

# Pruritus in Kidney Disease

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**Summary:** Pruritus is a common and distressing symptom in patients with chronic kidney disease. The most recent epidemiologic data have suggested that approximately 40% of patients with end-stage renal disease experience moderate to severe pruritus and that uremic pruritus (UP) has a major clinical impact, being associated strongly with poor quality of life, impaired sleep, depression, and increased mortality. The pathogenesis of UP remains largely unclear, although several theories on etiologic or contributing factors have been proposed including increased systemic inflammation; abnormal serum parathyroid hormone, calcium, and phosphorus levels; an imbalance in opiate receptors; and a neuropathic process. UP can present somewhat variably, although it tends to affect large, discontinuous, but symmetric, areas of skin and to be most symptomatic at night. A variety of alternative systemic or dermatologic conditions should be considered, especially in patients with asymmetric pruritus or other atypical features. Treatment initially should focus on aggressive skin hydration, patient education on minimizing scratching, and optimization of the aspects of chronic kidney disease care that are most relevant to pruritus, including dialysis adequacy and serum parathyroid hormone, calcium, and phosphorus management. Data for therapy specifically for UP remain limited, although topical therapies, gabapentin, type B ultraviolet light phototherapy, acupuncture, and opioid-receptor modulators all may play a role.

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Pruritus is a common and distressing symptom that affects patients with chronic kidney disease (CKD). Nephrology providers frequently underestimate the prevalence of pruritus among their patients,<sup>1-3</sup> and, when pruritus is identified, many clinicians are unaware of the effective treatments available.<sup>1</sup> Recently, a steering committee of patients, caregivers, researchers, and clinicians in Canada assembled a list of top 10 research priorities for kidney disease. Determining the causes, effective treatments, and preventative measures for itching was one of those 10 priorities,<sup>4</sup> emphasizing both that pruritus is a key symptom from which patients with kidney disease suffer and that there remain many obstacles to its effective identification and management.

We review the available evidence surrounding the symptom of pruritus as it affects patients with kidney disease. We outline the epidemiologic data reported

worldwide; describe what is known regarding the pathogenesis of pruritus in CKD; and outline its clinical presentation, assessment tools, and available treatment options. We highlight new investigative treatments that may be available for use in the near future.

## PATHOPHYSIOLOGY

Specialized cutaneous somatosensory nerve endings sense different types of stimuli that result in itch, pain, light touch, and other sensations. The physiology underlying pruritus in general increasingly has been elucidated over the past few decades, although much remains to be explained. The first neuron type that was found to transmit itch was the histamine-dependent, slow-conducting, unmyelinated C fiber, but a variety of nonhistaminergic neurons have been discovered more recently that also likely are involved in the neural pathways that produce itch, likely accounting for the fairly common clinical finding of pruritus unresponsive to antihistamines.<sup>5</sup>

Uremic pruritus (UP) has been studied less extensively than pruritus in general. Furthermore, pruritus in renal disease may be caused by mechanisms different than those underpinning pruritus from other etiologies. The abnormalities specific to uremia that have been found to activate itch fibers include the profound changes that occur with hyperparathyroidism-associated metabolic bone disease, structural alterations in the skin related to dehydration, and the increased systemic inflammation and immune dysregulation of uremia.<sup>6</sup>

Emerging evidence from clinical therapeutic reports has suggested that CKD patients also may have

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primary alterations in nociceptive sensory pathways in the peripheral and/or central nervous system. In one of the few studies to provide descriptive data on UP, the distribution of pruritus was in large, nondermatomal areas with “striking mirror symmetry,” which suggests a possible central neurogenic etiology.<sup>7</sup> In addition, an imbalance of opioid receptors not only in the central nervous system but also peripherally may occur in CKD, and UP may be produced by more of a neuropathic mechanism than the pruritus that occurs with other conditions. The efficacy of opioid modulators and gabapentin in the treatment of UP, as outlined in further detail later, fit with this theory. Itch in CKD may correlate better with uremic toxins than glomerular filtration rate, suggesting that uremic toxins either in the central nervous system or peripherally may play an important role in the pathophysiology.<sup>8,9</sup>

