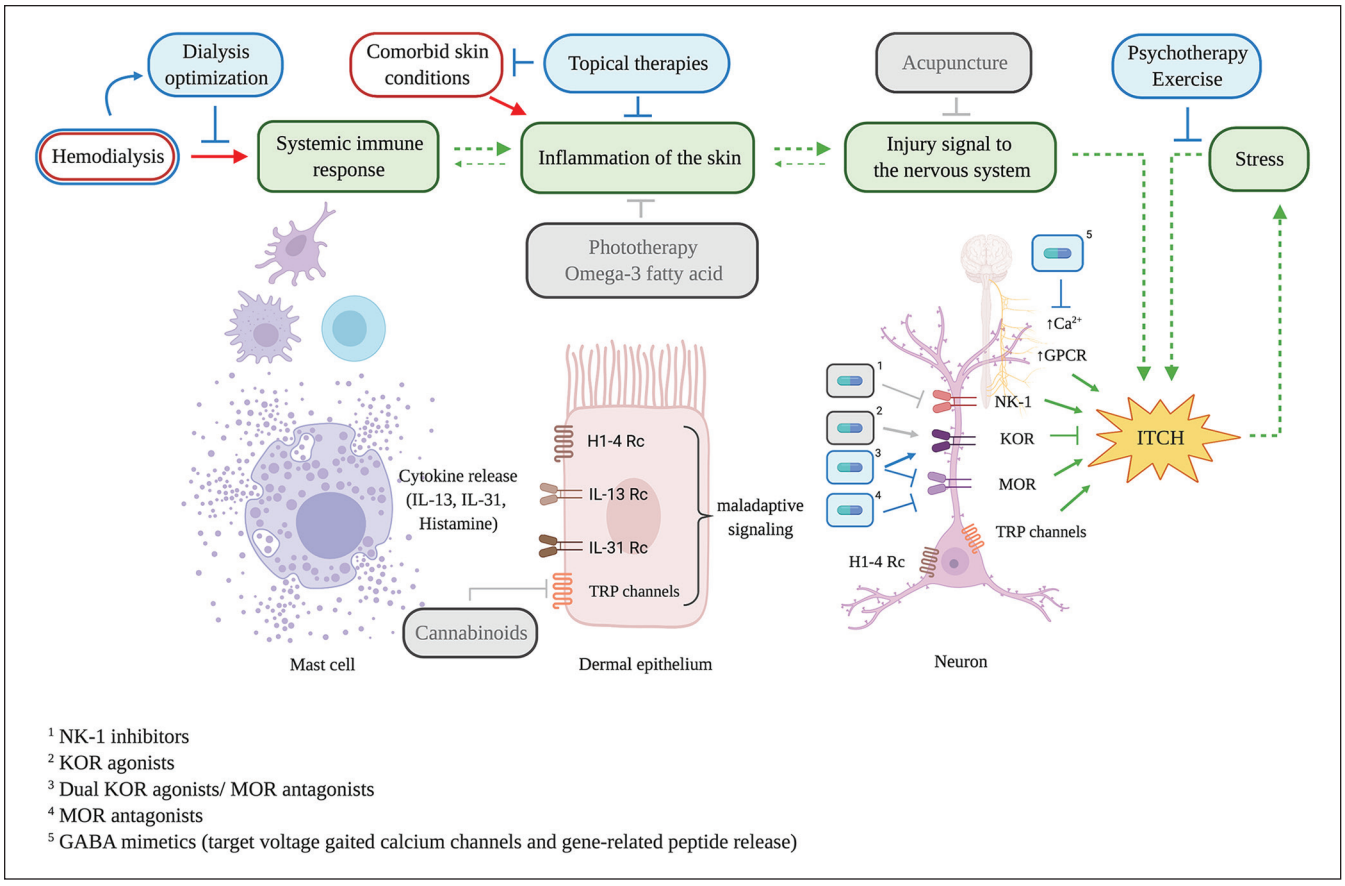

Figure 1. Uremic pruritus pathophysiology and management strategies. Hemodialysis may lead to the development of uremic pruritus in a mechanism that involves mast cell activation, maladaptive dermal cell signaling and the induction of the itch sensation via various nociceptive receptors within the peripheral and central nervous systems. Current (blue) and prospective (grey) uremic pruritus management strategies target various junctures of this mechanism, including receptors identified as itch modulators, which can be targeted by systemic pharmacological means (capsules; sharp-ended arrow = activation, flat-ended arrow = inhibition).
Note. Ca = calcium; GPCR = G protein-coupled receptor; NK-1 = neurokinin-1; KOR = κ-opioid receptor; MOR = μ-opioid receptors; TRP = transient receptor potential; GABA = gamma-aminobutyric acid.

