

# CKD-Associated Pruritus: New Insights Into Diagnosis, Pathogenesis, and Management



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Chronic kidney disease–associated pruritus (CKD-aP) is a common, troubling and in some cases debilitating problem for patients with CKD and end-stage renal disease. Despite a prevalence rate of approximately 20% in CKD and 40% in end-stage renal disease, and a clear association with poorer psychosocial and medical outcomes, this condition is often underreported by patients and overlooked by health care providers. This is likely due, in part, to uncertainty regarding its pathogenesis and treatment. Most commonly, CKD-aP is attributed to toxin build-up, peripheral neuropathy, immune system dysregulation, or opioid dysregulation. Prior treatment studies of CKD-aP have targeted these potential etiologies but have been limited by noncontrolled design, small sample size, and non-uniform definitions of CKD-aP. Recently, several large, randomized controlled trials targeting opioid dysregulation have yielded promising results. These trials have spurred new hope for understanding and treating this condition.

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KEYWORDS: chronic kidney disease; depression; end-stage renal disease; itching; pruritus; uremia

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In the general population, pruritus is often a disturbing, yet fleeting sensation. For patients with advanced CKD or on dialysis, however, pruritus can recur and persist, dramatically affecting quality of life and possibly survival. This condition, termed CKD-aP, also known as uremic pruritus, is common in dialysis patients, and despite over 50 years of research, remains poorly understood and undertreated. Recently, however, advances have been made in the understanding and treatment of chronic itching, including CKD-aP. In this narrative review, we explore the clinical presentation, prevalence, etiology, and treatment of CKD-aP. Our goal is to focus on newer developments in diagnosis and management in order to engender more confidence about treating this condition.

## Diagnosis

Chronic kidney disease–associated pruritus (CKD-aP) is defined as itching directly related to kidney disease, without another comorbid condition to explain itching. CKD-aP has a variable clinical presentation, making its identification difficult.<sup>1</sup> For example, its severity may vary over time from hardly appreciable, to incessant

and disturbing; it may be intermittent or persistent; and it may occur anytime in relation to dialysis—before, during, or after.<sup>2,3</sup> Furthermore, its distribution is variable.<sup>4</sup> It is generalized in up to 50% of patients,<sup>1</sup> and when generalized, it is often symmetrical,<sup>4</sup> but it can be localized, often occurring on the face, back, and shunt arm only.<sup>2,4</sup> Several situations have been known to worsen CKD-aP, including extreme hot or cold, stress, physical activity, and showering.<sup>5</sup> Finally, further complicating the identification of CKD-aP, is the fact that it can occur without any skin manifestations, can coexist with xerosis (dry skin) in 50%–85% of patients,<sup>6,7</sup> and can occur with superimposed complications of itching, including impetigo, crusts, papules, ulcerations, erosions, and prurigo nodularis<sup>1</sup> (Figure 1).