## EPIDEMIOLOGY

Pruritus is a common symptom in patients with progressive kidney disease. The most comprehensive epidemiologic data on UP comes from the Dialysis Outcomes and Practice Patterns Study (DOPPS),<sup>10</sup> a large-scale observational study of hemodialysis (HD) patient outcomes in 12 different countries including Australia, Belgium, Canada, France, Germany, Italy, Japan, New Zealand, Spain, Sweden, the United Kingdom, and the United States, in which 41.7% of the studied patients in 2002 to 2003 reported moderate to extreme pruritus. Earlier data from DOPPS-I, collected in 1996 to 2001, showed a slightly higher prevalence of pruritus of 44.9% in seven nations.<sup>10</sup> In addition to the DOPPS data, another 23 studies from 11 countries from 1973 to 2012 reported the incidence of pruritus in end-stage renal disease (ESRD) patients.<sup>7,11–31</sup> These data combined include 5,926 total independent dialysis patients, with a mean weighted prevalence of pruritus of 34.9%. Combining these data with the 13,300 patients in the DOPPS-I and DOPPS-II data<sup>10</sup> yields a total of 19,226 ESRD patients studied, with a mean weighted prevalence of pruritus of 40.6%. The most recent sizeable study of the prevalence of UP included the most recent DOPPS-III data specifically from Japan, and reported an overall incidence of moderate to extreme pruritus of 44% among 6,480 patients undergoing HD in 1996 to 2008.<sup>32</sup>

Pruritus severity is reported variably. As further outlined later, the severity of pruritus generally is assessed by a visual analogue scale (VAS), numeric rating scale, or questionnaire. Of the earlier-described prevalence studies, seven, including the DOPPS data, included an assessment of pruritus severity.<sup>10,11,14,15,18,21,29</sup> By combining these studies, the weighted mean prevalence of severe pruritus (including very much or extreme pruritus) was 24.5%

among 16,672 dialysis patients. If the DOPPS data were excluded, the weighted mean prevalence of severe pruritus decreased somewhat to 22.5% among 3,372 patients.

The prevalence of UP in patients on dialysis has declined significantly over the approximately past half century since the advent of dialysis,<sup>33</sup> presumably related to improvements in dialysis modalities, access, and adequacy. Over the past 2 decades, however, this decrease has appeared to abate, with prevalence continuing to decrease very slowly or even stabilize. The multinational DOPPS data showed a small but statistically significant 3% decrease in the prevalence of pruritus in 2002 and 2003 relative to the preceding 7 years,<sup>10</sup> whereas the more recent Japanese DOPPS data showed a prevalence that statistically was unchanged in 2005 to 2008 relative to the preceding 4 years.<sup>32</sup> Prevalence appears to vary significantly by geographic region and, within a given region, from center to center. The DOPPS study reported a prevalence of moderate to extreme pruritus that ranged from as low as 36% in France to as high as 50% in the United Kingdom, whereas the variation between facilities ranged from 5% to 75%.<sup>10</sup> A similar degree of interfacility variability was seen within nations, with the Japanese DOPPS study reporting a range of 20% to 70% in more than 60 facilities, a variability that was not explained by adjusting for patient characteristics.<sup>32</sup> The prevalence of UP in less-developed countries has not been well reported.

Limited data suggest that the prevalence of UP in ESRD patients specifically on peritoneal dialysis is similar to those on HD,<sup>16</sup> although the studies are few in number (seven), included relatively small numbers of peritoneal dialysis patients (range, 19–113), used varying measures of pruritus, and reported variable degrees of dialysis adequacy.

