NARRATIVE REVIEW

An Update on Pruritus Associated With CKD

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The prevalence of chronic kidney disease (CKD) and end-stage renal disease is increasing worldwide. Despite improvements in dialysis methods, including the development of novel biocompatible membranes and ultrapure dialysate, CKD-associated pruritus remains a common and significant public health issue. Not only does this distressing symptom profoundly impact on quality of life and sleep, recent evidence showed that pruritus also was associated with poor patient outcome. Nonetheless, nephrologists and other health care professionals often fail to recognize and adequately address the pruritus associated with CKD. The pathophysiological mechanism of CKD-associated pruritus is poorly defined, and, as a result, the development of specific therapies has proved to be a challenge. The purpose of this review is to highlight the importance of this neglected topic by providing an overview of recent epidemiological studies, outcomes data, proposed pathophysiological mechanisms, and emerging treatment options.

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INDEX WORDS: End-stage renal disease; pruritus; itch; dermatology; patient outcomes; treatment; pathophysiology; epidemiology; chronic kidney disease.

The prevalence and incidence of chronic kidney disease (CKD) has increased drastically during the past several decades worldwide, making it a major public health issue.[1,2] End-stage renal disease is defined as "renal insufficiency requiring dialysis or kidney transplantation for survival."[3] In 2003, there were more than 320,000 people with end-stage renal disease in the United States, and the prevalence is predicted to increase to 650,000 by 2010 and 2 million by 2030.[4-6] Pruritus, often overlooked by nephrologists, primary care physicians, and health care professionals, is one of the most common and distressing cutaneous symptoms of CKD. In patients who already have a compromised lifestyle, this additional nuisance can be a significant problem. Although pruritus was discussed regularly in the literature, the importance of this CKD-associated symptom has waned as physicians became more concerned with achieving numerical adequacy targets for biochemical and blood pressure parameters. The purpose of this review is to provide an overview of recent epidemiological studies, outcomes data, proposed pathophysiological mechanisms, and newer treatment options relating to the pruritus associated with CKD.

NOMENCLATURE AND DEFINITIONS

The itch associated with CKD has long been referred to as "uremic pruritus." However, pruritus is only a manifestation of chronic renal disease because it typically is not observed in patients with acute renal failure. We and others believe that uremic pruritus may be misleading, primarily because there is no true cause–effect relationship with uremia.[7,8] Although the term "uremia-associated pruritus" was proposed,[7] we believe that "CKD-associated pruritus" or "CKD itch" is a more precise nomenclature for this condition.

It also must be noted that CKD-associated pruritus may be difficult to differentiate from pruritus caused by nonrenal comorbidities frequently associated with CKD, such as liver disease (eg, hepatitis B and C infections) and endocrine disorders (eg, hyperthyroidism).[9-12] With such confounding factors, it may be difficult to truly ascertain a case as CKD-associated pruritus and the need for a uniform standardized definition for this complex symptom is emphasized.

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Such a definition also would make estimates of prevalence and trends more valid.

EPIDEMIOLOGICAL CHARACTERISTICS

The prevalence of CKD-associated pruritus varies substantially, ranging from 22% to 90%.[13-17] In the early 1970s, Young et al[15] reported that 85% of dialysis patients were affected by CKD itch. During the past 30 years, the prevalence appears to be decreasing. A German study in 2000 reported that only 22% of hemodialysis patients had pruritus.[14] This decrease was attributed to improvements in dialysis techniques and patient management. However, in the largest and most recent epidemiological study to date (2006), the prevalence of CKD-associated pruritus was 42%.[17] Although this is a lower prevalence than initially reported, pruritus in patients with CKD remains frequent and continues to be a significant public health concern. Although there are a few contradictory reports,[14,16-19] most published reports showed CKD-associated pruritus to be independent of sex, age, ethnicity, type of dialysis, and underlying renal disease.[15,17,19-23]