number of patients on hemodialysis (37) who underwent parathyroidectomy and experienced significant reductions in both the calcium-phosphate product and parathyroid hormone, with significant reduction in pruritus intensity within 1 week of surgery.[25] There remains a lack of evidence that other standard CKD-MBD treatments such as phosphate binders, activated vitamin D analogues, or Cinacalcet are effective in reducing uremic pruritus.

Kidney transplantation. Kidney transplantation, which substantially increases clearance of uremic toxins and improves CKD-MBD parameters beyond that of dialysis in most cases, relieves pruritus symptoms in the vast majority of cases. For instance, a prospective cohort study of 49 patients with uremic pruritus (and associated histological skin changes) who underwent successful kidney transplantation showed consistent resolution of the uremic pruritus skin changes following restoration of kidney function.[50] Thus, kidney transplantation should be considered in eligible patients suffering from uremic pruritus.

Topical therapies

Emollients and analgesics. Dry skin is exceedingly common in CKD and ESKD.[32,51] Emollients, particularly those with a high water content, are effective in reducing pruritus symptoms and improving quality of life.[51-53] In addition to emollients, topical analgesics, such as the neuropeptide-releasing agents Capsaicin and Pramoxine, are often prescribed to alleviate pruritus.[54-56] These function by blocking both the initiation and conduction of nerve impulses, leading to numbness. However, a systemic review of interventional trials, including 3 of which were for the treatment of hemodialysis-related pruritus, provided insufficient data for the efficacy of Capsaicin as a treatment.[27] Similarly, although early evidence suggested that topical Tacrolimus, an immunosuppressant, may be effective in reducing pruritus, its use is now discouraged due to the evidence of lack of efficacy[57] and a black box warning from the US Food and Drug Administration related to a potential increased risk of dermatological malignancies.

Cannabinoids. With the recent legalization of recreational marijuana in Canada and several US states, patients increasingly have access to cannabidiol (CBD)- and tetrahydrocannabinol (THC)-containing compounds, making this an important area for new research. A single study of 21 ESKD patients with uremic pruritus suggests a potential benefit of topical creams containing cannabinoids.[58] This study reported that after 3 weeks of therapy, 38% of patients experienced complete resolution of their pruritus symptoms while 81% experienced an improvement in their symptoms. The mechanism of action of cannabinoids in treating itch appears to be their ability to target inflammation and pain. The THC and CBD bind ionotropic transient receptor potential (TRP) ion channels (TRPV1-4, TRPA1, and TRPM8), which have been shown to play a role in the complex cutaneous intercellular communication network between epidermal keratinocytes, immune cells, and sensory nerves, leading to itch sensation.[29] Although there is promise in the possibility that antagonizing or desensitizing such TRP channels (using well-selected topically applied phytocannabinoids), it is not yet possible to draw conclusions from the few studies performed due to limitations in the reporting percentages of THC and CBD tested, small samples sizes, and short duration of studies.[30,31] Furthermore, as the long-term effect of cannabis use, especially in CKD, remains unclear, caution should be made in recommendation of use of its medicinal properties until further independent and controlled studies are undertaken.

Systematic pharmacological therapies

Antihistamines. Despite their common use, there is a lack of data on the efficacy of oral antihistamines in treating uremic pruritus. In fact, the limited data available suggest that these medications may be less effective in the CKD/ESKD population.[32,33] In these studies, oral antihistamines provided no benefit above emollients alone, and their antipruritic effects were diminished with advanced renal disease. This is likely due to the increasingly accepted hypothesis that uremic itch is a histamine-independent phenomenon.