Similarly, the prevalence of UP in patients with CKD not requiring dialysis or in patients with CKD stage 5 treated with conservative management (ie, without dialysis) has not been well reported, but it appears to be common, particularly in the conservatively managed group. In one small study of 49 ESRD patients managed without dialysis whose symptoms were analyzed in the month preceding death, pruritus, with a prevalence of 84%, was the second most common symptom, more common than the other 38 symptoms assessed except for lack of energy.<sup>34</sup> Furthermore, the pruritus was reported to be at least somewhat distressing in 82% of patients, and very distressing in 43%.<sup>34</sup> Likewise, in a study of 179 ESRD patients in Hong Kong, of whom 45 were managed with palliative care services without dialysis and of whom 134 received dialysis, pruritus, trailing only fatigue and cold aversion, was the third most common of 23 ESRD-related symptoms, with a

prevalence of 65.7% in the dialysis group and 57.8% in the nondialysis group (a difference that was not statistically different).<sup>35</sup> Pruritus was reported as the sixth most intense symptom overall of all the symptoms assessed, although, interestingly, the pruritus intensity was statistically lower in the palliative care group.<sup>35</sup>

Some literature reviews on UP report that pruritus is uncommon among patients after kidney transplant, even in patients with recurrent progressive kidney disease; however, data to substantiate this claim appear limited.<sup>33,36</sup> Interestingly, a single study published in 1999 of 199 children on dialysis in Germany suggested that pruritus among children on dialysis is both less common, with only roughly half the prevalence, and less severe than for adults on dialysis.<sup>33</sup>

A variety of patient characteristics and dialysis parameters have been associated, albeit somewhat inconsistently, with the increased burden of UP. These include lower dialysis adequacy,<sup>37</sup> use of low- (versus high-) flux dialyzer,<sup>37</sup> hepatitis C positivity,<sup>10,21</sup> higher serum C-reactive protein levels,<sup>21</sup> higher serum calcium and/or phosphorus levels,<sup>10,25,29</sup> low serum albumin level,<sup>10,38</sup> increased ferritin level,<sup>32</sup> current or recent smoking,<sup>10</sup> older age,<sup>10</sup> male sex,<sup>10,29</sup> and underlying depression.<sup>10,39</sup>

## CLINICAL SIGNIFICANCE

UP has been shown repeatedly to decrease quality of life (QoL), to contribute to other symptoms (especially poor sleep) that further impair QoL, to be associated with depression, to be an independent predictor of mortality, and to lead to other poor patient outcomes.<sup>7,10,12,18,29,39</sup> In the DOPPS cohort specifically, dialysis patients with moderate to extreme pruritus were found (by adjusted odds ratios) to be approximately four times more likely to feel drained, three times more likely to have poor sleep quality, and 1.5 times more likely to be diagnosed with depression by a physician.<sup>10</sup> The patients with extreme pruritus were found to have physical and mental QoL scores approximately 17% to 18% lower than patients without pruritus.<sup>10</sup> Interestingly, they also found a 17% increase in mortality rate associated with moderate to extreme UP, but this difference was no longer statistically significant when adjusting for sleep quality.<sup>10</sup> The association between UP and feeling more drained, poorer sleep quality, increased rate of depression, lower physical and mental QoL scores, and increased mortality were replicated in the more recent Japanese DOPPS cohort, with the exception that the mortality relationship persisted even after adjusting for sleep quality.<sup>32</sup>

In the next largest study of pruritus and QoL, a cross-sectional study of 980 HD patients in Brazil,