CLINICAL CHARACTERISTICS

In 2000, Yosipovitch et al[24] developed a questionnaire for the evaluation and measurement of pruritus, based on the McGill Pain Questionnaire. This questionnaire subsequently was tested in 145 hemodialysis patients with CKD-associated pruritus. It proved to be reliable and provided valid data for the sensory, affective, and overall intensity of CKD-associated pruritus.[25] This questionnaire, along with other similar questionnaires, subsequently was used in studies that attempted to characterize clinical features of this distressing symptom.[21,25-27] The development and use of a standardized questionnaire undoubtedly will provide a better understanding of CKD-associated pruritus, possibly facilitating discovery of a pathophysiological mechanism and allowing valid comparisons of different treatment options.

Clinical characteristics of patients with CKD-associated pruritus vary over time and between patients. Although some patients experience intermittent pruritus for only a few minutes each day, others report it continuously throughout the day.[15] Furthermore, this symptom can appear daily, weekly, or monthly, but tends to be more severe at night.[21,25,27] The most prevalent body site affected is the back; however, arms, head, and abdomen also commonly are affected.[21] In addition, the intensity of CKD-associated pruritus shows considerable variation when quantified using a visual analogue scale with a range from 1 to 10 units.[16]

Several studies investigated the effects of daily activities on CKD pruritus.[21,25,27] Although there were contradictory findings between reports, common exacerbating factors appear to include rest, dry skin, heat, sweat, and stress. Major alleviating factors include activity, cold ambient temperatures, and hot or cold showers.

Pruritus was reported to increase just before the hemodialysis treatment and be relieved afterward,[21] possibly explained by dialytic removal of causative molecules (possibly bile acids, urea, and other uremic toxins). Conversely, others reported a greater intensity of itch during or after hemodialysis, possibly explained by hypersensitivity to such components of the extracorpeal circuit as blood tubing, dialysis catheters, cellophane adhesives, and nickel-containing needle tips.[26] Interestingly, hemodialysis with cuprophane dialyzer membranes promoted rapid activation of the complement system (C3a and C5a).[28]

Szepietowski et al[19] (2002) reported that patients dialyzed using polysulfone membranes more commonly experienced pruritus than those using hemophane or cuprophane dialysis membranes. However, in a more recent study, we observed no correlation between pruritus intensity and type of dialysis membrane.[26] In addition, CKD-associated pruritus was reported to completely resolve after renal transplantation,[29] although in our experience, some patients continue to experience pruritus posttransplantation.

EFFECTS AND OUTCOMES

CKD-associated pruritus frequently is a disabling and distressing symptom that has a significant impact on the mental and physical capacity of patients, contributing to daytime fatigue, agitation, and depression.[17,21,27] Pruritus also profoundly impacts on sleep.[17,25,27] Hemodialysis patients who had moderate to extreme itch also reported a significantly greater chance of remaining awake at night, feeling sleepy during the day,

and sensing a lack of sufficient sleep relative to those without itch. Furthermore, nocturnal awakenings and difficulty falling asleep were attributed to CKD-associated pruritus.[25,27]

The sleep disturbance in dialysis patients caused by pruritus may have important effects on patient outcome. In the international Dialysis Outcomes and Practice Patterns Study, which evaluated more than 18,000 patients on hemodialysis therapy, pruritus was associated with a 17% greater mortality risk, an effect that was no longer significant after adjustment for measures of sleep quality.[17] This observation suggests that sleep disturbances may have an important role in the greater mortality risk associated with CKD-associated pruritus and highlights the need for good-quality sleep in patients on dialysis therapy. In the largest population-based study to date, severe CKD-associated pruritus was associated independently with death in Japanese hemodialysis patients.[16] A disturbing aspect of these observations is that both physicians and health care professionals continue to underappreciate and inadequately address pruritus in patients with CKD. Conversely, pruritus is given utmost importance in the setting of hepatic failure and is considered an indication for liver transplantation.[30] Although we do not believe CKD-related pruritus is an indication for early renal transplantation in all patients, it may be indicated in those who have pruritus genuinely refractory to medical management and as a result greatly diminished quality of sleep.