Gabapentin/pregabalin. The neuropathic/anticonvulsant agents Gabapentin and Pregabalin are the mostly widely studied systemic medications for treating uremic pruritus. They were initially designed to mimic the neurotransmitter gamma-aminobutyric acid (GABA); however, they do not bind to GABA receptors. Rather, their mechanism of action likely involves negative modulation of the alpha 2 delta subunit of voltage-gated calcium channels and/or inhibition of the release of calcitonin gene–related peptide (a mediator of itch) from primary afferent neurons.[34] It has also been hypothesized that modulation of μ-opioid receptors (MORs) may be involved in its anti-itch properties.[35] Across numerous studies, Gabapentin and Pregabalin, administered in reduced doses (due to renal insufficiency), have repeatedly been shown to be effective in reducing pruritus in patients undergoing dialysis.[57,59-68] When compared with one another, there is no significant difference in efficacy between Gabapentin and Pregabalin[60]; however, if one of these medications is ineffective, patients may receive benefit from being switched to the other.[62] Adherence to these reduced doses in patients with renal insufficiency are essential, as side effects from somnolence and unsteadiness on the feet to mononucleosis have been reported in these populations.[36]

Opioid receptor modulators. Opioid-based interventions are increasingly recognized as effective in reducing pruritus symptoms, and their refinement remains a frontier in uremic pruritus treatment. Opioid receptors collectively contribute to a wide range of physiological and pathophysiological activities, including mediation of neurological sensations such as pain modulation,[69] which occurs collectively through MOR, δ-opioid receptor (DOR), and κ-opioid receptor (KOR) (reviewed thoroughly elsewhere).[70] An imbalance of μ and κ receptors has been hypothesized to contribute to uremic pruritus[71] as well as other forms of chronic itch.[72] When stimulated, the μ-receptor promotes pruritus, whereas the κ-receptor inhibits it. More recently, selective KOR agonists (Nalfurafine [TRK-820]; approved in Japan).[6,41,42] and Difelikefalin (CR845; stage III clinical trial complete)[7] have become an attractive target for inhibition of itch over MOR antagonists (such as Naltrexone, Naloxone), which appear to be effective in only a subset of patients with frequent adverse effects (primarily gastrointestinal).[37,73] A major benefit to the use of KOR agonists is that they are physiologically safe and do not promote euphoria,[74] limiting the likelihood of abuse. Recently, a large double-blind, placebo-controlled, randomized controlled, phase 3 trial of intravenous Difelikefalin was completed. Results demonstrated a significant decrease in pruritus based on a numerical rating scale compared with placebo (52% vs 31% improvement) as well as an improvement in quality of life in the Difelikefalin group,[7] garnering optimism within the field about its potential impact on treating uremic pruritus. However, independent verification of efficacy and long-term safety data for Difelikefalin is still needed before mainstream use.

The molecular mechanism underlying KOR activity and itch relief is not well understood, but basic research is emerging around the signaling events that contribute to anti-itch action downstream of KOR activation. It has been suggested that the activation of KOR induces an anti-inflammatory response through the downregulation of cytokine, chemokine, and chemokine receptor expression, which may contribute to their antipruritic effects.[75] A recent study also found evidence that KOR activation attenuates histamine-independent acute and chronic itch in mice in a mechanism that involves another G protein-coupled receptor (GPCR) that functions in itch sensation, the gastrin-releasing peptide receptor,[76-78] via a calcium-independent phospholipase C-protein kinase C-δ pathway.[78] To our knowledge, the contribution of gastrin-releasing peptide receptor signaling to

the development of uremic pruritus remains fully unexplored and represents a new avenue for future investigations into its treatment.