Lopes et al<sup>18</sup> found that patients with severe pruritus had a 25% decrease in kidney disease burden–related QoL; they found that this decrease was driven primarily by sleep disturbances, depressive symptoms, and dry skin. Mathur et al<sup>7</sup> also found a statistically significant relationship between the intensity of UP and health-related QoL, particularly with regard to mood, social relations, and sleep; they noted that a decrease in intensity of UP of 20% was sufficient to produce a significant improvement in health-related QoL. Kosmadakis et al<sup>19</sup> in the United Kingdom noted that 54% of patients with UP reported that it seriously affected their QoL. Tessari et al<sup>12</sup> in Italy found that UP was associated with a statistically significant and dramatic increase in poor sleep (59% versus 11%) as well as decreased QoL with regard to social function, emotion, and symptoms. The relationship between depression and pruritus was elucidated further by Yamamoto et al,<sup>39</sup> who, by longitudinally following up the Japanese DOPPS cohort, showed, interestingly, that baseline depressive symptoms predicted the subsequent development of severe pruritus in HD patients.

## CLINICAL PRESENTATION

The clinical presentation of pruritus in patients with CKD varies greatly from patient to patient. As referenced earlier, Mathur et al<sup>7</sup> recently published a prospective observational study of 103 patients in the United States on HD followed up over 12 weeks, detailing a variety of the clinical aspects of UP. The majority of patients (84%) had itching daily or nearly daily, and most patients had itching that affected large, discontinuous, but bilateral and symmetric, areas of skin.<sup>7</sup> In general, itching was characterized as worse at night than during the day.<sup>7</sup> Another study showed that the most common areas affected are the back and arms,<sup>16</sup> but other areas of the body often are bothersome as well. The area affected may remain constant or migrate over time.<sup>7</sup> Patients vary significantly with regard to the circumstances that precipitate or aggravate pruritus; common factors reported include heat, dialysis, stress, cold, physical activity, and showering.<sup>16,19,20</sup> Unfortunately, most patients affected by pruritus will continue to have the symptom for months to years.<sup>7</sup>

Because the presentation of pruritus in CKD can be variable, it may be difficult to differentiate it from other causes of itching. In general, a nonuremic cause for pruritus should be considered in patients who are refractory to a reasonable treatment trial, whose symptoms largely are asymmetric, with bullous or ulcerating lesions, or who manifest with clinical findings characteristic of other systemic diseases. In addition, pruritus may manifest as a drug reaction from recently initiated or long-standing pharmacologic treatment. [Table 1](#)

**Table 1.** Nonuremic Causes of Itch

Primary dermatologic conditions
Drug-induced hypersensitivity and other allergies
Contact dermatitis
Psoriasis
Dermatophytosis (tinea cruris, tinea pedis, tinea corporis)
Bullous pemphigoid
Infestations
Bed bugs
Scabies
Lice
Systemic conditions
Hypercalcemic states
Cholestasis
Viral hepatitis
Primary biliary cirrhosis
Hematologic malignancy
Hodgkin's lymphoma
Cutaneous T-cell lymphoma
Polycythemia vera
Post-herpetic neuralgia
Human immunodeficiency virus

outlines a differential diagnosis of nonuremic and treatable causes of itching that are common in patients with CKD.

## EVALUATION

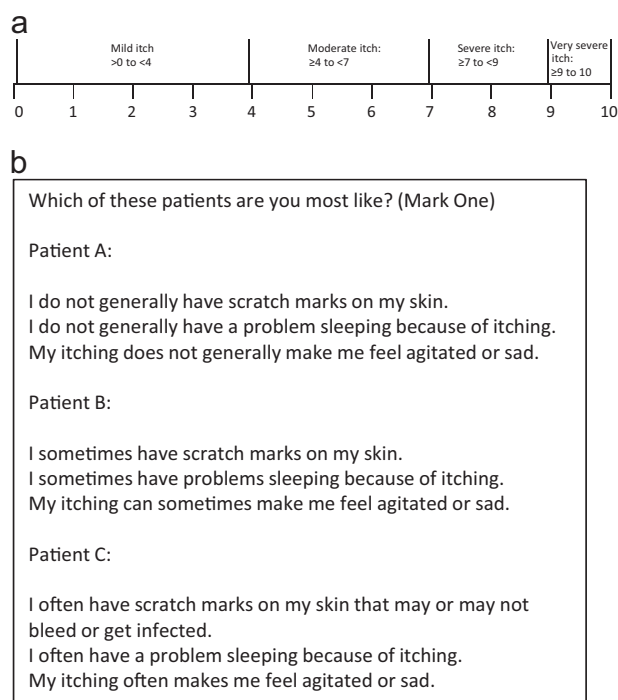
Before initiating treatment for pruritus, it is helpful to obtain objective information regarding its severity to track the response to therapy. There are many treatment