PATHOPHYSIOLOGICAL MECHANISM

The pathophysiological mechanism of CKD-associated pruritus remains poorly understood. Present data point toward central roles for the immune and opioidergic systems.[18] It was postulated that the itch associated with CKD is a manifestation of an immune system derangement that results in a proinflammatory state. In concordance with this theory, such immunomodulators as ultraviolet B (UVB) light,[31] tacrolimus,[32,33] and thalidomide[34] decreased CKD-associated pruritus to some degree. These 3 treatment modalities are known to decrease the production of proinflammatory cytokines through various mechanisms. More specifically, UVB light attenuates T-helper cell type 1 differentiation and decreases interleukin 2 production.[35,36] Thalidomide inhibits T-helper cell type 1 activation by decreasing tumor necrosis factor α levels,[37] whereas tacrolimus suppresses T-lymphocyte activation by inhibiting activity of the phosphorylase enzyme calcineurin.[38] In addition, it was reported that hemodialysis patients with pruritus showed significantly increased T-helper cell type 1 differentiation, as well as greater serum C-reactive protein and interleukin 6 levels.[39] Furthermore, Pisoni et al[17] (2006) recently showed that a white blood cell count greater than $6.7 \times 10^3/\mu L$ ($>7 \times 10^9/L$) is a significant predictor of moderate to severe pruritus in patients on hemodialysis therapy. This study also reported that patients with lower levels of serum albumin, a negative acute-phase reactant, were significantly more likely to have moderate to severe itch.[17] Hemodialysis patients receiving statin therapy were less prone to pruritus, perhaps explained by the capacity of this drug class to decrease serum proinflammatory cytokine and C-reactive protein levels.[26] Of note, inflammation was associated with greater mortality rates in patients on both peritoneal dialysis and hemodialysis therapy,[40,41] potentially providing an explanation linking CKD-associated pruritus with poor patient outcomes.

Imbalance in the endogenous opioidergic system received recent attention in terms of the pathophysiological mechanism of pruritus per se, as well as in patients with CKD-associated pruritus.[42] Different opioid receptors have contrasting effects on pruritus (Fig 1). Both μ-opioid and κ-opioid receptor antagonists can induce itch, whereas μ-receptor antagonists and κ-receptor agonists can decrease it.[43] Kumagai et al[44] (2004) reported an increased ratio of serum β-endorphin to dynorphin A in hemodialysis patients compared with healthy controls, and this ratio increased with severity of pruritus. Dynorphin A is a κ-receptor agonist, whereas β-endorphin is a μ-receptor agonist, suggesting that this imbalance and resulting overactivity of the μ-receptor opioid system has a role in CKD-associated pruritus.[44] Although there are conflicting reports,[14] naltrexone, a μ-receptor antagonist, was reported to show short-term efficacy in decreasing CKD-associated pruritus in hemodialysis patients.[45] In addition, nalfurafine, a κ-receptor agonist, significantly decreased pruritus

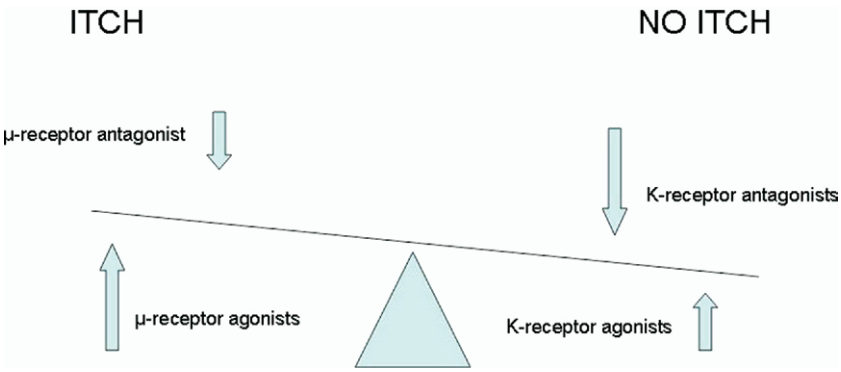

Figure 1. Contrasting effects of different opioids on pruritus: the proposed imbalance of opioids in the pathophysiological mechanism of chronic kidney disease–associated pruritus.