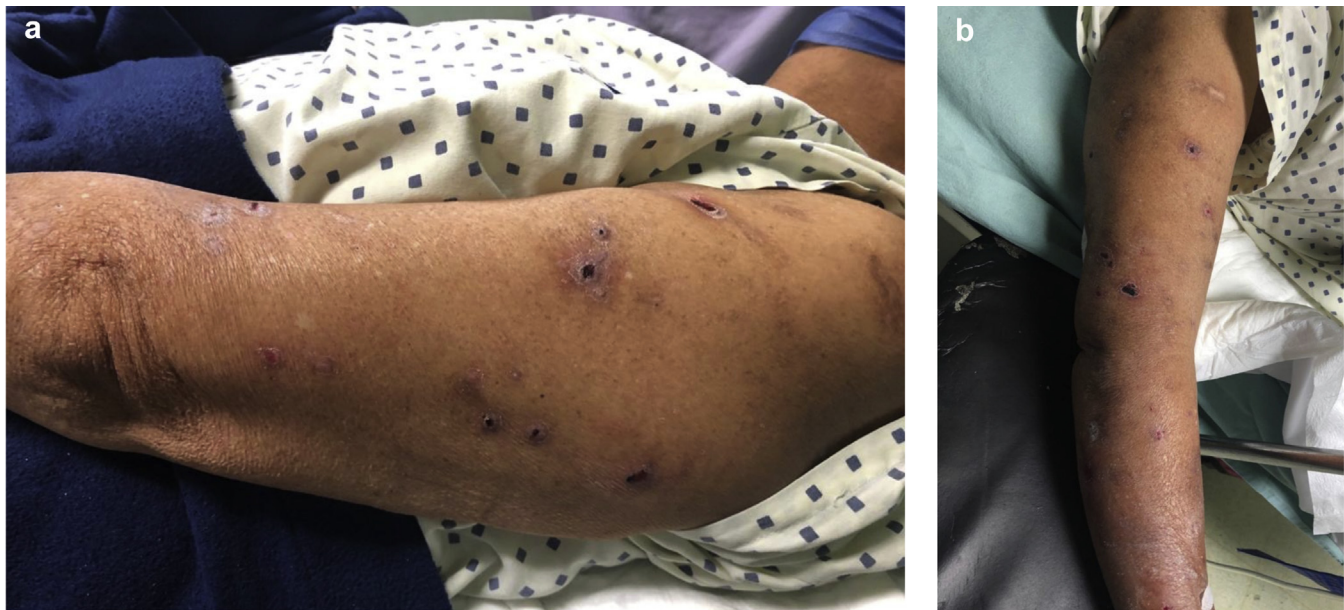
Due to this clinical variability, and because CKD-aP is a common condition in dialysis patients, providers should consider any itching in this population related to CKD-aP, unless there is a clear alternative explanation.<sup>1</sup> Potential alternative explanations for itching include comorbid liver, hematologic, and skin conditions, and medications such as opioids.<sup>1,8</sup>

## Quantifying CKD-aP

There are no universally accepted methods to measure CKD-aP, and this has led to a wide range of prevalence estimates. Currently used scales can be divided into those that measure severity, multidimensional scales

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**Figure 1.** Chronic kidney disease–associated pruritus with xerosis and superimposed complications of itching including crust, erosions, and papules.

that measure several itch characteristics, and scales that measure the impact of itching on quality of life (QOL).

### Severity Scales

Four scales are commonly used to measure itching severity: the visual analog scale (VAS), the numeric rating scale (NRS), the verbal rating scale (VRS), and the Kidney Disease Quality of Life-Short Form (KDQOL-SF). The VAS is the most commonly used scale to measure CKD-aP severity.<sup>9</sup> Originally developed to evaluate pain, the VAS has been adapted to measure itching. It depicts a horizontal or vertical line, generally 10 cm in length, in which the extreme left represents no itching and the extreme right represents the worst itching imaginable. Similarly, the NRS grades itching severity on a numerical scale from 0 to 10, and the VRS includes 4 itching severities: no, low, moderate, and severe.<sup>10</sup> The 24-hour worst itching intensity NRS is a validated version of the NRS in which patients grade the overall severity of the worst level of their itching in the previous 24 hours.<sup>11</sup> The VAS, NRS, and VRS have similar reliability and validity.<sup>10</sup> The KDQOL-SF includes 43 kidney disease–specific questions and the 36-item short-form health survey (SF-36).<sup>12</sup> Originally designed to test QOL in dialysis patients, this survey includes 1 question (question 20) about itching severity: “During the past 4 weeks, to what extent were you bothered by: itchy skin?” Choices include, “(1) not at all bothered, (2) somewhat bothered, (3) moderately bothered, (4) very much bothered, and (5) extremely bothered.” This question has been the basis of the largest international studies of CKD-aP prevalence in dialysis.<sup>3,13</sup>

### Multidimensional Scales

The most commonly used multidimensional itching scales are the 5-D itching scale and the itching severity scale (ISS).<sup>14,15</sup> The 5-D itching scale evaluates intensity of itching, itching duration, itching pattern, and its effect on QOL. This scale is reliable, correlates well with the VAS, and validly measures changes in pruritus over time.<sup>14</sup> The ISS measures duration, frequency, pattern, intensity, treatment, symptoms, sensation, and effect of itching on QOL. It is a valid and reliable measure of itching.<sup>15</sup>