scales that have been validated for use in UP. A recent review published by a special interest group of the International Forum for the Study of Itch recommended a set of measures that have been validated for use in clinical trials for the assessment of pruritus, including pruritus intensity scales and instruments for the assessment of scratch lesions, chronic pruritus course, quality of life, and patient benefit from therapy.<sup>40</sup>

Pruritus is a symptom and thus inherently is subjective. Scratch lesions can be quantitated; however, this assessment method often is inaccurate in measuring the significance of the symptom to the patient. Therefore, pruritus typically is assessed via patient-reported outcomes (PROs). Several PRO scales are available for the assessment of pruritus intensity. These include both unidimensional measures, such as the VAS, that address one symptom at a time with one scale, as well as multidimensional measures that track more than one symptom, change in symptoms over time, or more than one assessment of a particular symptom.<sup>40</sup> Because quality of life, sleep disturbance, anxiety, and depression are associated strongly with pruritus intensity, these measures often are included in multidimensional UP assessment tools. **Table 2** lists key PRO scales validated for use in UP and clinical recommendations for their use. **Figure 1** provides one example each of unidirectional and multidimensional scales. Although the VAS (**Fig. 1A**) first was developed for pain, it has been validated for use in evaluating pruritus as well.<sup>40</sup> Among the multidimensional scales, the ABC questionnaire (refers to the

**Table 2.** Symptom Scales Validated for Use in the Evaluation and Treatment of Uremic Pruritus

Measurement	Tool (and Reference)	Advantages	Disadvantages	Recommended Use
Pruritus intensity (unidimensional)	VAS, <sup>81</sup> numeric rating scale (NRS) <sup>80</sup>	Simple and fast	Score may reflect other non-itch factors, highly subjective	Routine clinical use, recommend trying a test run with patient before use
Pruritus intensity (multidimensional)	Self-Assessed Disease Severity (ABC scale) <sup>7</sup>	Simple and fast	Not quantitative	Routine clinical use and screening for clinical trials
	Brief Itching Inventory <sup>7</sup>	Assesses quality of life and dermographic distribution	Not quantitative	Clinical trials
	Skindex-10 <sup>7</sup> Itch MOS (Medical Outcomes Study) <sup>7</sup>	Assesses quality of life Assesses sleep disturbance	Not quantitative	Clinical trials Clinical trials
Pruritus course	5-D questionnaire <sup>82</sup>	Comprehensive	Not yet evaluated conclusively	Clinical trials
Tracking response to treatment	Patient Benefit Index for pruritus (PBI-P) <sup>83</sup>	Assesses response to treatment	As a longer survey (with 27 variables), more difficult to use systematically in a dialysis unit	Especially useful for setting therapy goals with patient



**Figure 1.** Examples of (A) unidirectional and (B) multidirectional PRO scales. (A) VAS. Data from Reich et al.<sup>80</sup> (B) Self-assessed disease severity (ABC scale). Adapted with permission from Mathur et al.<sup>7</sup>

A B C patient type in figure 1), also known as “Self-Assessed Disease Severity” (Fig. 1B), is simple, accurate, and particularly practical for use in routine clinical nephrology practice and recently was validated in the dialysis population.<sup>7</sup>

## TREATMENT

Clinicians and investigators have tested numerous topical and systemic treatments for pruritus. In general, most of the published data regarding treatment of uremic pruritus either are retrospective or underpowered prospective studies; therefore, recommended treatment regimens remain largely based on expert opinion. Here, we outline the most common available therapies for uremic pruritus and the data that support them.