and excoriations in hemodialysis patients in a double-blind placebo-controlled clinical trial.[46]

A number of studies showed increased serum calcium and phosphate levels in patients with CKD-associated pruritus.[16,17,26,47,48] This can lead to the formation of precipitated calcium phosphate crystals, which correlated with itch intensity in hemodialysis patients,[49] which, in turn, may stimulate itch receptors. Momose et al[50] (2004) recently showed that calcium ion concentrations were greatest in the deepest layer of the epidermis, suggesting that disrupted calcium ion gradient in the skin may be involved in the development and/or maintenance of CKD-associated pruritus. In addition, Duque et al[26] (2006) showed that pruritus in hemodialysis patients was associated not only with greater serum calcium levels, but also with higher Kt/V, an expression of small-molecular-weight uremic toxin clearance. This is in direct contrast to the empiric observation that some pruritic dialysis patients have temporary relief of itch immediately after dialysis.

Recent neurophysiological research has enabled a more accurate definition of the neural pathways of itch. Microneurographic studies of human C nerve fibers showed that a particular subgroup of mechanically insensitive C-fibers in human skin discharged a pattern that matched the perception of itch.[51] These nerve fibers activate spinal neurons in lamina I of the dorsal horns, which project to the thalamus.[52] Histamine-induced pruritus was significantly greater in hemodialysis patients with pruritus than in nonpruritic hemodialysis patients and healthy subjects, indicating augmented sensitivity to pruritogens in these patients.[53] Furthermore, indirect immunohistochemistry showed neuron-specific enolase immunoreactive nerve fibers sprouting throughout the epidermis in 12 hemodialysis patients, 9 with pruritus, but in none of 15 controls.[54] Although there are contradictory reports,[55] this finding suggests that hemodialysis patients and possibly specifically those with pruritus develop an abnormal pattern of cutaneous innervation. Furthermore, gabapentin, an anticonvulsant used for neuropathetic pain, was highly effective in the treatment of patients with CKD-associated pruritus.[56,57] These observations may be interpreted as supporting a neuropathic mechanism for CKD-associated pruritus.

Many other factors have been considered in the pathophysiological process of CKD-associated pruritus, including xerosis,[15,58,59] abnormalities in afferent pain fibers,[60] hypervitaminosis A,[61] cutaneous divalent ion content,[62] alterations in number of skin mast cells,[63] allergic sensitization,[64] and inadequate removal of middle-molecular-weight uremic toxins.[63] Additional factors implicated include high serum levels of magnesium,[47] parathyroid hormone,[63,65] aluminum,[49] β_2-microglobulin,[16] bile acids,[66] blood urea nitrogen,[16] histamine,[67,68] and substance P.[69] Despite this vast array of possible explanations, none consistently have been demonstrated to be the underlying cause of the pruritus associated with CKD. Large epidemiological studies ultimately may facilitate our understanding of the elusive pathophysiological process of this distressing symptom.