NK-1 inhibitors. The substance P(SP)/neurokinin-1 (NK-1) pathway is important in histamine-independent pruritus (comprehensive recent review elsewhere).[47] Inhibition of NK-1 receptors, the primary receptor of SP, has been shown to decrease the perception of itch. Aprepitant, an NK-1 inhibitor, has demonstrated efficacy in the treatment of other pruritus-related disorders, and it was at one point identified as a promising new option for the treatment of uremic pruritus. However, interactions with other medications restrict its use in some patients. Serlopitant, another NK-1 inhibitor, was successful in a recent phase II clinical trial of reducing pruritus in patients with chronic itch with minimal adverse effects.[48] However, enrollment of patients with uremic or cholestatic pruritus was minimized to reduce possible confounding effects from these comorbidities. Thus, it remains unknown whether Serlopitant might be successful for alleviating uremic pruritus. An earlier, smaller study using Serlopitant in patients, including several with CKD,[49] showed a strong inhibition of pruritus with few adverse effects. However, the study was a nonrandomized trial and had very few participants, making it difficult to draw conclusions. Increased investigation of the efficacy of NK-1 inhibitors in uremic pruritus will hopefully shed light on its therapeutic potential in the near future.

Nonpharmacological therapies. Research on nonpharmacological therapies for uremic itch in CKD has focused on phototherapy, acupuncture, omega-3 fatty acid intake, aromatherapy, and exercise, although evidence is generally limited to small studies with methodological issues that limit conclusions to be drawn. Phototherapy is believed to be beneficial due to cutaneous immunosuppression at the cellular level, which is beneficial for skin diseases (eg, psoriasis) that have T-cell hyperactivity.[79] A systematic review identified 4 randomized controlled trials examining the effects of phototherapy in patients with CKD stage $\geq$3; the 2 trials examining broadband UV-B therapy found it to be effective compared with ultraviolet light A (UV-A), whereas the other 2 trials examining narrow-band UV-B therapy or far-infrared ray thermal therapy did not report similar benefit.[80] Evidence suggesting UV-B therapy is a safe treatment with no increased risk of skin cancer[79] indicates it can be safely used in populations with CKD. However, larger randomized controlled trials that address limitations in existing evidence, such as inadequate blinding of participants and personnel and selective reporting of results, are needed to confirm its efficacy.

Acupuncture and acupressure are alternative treatments used to reduce pruritus, possibly via parasympathetic activation and positive functional connectivity of the putamen-posterior midcingulate cortex.[81] A systematic review found that, although several randomized controlled trials have reported positive uremic pruritus outcomes associated with acupuncture or acupressure, there was a high risk of bias in the trials[82] and a need for further trials with adequate blinding, appropriate control groups, and systematic allocation.

Omega-3 fatty acid supplementation has been proposed to target uremic pruritus by reducing essential fatty acid deficiency and inflammation.[83] Four studies have reported beneficial effects of omega-3 fatty acid supplementation, including 3 small randomized controlled trials, suggesting larger trials are warranted to better understand its efficacy.[83] In addition, a small number of exploratory studies have investigated the effects of aromatherapy on uremic pruritus severity and reported beneficial effects[84-86]; however, randomized controlled trials are needed to address a lack of randomization and blinding in existing evidence.

Finally, a prospective pre-post study investigated the effects of a 12-week aerobic exercise program on symptom burden and reported improvements in symptoms, including pruritus, after the program.[87] Randomized controlled trials are therefore needed to better understand the impact of exercise on uremic pruritus, given its various other known benefits in patients with CKD. For example, it would be prudent to investigate the impact of intradialytic exercise on uremic pruritus in hemodialysis patients, given that intradialytic exercise is a more feasible approach to exercise for patients that is associated with a reduction in other symptoms, such as restless legs syndrome and fatigue.[88,89] Studies are also needed to understand the mechanisms of the potential effects of exercise.

There are also several unexplored interventions that may have the potential to improve symptom severity and quality of life in people with uremic pruritus. For example, the amplifying effect of stress on the perception of symptoms, including itch, has previously been noted.[90] Psychotherapeutic techniques such as cognitive-behavioral therapy, mindfulness meditation, and relaxation training are purported to reduce symptom burden by interrupting maladaptive automatic thought and behavioral reactions that amplify the experience of an unpleasant symptom stimulus.[90] These approaches have been studied for their effects on symptoms, including pain, fatigue, and pruritus in non-CKD populations, with several studies suggesting positive effects.[91-93] The possibility that stress reduction techniques might be able to reduce the saliency and distress of pruritus therefore warrants further investigation in individuals with CKD. The implementation of routine, systematic symptom assessments in CKD has also been proposed as a way to address underreporting of symptoms in general, identify patients in need of intervention, and trigger more timely and consistent intervention.[94] Studies are currently underway that will shed light on the impact of routine symptom assessment protocols on patient outcomes, including pruritus and other common symptoms of CKD.