### Topical Treatments

The cornerstone of UP therapy is adequate skin hydration. Xerosis is found in most patients with ESRD and frequently aggravates pruritus.<sup>20,41</sup> Skin hydration with aqueous cream emollient<sup>41</sup> and baby oil<sup>42,43</sup> both have been shown to reduce skin dryness and the severity of UP effectively and to improve patient quality of life when applied two to four times daily. In addition to skin hydration, other topical agents have been used with some success to treat pruritus. Several small placebo-controlled trials have shown

symptom relief with 0.025% to 0.03% capsaicin ointment applied two to four times daily to affected areas.<sup>44–46</sup> Capsaicin generally was well tolerated without significant side effects other than initial burning on application.<sup>44–46</sup> Presumably, capsaicin ointment is likely to be more effective in patients with localized symptoms rather than in patients experiencing generalized pruritus. Similarly, 1% pramoxine hydrochloride lotion was tested in a single-center, randomized, double-blind study of patients on HD and showed statistically significant effectiveness when applied two times daily for 4 weeks.<sup>47</sup> Both topical capsaicin and pramoxine are available in a variety of formulations and US brand names.

Tacrolimus, formulated as a 0.1% or 0.03% ointment (Protopic; Astellas Pharma US, Inc, Northbrook, IL), is used topically as a nonsteroidal immunomodulating agent and has been approved for the treatment of moderate to severe atopic dermatitis. Its use in treating pruritus in patients on dialysis has been tested in a few small single-center studies with conflicting results.<sup>48–50</sup> In addition, in response to case reports and animal studies reporting rare associations with malignancies such as lymphoma and skin cancer, the Food and Drug Administration issued a black box warning for tacrolimus ointment and recommended that its use be limited to those who have failed other therapies and to treatment periods of less than 6 weeks.

### Systemic Treatments

Of all the systemic therapies currently used for the treatment of UP, gabapentin (Neurontin; Pfizer, Inc, New York, NY) has been shown the most consistently to be successful in clinical trials. Recently, Cheikh Hassan et al<sup>51</sup> published their results from a single-center retrospective cohort study testing the safety and efficacy of gabapentin for the treatment of restless legs syndrome and pruritus in patients with renal disease ranging from stage 3 CKD to ESRD. They specifically assessed gabapentin use in a group of 34 patients managed conservatively (ie, without dialysis) and compared the results with results from a group of 15 patients on dialysis.<sup>51</sup> In the conservatively managed patients they found that gabapentin successfully reduced pruritus with a median daily dose of 100 mg, but 47% of patients experienced one or more side effects, leading to a 17% rate of permanent treatment discontinuation.<sup>51</sup> In the comparison group of patients on dialysis, gabapentin was found to be similarly effective at a similar average dose; however, the rate of side effects in the dialysis group was significantly lower at only 14%, although the rate of drug discontinuation was not statistically different.<sup>51</sup> Gunal et al<sup>52</sup> enrolled 25 patients on HD in a randomized, placebo-controlled, double-blind trial of gabapentin at 300 mg

three times per week for 4 weeks after dialysis and reported a significant response, namely a decrease in mean VAS score from 7.9 to 1.2, with no participants needing to drop out because of secondary side effects. Other small-scale studies have shown similar improvement in pruritus with doses of 100 or 300 mg of gabapentin after hemodialysis.<sup>53,54</sup> Pregabalin (Lyrica; Pfizer, Inc, New York, NY) has been shown to be similarly effective for the treatment of pruritus in two small single-center prospective studies of patients on HD at doses of 25 or 75 mg at nighttime and could be considered for patients who do not tolerate gabapentin.<sup>55,56</sup>