### QOL Scales

The dermatology QOL index (DLQI) and the Skindex have been developed and validated to measure the impact of skin disease on QOL.<sup>16,17</sup> The DLQI contains 10 questions that measure the effects of itching on symptoms/feelings, daily activities, leisure, work/school, personal relationships, and treatment.<sup>16</sup> The Skindex contains 61 questions that measure the effects of skin disease on QOL, including psychosocial effects that are cognitive, social, or emotional, and physical effects related to discomfort or limitations.<sup>17</sup> The original scale was found to be internally reliable, reproducible, and valid.<sup>17</sup> A shorter version has been used in studies of CKD-aP outcomes.<sup>4,18,19</sup>

### Prevalence

One of the first studies to measure CKD-aP in dialysis patients was published almost 50 years ago.<sup>20</sup> At that time, the prevalence in 36 hemodialysis (HD) patients was 86%.<sup>20</sup> Since then, the prevalence of this condition in HD patients has decreased to approximately 40%.<sup>3</sup>

Recent large studies defining prevalence rates of CKD-aP in HD, peritoneal dialysis (PD), and CKD patients are summarized in Table 1. To date, the largest studies of CKD-aP prevalence have been from the Dialysis Outcomes and Practice Patterns Study (DOPPS).

### DOPPS

DOPPS is an international cohort study of adult dialysis patients designed to inform providers of practices that lead to the best outcomes.<sup>27</sup> Study patients are enrolled randomly from select multinational dialysis units. Collected data include demographics, diabetes as cause of ESRD, mortality data, the KDQOL-SF, the Center for Epidemiologic Studies Short Depression survey (CES-D-10), a patient satisfaction measure, and a medical director survey.

Since its initiation in 1996, there have been 6 phases of the study. In the first phase (1996–2001), 17,034 patients from 308 randomly selected HD units from 7 countries participated. In phase 5 (2012–2015), 36,743 patients from 508 randomly selected HD units from 21 countries participated.

In the second year of the phase V study, questions from the Skindex-10 that measured the psychosocial effects of itching were included. In 2013, medical directors were asked to estimate CKD-aP prevalence in their units, and to describe how they treat CKD-aP.

### HD

In phase 5 of DOPPS, 6256 of 8621 (73%) HD patients answered question 20 of the KDQOL-SF survey related to itching. A total of 37% were at least moderately bothered by itching, and 18% were very much or extremely bothered by itching.<sup>3</sup> As was seen in previous phases of the study,<sup>13</sup> these percentages were similar across 19 countries. The highest percentage of patients at least moderately bothered by itching was in the UK (48%), and the lowest was in Germany (26%). These prevalence rates have decreased steadily since DOPPS I (1996–2001) when 46% of HD patients were at least moderately bothered by itching and 28% were very much or extremely bothered by itching.<sup>3</sup>

Similar prevalence rates have been found in 2 other large HD cohorts.<sup>21,22</sup> An analysis of 6480 Japanese HD patients found that the prevalence of moderate to severe pruritus, using a modified VRS scale, was 44%.<sup>22</sup> A study of 38,315 US HD patients (approximately 40% African American) found that the prevalence of at least moderate itching, using question 20 of the KDQOL SF-36 survey, was 30%, and 14.5% were very much or extremely bothered by itching.<sup>21</sup>

### PD

Few studies have reported on the prevalence of CKD-aP in PD patients. In a study of 362 Chinese PD patients, the prevalence of mild to moderate pruritus was

52.5%, and severe pruritus 12.7%.<sup>26</sup> In a study of 223 patients on PD and 425 HD patients from Korea, the prevalence of at least mild pruritus was 62.5% in HD patients and 48.3% in patients on PD.<sup>24</sup> A meta-analysis of 6 cross-sectional prevalence studies (2 PD-only and 4 mixed HD and PD) showed a prevalence of CKD-aP of 56% (95% CI, 44%–68%)<sup>28</sup>; however, the severity of this pruritus was not reported.