Table 2. Clinical Studies Discussing the Effect of Sex on UP in Dialysis Patients.

Study	No. of participants	Dialysis regimen	Country	Sex-related observations
Mistik et al[100]	341	Continuous ambulatory peritoneal dialysis and HD	Turkey	UP ↑ in males
Pisoni et al[101]	21 075	HD only	12 countries (DOPPS registry)	UP ↑ in males
Narita et al[102]	1773	HD only	Japan	UP ↑ in males
Wikström et al[103]	6137	HD only	7 countries (DOPPS registry)	UP ↑ in males
Nahidi et al[115]	26	HD only	Iran	UP ↑ in males (NS)
Szepietowski et al[108]	130	HD only	Poland	UP ↑ in females
Dar et al[107]	100	HD only	Pakistan	UP ↑ in females
Ko et al[22]	111	HD only	Taiwan	UP ↑ in females
Ramakrishnan et al[104]	68 426	HD and PD	United States	Females tend to report more high itch intensity scores
Ersoy et al[106]	181	HD only	Turkey	UP ↑ in females (NS)
Jamal et al[105]	100	HD only	Saudi Arabia	UP ↑ in females (NS and subjected to age >45 y)
Ståhle-Bäckdahl et al[114]	28	HD only	Sweden	No difference
Zucker et al[113]	219	HD only	Israel	No difference
Akhyani et al[8]	167	HD only	Iran	No difference
Razeghi et al[112]	34	HD only	Iran	No difference
Mathur et al[111]	103	HD only	United States	No difference
Hu et al[110]	382	HD, PD, and chronic kidney disease w/o dialysis	China	No difference
Hu et al[109]	11 800	HD and PD	17 countries	No difference

Note. UP = uremic pruritus; HD = hemodialysis; DOPPS = Dialysis Outcomes and Practice Patterns Study; NS = nonsignificant; PD = peritoneal dialysis.

Sex Differences in Uremic Pruritus

Sex is increasingly recognized as a key variable in the study of diseases,[95] including CKD[96] and several skin disorders.[97-99] Although the role of sex in uremic pruritus has not been a focus of published studies, we have identified 18 reports discussing the role of patient sex on its incidence and severity (Table 2). Five of these studies suggest an association between male sex and the development of uremic pruritus.[17,71,100-103] To our knowledge, the largest effort in which the effect of sex was evaluated was a retrospective analysis of 21 075 patients on hemodialysis from 12 countries; Pisoni et al observed that males showed higher odds of having moderate to extreme pruritus.[101] Male sex was also identified as a predictor of pruritus in a study of 6137 patients on hemodialysis across 7 countries,[103] and as an independent risk factor for severe uremic pruritus in prospective studies of 1773[102] and 341 patients on hemodialysis.[100] Other studies defend that female sex predisposes to uremic pruritus,[22,104-108] but most were limited by small sample size. By contrast, 7 studies concluded that sex does not influence its development.[8,109-114] Six of these studies were limited by few patients on dialysis, unadjusted analyses, and/or imbalanced male-to-female ratio.[8,110-114]

Effect of sex on the pathogenesis of disease. Interest in the inclusion of sex as a consideration in uremic pruritus disease is bolstered by well-established relationships between sex and itch-related mechanisms. Mast cells express androgen and estrogen receptors and respond to sex hormones,[116-118] and mast cell number and degranulation are sex-dependent.[119,120] Moreover, male and female mast cells are transcriptionally different and respond differently to stress.[121] In vitro, testosterone induces IL-33 in male-derived, but not female-derived, mast cells.[122] Androgen receptor signaling is similarly linked to IL-33-mediated activation of type 2 innate lymphoid (ILC2) cells via the suppression of tumorigenicity 2 receptor (ST2), a mechanism that might also participate in uremic pruritus.[122-124] Upregulation of the IL-33/ST2 axis by androgens stops Th17 immune cells from triggering destructive responses and may be protective in autoimmunity.[122,125] However, excessive androgen/IL-33-mediated mast cell degranulation could exacerbate histamine and cytokine secretion and play a pathogenic role in its development. Further exploration of these mechanisms and consideration of their bearing on the sex-related differences in uremic pruritus may provide an opportunity for more target therapies in the future.