Antihistamines are used commonly to treat pruritic symptoms in patients with CKD. However, antihistamines have been, at best, inadequately tested for the treatment of UP, with a few studies as well as a significant number of reviews all pointing to their general lack of efficacy in treating UP, and several reviews speculating that any perceived benefit seen with antihistamines was caused by sedation rather than a true antipruritic effect.<sup>20,57–63</sup> One small study specifically suggested that antihistamines are no more effective than emollients.<sup>20</sup> Another interesting small study documented that the ability of antihistamines to prevent pruritus, which can be reproduced experimentally in normal control patients, is specifically lost in patients with UP.<sup>63</sup> Furthermore, given the risk of side effects, such as confusion and sedation, particularly in an ESRD population that often is older with multiple comorbidities, antihistamines generally are not recommended as first- or second-line therapies for UP.

Given clinical observations that  $\mu$ -receptor agonists can cause or worsen pruritus, a variety of studies have investigated opioid-receptor modulators for the treatment of UP. Naltrexone (Naltrexone Hydrochloride; Teva Pharmaceuticals USA, Inc, Sellersville, PA), a  $\mu$ -opioid-receptor antagonist, was tested in two studies of the treatment of UP in patients with ESRD at a dose of 50 mg/d by mouth with conflicting results, with the first study reporting a large and statistically significant clinical benefit, whereas the second study showed no benefit.<sup>30,64</sup> In both studies, naltrexone use resulted in very few side effects.<sup>30,64</sup>

Nalfurafine (Remitch; Toray Industries, Inc, Chūō, TKY Japan), a  $\kappa$ -opioid-receptor agonist, has been tested in oral and intravenous form in the treatment of UP. In an open-label single-arm prospective trial of 211 HD patients treated for 52 weeks with 5  $\mu$ g of nalfurafine orally, 145 patients completed the study and experienced a significant decrease in the mean VAS score from 75.2 to 30.9 at study termination.<sup>65</sup> The investigators reported no evidence of psychological or physical dependence of the drug during the trial, although 48.8% of patients had adverse drug reactions, most commonly insomnia (19.4%) and constipation

(7.1%).<sup>65</sup> At study termination, treatment effects of the medication appeared to reverse rapidly but the subjects were not followed up long enough to determine if VAS scores returned to baseline.<sup>65</sup> Similarly, Wikstrom et al<sup>66</sup> reported a statistically significant effect of two randomized, double-blinded, placebo-controlled trials of 144 patients on HD with UP who received 5  $\mu$ g of intravenous nalfurafine three times per week after HD for 4 weeks. Given these positive results, several groups of investigators currently are pursuing additional studies of  $\kappa$ -receptor agonists in the treatment of UP (see later).

### Phototherapy

In the late 1970s, Gilchrest et al<sup>67–69</sup> published several small studies of patients with chronic renal failure that showed success with type B ultraviolet light (UVB) therapy in the treatment of UP, noting that some patients had generalized improvement in symptoms even when only part of the affected body parts were treated. Tan et al<sup>70</sup> published a meta-analysis of randomized controlled trials of UP treatments in 1991 and identified UVB phototherapy as the only treatment that successfully fulfilled the criteria for clinical significance. However, the most recent randomized controlled trial testing UVB therapy efficacy, published in 2011, did not show a significant benefit.<sup>71</sup> Much still is unknown about the long-term effects of UVB therapy and its use should be considered carefully before initiation, particularly in patients who are chronically immunosuppressed or in patients who may soon undergo renal transplantation.

### Acupuncture

Acupuncture is used commonly worldwide as a primary, adjunct, or alternative treatment for pain and other symptoms. Kim et al<sup>72</sup> published a meta-analysis of prospective clinical studies of needle acupuncture for UP in patients with ESRD and concluded that, despite six separate trials reporting the beneficial effects of acupuncture, most of the trials showed a high risk of bias and therefore current evidence is insufficient to support its efficacy. However, acupuncture has virtually no lasting side effects and therefore could be offered very reasonably as an alternative therapy to interested patients with UP who do not respond to first-line treatments, who are unwilling to take systemic medications, or who have a particular interest in acupuncture.