TREATMENT

The evaluation and management of patients with CKD-associated pruritus can be challenging. Based on our own experience, important

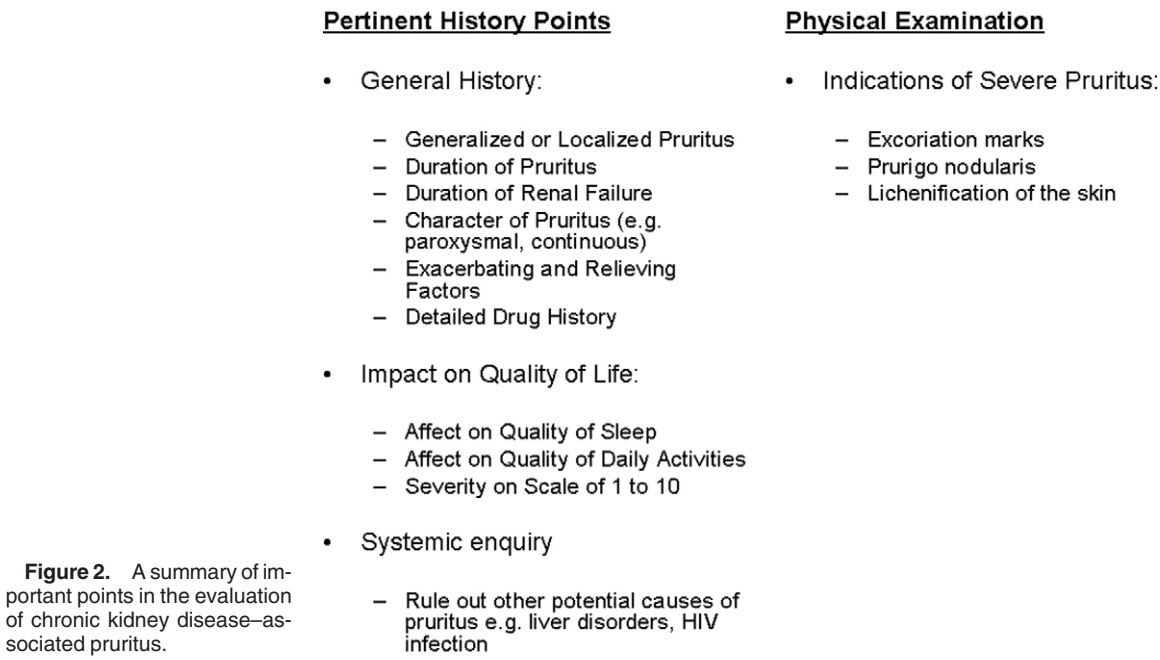

Figure 2. A summary of important points in the evaluation of chronic kidney disease–associated pruritus.

aspects of evaluation and a suggested approach to treatment are shown in Figs 2 and 3, respectively. Because of the poorly understood pathophysiological mechanism, the development of effective treatment modalities for patients with CKD-associated pruritus has proved to be particularly difficult. Numerous therapies were attempted based on the potential underlying mechanisms and are listed in Table 1. However, no definitive therapy has been established from this myriad of therapeutic options. Outlined next are some emerging treatment alternatives for patients with CKD-associated pruritus.

Topical Treatments

Emollients were shown to be beneficial in patients with CKD-associated pruritus[58] and should be used as first-line treatment in the opinion of the authors.[83] Okada and Matsumoto[84] (2004) recently reported that emollients with high water content decreased itch and xerosis in hemodialysis patients with mild pruritus, while also improving their men-