Effect of sex on the opioid-cannabinoid system. Levels and localization of MOR, DOR, and KOR vary across sexes,[126-128] and sex hormones play a crucial role on their regulation.[129] For example, MOR activation by oxycodone administration

promotes a sex-specific hippocampal redistribution of opioid receptors,[126] and chronic morphine exposure induces MOR mobilization from the membrane to the cytoplasm exclusively in male rat neurons.[127] Age-dependent changes in the KOR system are also sex-specific, and more pronounced in males, which were also more altered on administration of the KOR agonist U69593.[128] The GPCR signaling (likely involved in antipruritogenic actions of KOR) overlaps with these sex hormone–related mechanisms.[130] Estrogens trigger extranuclear signaling on ligation to membrane G-coupled estrogen receptors,[131] leading to calcium release, cyclic adenosine monophosphate fluctuations, and induction of extracellular receptor kinase and phosphoinositide 3-kinase/protein kinase B signaling.[28,132-134] Reinforcing this concept in relation to the cannabinoid system, estrogens have shown to increase neural TRPV1 expression and sensitization and to prevent capsaicin-induced TRPV1 receptor desensitization. Androgens also induce GPCR-related pathways via the GPCR family member AGPRC6A.[38,39] Supporting the link between sex, GPCR, and opioids, gene-by-sex interaction analysis identified that polymorphisms of the G-coupled receptor, adhesion G protein-coupled receptor V1, influenced the risk of opioid dependence in African American men.[126] By sitting at the nexus between opioid receptor and sex hormone-induced pathways, GPCR-related mechanisms could represent targets for a sex-directed treatment of uremic pruritus.

Effect of sex on the NK-1 system. Sex affects the levels, distribution, and activation of the SP/NK-1 pathway and pain receptors involved in uremic pruritus.[135-140] Female subjects display a higher concentration of SP before and after exposure to allergens.[135] In agreement, female rats show increased SP release and NK-1 internalization in sensory neurons compared with male counterparts. This effect was directly linked to the actions of estradiol and may contribute to sex differences in central pain sensitization.[136] Female steroids also regulate the sensitivity of mast cells to SP.[141] In turn, androgen administration to female rats reduced SP activity in the pituitary gland.[142] The pattern of NK-1 distribution is also sex-specific. With increasing age, male sex was associated with a decrease in NK-1 availability in the amygdala and temporal cortex, whereas females had lower NK-1 in the thalamus.[138]

The effect of sex on the pharmacological modulation of the SP/NK-1 pathway has also been studied.[130,143-145] In a mouse model of acute pruritus, the desire to scratch induced by SP administration did not differ between sexes.[144] In contrast, data from human studies suggest that females benefit more than males from aprepitant-mediated NK-1 inhibition. In these studies, aprepitant was given to minimize nausea and vomiting after surgery or cisplatin-induced chemotherapy.[130,144] Along these lines, antagonism of NK-1, but not NK-2 signaling, attenuated opioid-mediated contact hypersensitivity to a greater extent in female rats.[145] The upregulation of SP associated with female sex and estrogens may explain, at least in part, the more evident response to NK-1 inhibition in female subjects. However, additional research is needed to evaluate the role of sex in the pharmacological modulation of itch- and pain-related pathways in the setting of uremic pruritus.