### Novel Therapies for UP

As alluded to earlier, there are a series of trials underway to further investigate opioid-receptor modulators for the treatment of UP (Table 3). A larger phase

**Table 3.** Opioid Receptor Modulators Currently Under Investigation for the Rreatment of Uremic Pruritus

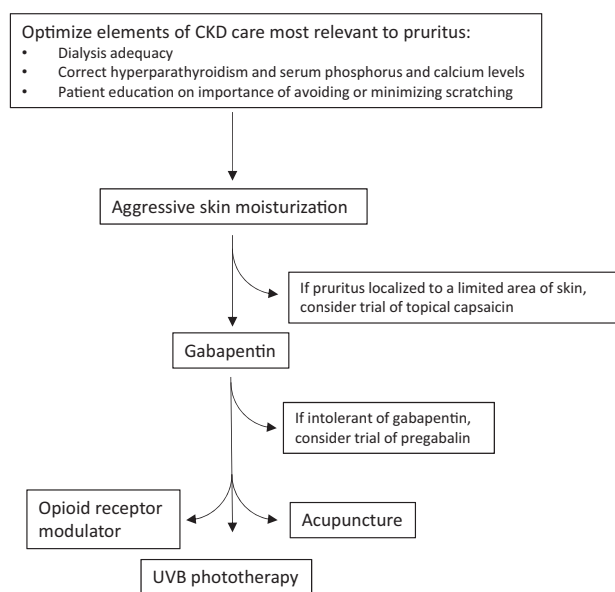
Drug Name	Company	Mechanism	Route	Trial Stage
AC-820 (nalfurafine)	Acologix, Inc	$\kappa$ -opioid-receptor agonist	Oral	Phase 3
Nalbuphine HCl ER	Trevi Therapeutics, Inc	Mixed $\kappa$ -opioid-receptor agonist and partial $\mu$ -opioid antagonist	Oral	Phase 2
CR-845	Cara Therapeutics, Inc	$\kappa$ -opioid-receptor agonist, peripherally restricted (ie, does not cross blood-brain barrier)	IV	Phase 2

3 study is being performed in the United States by Acologix, Inc (Hayward, CA) to evaluate the safety and efficacy of the oral  $\kappa$  agonist nalfurafine and currently is enrolling subjects.<sup>73</sup> In addition, a randomized, double-blind, placebo-controlled trial of an oral extended-release formulation of nalbuphine (Trevi Therapeutics, Inc, New Haven, CT), a semisynthetic mixed  $\kappa$ -opiate agonist and partial  $\mu$ -opiate antagonist, has been approved to test its efficacy in the treatment of UP.<sup>74</sup> Cara Therapeutics (Shelton, CT) is advancing their intravenous peripherally restricted  $\kappa$  agonist, CR845, in a small prospective phase 2 study for the treatment of UP.<sup>75</sup>

Furthermore, cannabinoids, systemically, topically, and as novel peripherally restricted agents, have been shown in some preliminary studies to be useful for pruritus in other settings<sup>76</sup> and may hold promise in the treatment of UP.

### Approach to Therapy

There are no formal published guidelines regarding the treatment of UP; however, many reviews have published treatment recommendations.<sup>6,77–79</sup> Most experts



**Figure 2.** Step-by-step approach to the treatment of uremic pruritus.

recommend taking a stepwise approach to the treatment of UP, beginning with optimization of dialysis adequacy, calcium and phosphorous levels, skin hydration, and nutrition, and with patient education on the importance of avoiding or minimizing scratching. If symptoms persist, providers may offer pharmacologic and/or nonpharmacologic therapy (Fig. 2). Providers should approach treatment according to patient preference and with consideration of available resources, of potential drug–drug interactions and adverse drug reactions, and of their own comfort level in prescribing the various therapies.

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