Studies comparing CKD-aP prevalence rates in HD and PD patients have yielded mixed results. Two studies found no difference in pruritus rates<sup>29,30</sup>; 1 study found higher rates of pruritus in PD patients<sup>24</sup>; and 1 found higher rates of pruritus in HD patients.<sup>31</sup>

### CKD

The largest study of CKD-aP prevalence in patients with CKD, not yet on dialysis, comes from the CKD Outcomes and Practice Patterns Study (CKDopps).<sup>7</sup> CKDopps is an international, prospective, nephrology clinic-based cohort study of 5658 adult patients with stage 3–5 CKD (nondialysis) from the US, Brazil, and France. Demographic data, comorbid conditions, labs, medications, KDQOL-SF, and CES-D-short form are collected. In a recent study of CKD-aP prevalence from this database, 67% of patients completed relevant survey data.<sup>7</sup> The studied population included 15% with stage 3a, 34% with stage 3b, 44% with stage 4, and 7% with stage-5 CKD. The prevalence of at least moderate pruritus was 24% (24% in Brazil, 29% in the US, and 23% in France), and of severe to extreme pruritus was 11% in Brazil, 13% in the US, and 10% in France. The prevalence of moderate-to-extreme pruritus increased with CKD stage, and the adjusted rate was 19% higher in stage-5 compared to stage-3 disease.

Similar prevalence rates have been found in other CKD cohorts. In a cross-sectional study of 402 stage 2–5 CKD patients, the prevalence of CKD-aP was 18.9%.<sup>32</sup> Pruritus was not affected by CKD stage. Studies of patients with advanced CKD (stages 4 and 5) referred to renal palliative care clinics have found a high prevalence of pruritus: 56% in 55 patients with stage-4 and stage-5 CKD,<sup>33</sup> and 74% in 66 patients with stage-5 CKD.<sup>34</sup>

### Underestimation

Despite a prevalence of at least moderate itching of approximately 40% in HD patients, nephrologists substantially underestimate the number of their patients affected by pruritus. In a national, cross-sectional, German study of 204 nephrologists (14% response rate), 85% estimated that  $\leq 30\%$  of their HD patients suffered from pruritus, and 38% estimated that  $\leq 10\%$  suffered from pruritus.<sup>35</sup> These percentages are dramatically less than international CKD-aP prevalence rates. In phase V of DOPPS, 65% of medical



**Table 1.** Select studies examining the prevalence, characteristics, and outcomes of chronic kidney disease-associated pruritus (CKD-aP)