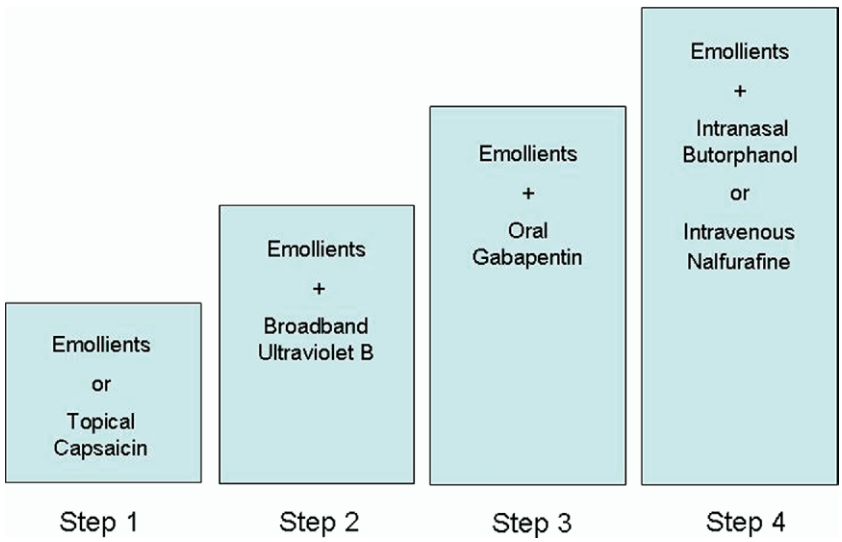

Figure 3. A proposed treatment ladder for chronic kidney disease–associated pruritus.

Table 1. Treatment Options for Chronic Kidney Disease–Associated Pruritus

Topical Treatments	Systemic Treatments	Dialysis Techniques
Skin emollients[58] (B)	Gabapentin[56] (A)	Intensive efficient dialysis[79] (C)
Capsaicin[70] (A)	Nalfurafine[46] (A)	Magnesium-free dialysis[80] (A)
Bath oil therapy containing polidocanol[71] (B)	Antihistamines[72] (A)	
	Naltrexone[45] (A)	
	Oral activated charcoal[73] (A)	
	Ondansetron[74] (A)	
	Cholestyramine[75] (A)	
	Erythropoietin[76] (A)	
	Ketotifen[67] (D)	
	Nicergoline[77] (A)	
	Thalidomide[34] (A)	
	Intravenous lidocaine[78] (A)	

Surgical Treatments	Physical Treatments	Alternative Therapies
Parathyroidectomy[81] (B)	Ultraviolet B therapy[31] (B)	Electrical acupuncture[82] (C)

Note: Level of evidence in parentheses for each trial defined as follows: A, double-blind study; B, clinical trial containing 20 or more subjects; C, clinical trial containing fewer than 20 subjects; and D, case series containing 5 or more subjects.

tal well-being. Although there were contradictory reports regarding the relationship between degree of xerosis and pruritus,[85,86] an increase in water content of the stratum corneum after emollient application may be clinically important in patients with CKD-associated itch. Szepietowski et al[87] (2005) showed that a topical preparation containing structured natural lipids and endocannabinoids could be of benefit in controlling pruritus and xerosis in maintenance hemodialysis patients. Of 21 patients recruited in this study, 14 and 17 patients reported complete resolution of pruritus and xerosis after 3 weeks of treatment, respectively. The investigators suggested that the antipruritic action might be related to the endocannabinoids, as well as the moisturizing effect of the cream.[87]

Essential fatty acids and their derivatives are necessary for normal cutaneous function.[88] Tamimi et al[89] (1999) found that primrose oil rich in the essential fatty acid γ-linolenic acid (GLA) may be beneficial in alleviating CKD-associated pruritus, although findings did not reach statistical significance. Chen et al[90] (2006) reported that topical GLA-rich cream had a significant antipruritic effect in 17 long-term dialysis patients. Oral supplementation of GLA significantly increased plasma levels of dihomo-gammalinolenic acid, a precursor of anti-inflammatory eicosanoids.[91] It was postulated that systemic GLA ameliorates CKD-associated pruritus through suppression of inflammatory cytokine production and augmentation of the anti-inflammatory response.[92] Chen et al[90] (2006) hypothesized that transepidermal absorption of GLA or its metabolites mediated a local anti-inflammatory and immunoregulatory effect, providing relief from CKD-associated pruritus.

Topical preparations of the calcineurin inhibitor tacrolimus have anti-inflammatory properties. Pauli-Magnus[33] et al (2000) reported a case series in which tacrolimus 0.03% ointment resulted in a dramatic decrease in pruritus in 3 patients on peritoneal dialysis therapy. However, Duque et al[93] (2005) did not replicate this observation in a follow-up randomized double-blind vehicle-controlled study consisting of 22 hemodialysis patients.