Consideration of race in reporting of sex differences in uremic pruritus. A systematic review and meta-analysis of 42 studies revealed that the prevalence of uremic pruritus among adult dialysis patients was higher in China and not influenced by sex.[109] It should be noted that this meta-analysis exhibited several key limitations, including inconsistency in the reported number of studies, predominance of studies of small sample size, and inclusion of articles from nonindexed journals. The more predominant representation of Asian countries in the analysis may suggest that ethnicity may influence sex effects on uremic pruritus. Supporting this idea, it is generally accepted that the effect of sex in CKD is influenced by ethnicity and other factors such as age, diabetes/hypertension, and lifestyle.[146-149] These observations may explain the discrepancies observed in smaller studies. Nephrologists recognize that patients of all races are susceptible to develop uremic pruritus.[150] However, racial differences in the composition and functions of skin have been associated with differences in skin reactivity and susceptibility to pathological stimuli,[126] reinforcing the importance of considering the effects of race when studying skin disorders such as uremic pruritus. Some evidence points toward Asians being more sensitive to skin irritation than Blacks, Hispanics, or Caucasians, but the molecular reasoning behind this observation is unclear.[127,128] To our knowledge, whether race influences the severity of uremic pruritus has not been yet explored in well-balanced studies. As an example, in a longitudinal study in patients on hemodialysis, Mathur and colleagues reported that race did not play a role in the severity of uremic pruritus. However, Asian ethnicities were not numerically represented in the patient cohort, which was dominated by African American (68%) and Caucasian (32%) individuals.[111] Overall, sex[104,129,131-133] and race[134] differences have been noted on the perception of itch, the emotional impact of pruritus, and the subject ability to report discomfort, and it is possible that both influence data outcomes. Prospective, nation-wide studies should be conducted in race- and sex-balanced cohorts of patients with uremic pruritus to directly evaluate these important variables in an adjusted fashion.

Conclusion and Future Directions

Uremic pruritus is a common comorbidity in patients with CKD and is associated with reduced quality of life and increased mortality. No formal published guidelines for the treatment of uremic pruritus exist, and data supporting present therapies remain limited. Thus, there remains no clear algorithm to guide clinicians on how best to manage this condition. As it is probable that the pathogenesis of uremic

pruritus is multifactorial, a combination of pharmacological and nonpharmacological therapies, which remain a largely untapped resource, likely provides the best current treatment strategy for patients.

Recent evidence argues that research efforts focus on further understanding the role of systemic inflammation and pain receptor function in uremic pruritus development and management. Lessons can be learned from innovative research approaches that enable the study of the interplay between different cell types in bioengineered models that mimic physiological environments (eg, organotypic 3-dimensional models of human skin and immune cells).[127,128] The development of these in vitro models specific to uremic conditions would serve to enhance our understanding of the cross talk between skin cells, neurons, and patient-derived immune cells and the reasons behind the sex-specific differences seen with uremic pruritus. This may allow for the identification of novel treatment targets specific to the initial inflammatory activation of skin cells, prior to the perpetuation of the itch response.

Efforts toward the understanding of nociceptive responses have already identified roles for cannabinoid-responsive, gastrin-releasing peptide receptor (GRPR), NK-1, and opioid receptors in chronic pruritus. Initial reports have highlighted modulation of many of these pathways as promising uremic pruritus treatments; however, transformation of these preliminary discoveries to genuine advancements at the bedside remains mired by the absence of independent, well-controlled, widespread trials with adequate sample sizes. Given the prevalence of uremic pruritus in patients suffering with CKD, we implore groups to sequel initial efforts on prospective therapies with well-designed trials and to provide retrospective analyses of their efficacy. Only then will we delve deeper than the surface in the treatment of uremic pruritus.

List of Abbreviations

CBD, cannabidiol; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–metabolic bone disorder; DOR, δ-opioid receptor; ESKD, end-stage kidney disease; GABA, gamma-aminobutyric acid; GPCR, G protein-coupled receptor; HD, hemodialysis; KOR, κ-opioid receptor; MOR, μ-opioid receptor; NK-1, neurokinin-1; PD, peritoneal dialysis; PKC, protein kinase C; PTH, parathyroid hormone; SP, substance P; THC, tetrahydrocannabinol; TRP, transient receptor potential.

Ethics Approval and Consent to Participate

No patient consent was required for this narrative review.

Consent for Publication

The authors have consented publication of this article.

Availability of Data and Materials

No additional data or materials are available for this review. Please contact corresponding author with any requests.

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