Systemic Treatments

Sedating antihistamines commonly are used in patients with CKD-associated pruritus, probably exerting a beneficial effect through their soporific properties. Gabapentin, a γ-aminobutyric acid analogue anticonvulsant, is used in patients with a variety of neuropathic pain syndromes. Gunal et al[56] (2004) were the first to observe coincidental improvement in pruritus in hemodialysis patients receiving gabapentin treatment for peripheral diabetic neuropathy. Subsequently, these investigators showed that 300 mg of oral gabapentin administered after each hemodialysis session was a safe and

effective treatment option for patients with CKD-associated pruritus through a randomized placebo-controlled double-blind trial.[56] Of 25 patients enrolled, only 1 patient's symptoms did not improve significantly with gabapentin. Of note, renal excretion of gabapentin is decreased in dialysis patients. Manenti et al[57] (2005) made a similar observation, but suggested using a lower dose of gabapentin (100 mg after each hemodialysis session under nurse surveillance), with slow upward titration to decrease the risk of gabapentin-induced neurotoxicity and/or coma in patients with decreased renal function. We also observed beneficial results with the use of gabapentin.

As discussed, the opioidergic system may have an important role in the pathophysiological process of CKD-associated pruritus. Wikström et al[46] (2005) conducted a meta-analysis of 2 multicenter, randomized, placebo-controlled, double blind trials that recruited 144 patients with CKD-associated pruritus and assigned them to postdialysis treatment with either nalfurafine, a κ-receptor agonist, or placebo for 2 to 4 weeks. Nalfurafine treatment for 2 weeks resulted in significant, but modest, decreases in "worst itch," itch intensity, and sleep disturbance compared with placebo. Furthermore, decreases in pruritus and excoriations were observed in nalfurafine-treated patients again after 2 weeks of treatment. It must be noted that statistical benefit for "worst itch" intensity did not persist for a subgroup of patients who continued treatment for 4 weeks.[46] These observations suggest that nalfurafine is unlikely to have a radical impact on the way one treats this distressing symptom. In addition, butorphanol, an opioid analgesic, may have a beneficial therapeutic effect on CKD-associated pruritus. Butorphanol is a κ-opioid receptor agonist and μ-receptor antagonist that we reported to be effective in the treatment of chronic intractable itch when administered intranasally at concentrations of 1 mg once daily.[94] We also successfully used this agent in patients with CKD-associated pruritus.

Physical Treatments

Broadband UVB phototherapy is considered by many to be the treatment of choice for patients with CKD-associated pruritus.[95] Ada et al[36] (2005) showed that narrowband UVB also may be an effective treatment option for patients with pruritus in an open pilot study in which 8 of 10 hemodialysis patients responded to treatment. Narrowband UVB is less erythemogenic[96] and has a lower pruritogenic potential than broadband UVB,[97] as well as generally being accepted as a safer option. These advantages may have important implications in terms of therapeutic options. In addition to the decrease in proinflammatory cytokine levels, UVB also may mediate its beneficial effects in patients with CKD-associated pruritus by inducing mast cell apoptosis.[98]

In conclusion, although the prevalence of CKD-associated pruritus is less than previously reported, it remains a relatively frequent symptom and significant public health issue. CKD itch clearly has a profound impact on quality of life and sleep in patients who already have a compromised lifestyle. Most significantly, despite recent evidence that pruritus in patients with CKD is associated with poorer patient outcomes, many physicians and health care professionals continue to neglect this disabling symptom. The pathophysiological mechanism of CKD-associated pruritus remains poorly understood, and as a result, the development of specific treatment modalities has proved to be a challenge. Although a number of promising therapies are emerging, additional work remains to be performed on this frequently overlooked symptom.

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