Author, yr	Study design and population	Itching and outcome tools	Prevalence	Characteristics	Outcomes
<b>Hemodialysis</b>					
Rayner <i>et al.</i> , 2017 <sup>3</sup>	35,452 HD patients from 17 countries from DOPPS I-V (1996–2015); 6256 HD patients from DOPPS V (2012–2015); 268 medical directors	Itching severity: VRS (5-grade); QOL: Skindex-10 scale (6-grade); intervention by medical directors: first, second, and third line for acute and chronic use	74% with some itch, 46% moderate–extreme (DOPPS I); decreased to 69% some and, 37% moderate–extreme (DOPPS V)	Higher AOR of moderate to severe pruritus with older age, higher CRP, low serum albumin, presence of hepatitis B or C; No association with Phos, Ca, Ca-Phos product, PTH, Kt/V, or hemodiafiltration	Patients very much or extremely bothered by, also bothered by dry skin (84%), restless sleep (60%) Medical directors underestimated pruritus in 69% of facilities 57% of medical directors used oral antihistamines for first-line treatment Gabapentin was used by 45% as first, second, or third treatment
Ramakrishnan <i>et al.</i> , 2013 <sup>21</sup>	71,000 US HD and PD patients	Itching severity: VRS scale from the KDQOL survey (5-grade); QOL: SF-12	60% “some itching”; 14.5% “very much or extremely bothered”	Itching associated with younger, female, DM, CAD, COPD, liver disease, dialysis vintage, BMI; lower Hgb and albumin; higher Ca, Phos, PTH, ferritin	Itching severity associated with (i) Decrease in QOL (ii) Increased medication use: (i.v. antibiotic, i.v. ESA, and i.v. iron) (iii) Increase in missed HD sessions
Kimata <i>et al.</i> , 2014 <sup>22</sup>	6480 Japanese HD patients from JDOPPS (1996–2008); 60–65 facilities followed for a median of 1.9 yr	Itching severity: VRS (5-grade); QOL: SF-36, SF-12; Sleep quality: self-report: “very bad” or “fairly bad”	44% of patients experienced moderate to severe itching	Higher AOR of moderate to extreme pruritus: older, male, smoking, HTN, AVG, ascites, hepatitis C; higher Ca, Phos, or PTH levels; lower albumin, aluminum levels Lower odds: ESRD ≤ 1 yr	Patients with moderate to extreme pruritus compared to no/mild pruritus (i) Feel drained (AOR = 2.2–5.8) (ii) Poor sleep (AOR = 1.9–3.7) (iii) Lower QOL mental and physical composite scores (adjusted) Pruritus in HD patients associated with a 23% higher adjusted mortality (P = 0.09)
Pisoni <i>et al.</i> , 2006 <sup>13</sup>	18,801 adult HD patients from 308 dialysis centers in DOPPS I (1996–2001) and 322 centers in DOPPS II (2002–2004)	Itching: VRS (5-grade); Sleep quality: 3 self-report questions; QOL: SF-36 or SF-12	Moderate to extreme pruritus in 42% of patients in DOPPS II and 45% in DOPPS I	Higher AOR of moderate to extreme pruritus: male, lung disease, CHF, neuro disease, ascites, hepatitis C; higher Ca, Phos, WBC; lower albumin Lower adjusted odds: high serum ferritin, ESRD vintage ≤3 mo or lived with ESRD >10 yr	Patients with moderate to extreme pruritus compared to none (i) 13% higher adjusted mortality risk in DOPPS I, 21% higher in DOPPS II (ii) Feeling drained (AOR = 2.3–5.3) (iii) Depression (AOR = 1.3–1.7) (iv) Poor sleep (AOR = 1.4–4) (v) Worse QOL. No itch had MCS/PCS scores 8.6/6.4 points higher than those with extreme itchiness
Narita <i>et al.</i> , 2006 <sup>23</sup>	1773 adult Japanese HD patients followed for 2 yr or until death	Itching: VAS: No/mild = <4; moderate = 4–6.9; severe = ≥7; Frequency (graded 1–5); Sleep disturbance (graded 1–4)	No/mild = 19.5%; moderate = 27.9%; severe VAS = 25.5%	Male, BUN, β2-microglobulin; higher Ca and Phos were risk factors for severe pruritus (adjusted) Low Ca and PTH associated with reduced risk	Severe pruritus is an independent predictor of death (HR = 1.60). In patients with severe pruritus, more than 70% complained of grade 2–4 sleep disturbance (unadjusted).
<b>Pre-dialysis CKD</b>					
Sukul <i>et al.</i> , 2019 <sup>7</sup>	3780 patients with CKD 3–5 from the US, Brazil, and France	Itching severity: NRS (5-grade), PCS score; QOL: SF-36; Depression: CES-D short form, MCS score	24% with moderate to severe itching	Higher APR of moderate to extreme pruritus: older age, female sex, stage-5 CKD, lung disease, DM, physician-diagnosed depression; higher Phos and lower Hgb; Lower I with male sex	Patients with extreme pruritus compared to none (i) Lower QOL—7.6- and 6.2-point decrease in PCS and MCS scores, (ii) More depression (APR = 2.55), (iii) More restless sleep (APR = 2.1)
<b>Peritoneal dialysis</b>					
Min <i>et al.</i> , 2016 <sup>24</sup>	425 HD and 223 PD patients from Korea	Itching intensity: VAS, modified Pauli-Magnus scale <sup>25</sup>	PD > HD— 62.6% vs. 48.3% with VAS ≥ 1	Pruritus negatively correlated with Kt/V and positively correlated with dialysis vintage, BP, cholesterol (adjusted)	PD associated with higher odds of pruritus than HD (AOR = 1.76) Pruritus associated with higher BMI (AOR = 1.06)
Li <i>et al.</i> , 2015 <sup>26</sup>	362 Chinese PD patients	Itching intensity: VAS (No = 0, mild–moderate = 1–5, severe >5) Sleep quality: PSQI Depression: BDI QOL: SF-36	No = 34.8%; Mild–moderate = 52.5%; severe = 12.7%	Pruritus associated with dialysis vintage (AOR = 1.04) and higher PTH (AOR = 1.3)	Severe pruritus associated with higher (i) PSQI, BDI (adjusted) (ii) Lower SF-36 PCS scores (unadjusted)

AOR, adjusted odds ratio; APR, adjusted prevalence ratio; AVG, arteriovenous graft; BDI, Beck’s Depression Inventory; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; Ca, calcium; CAD, coronary artery disease; CES-D, Center for Epidemiologic Studies Depression Scale; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; DOPPS, Dialysis Outcomes and Practice Patterns Study; ESA, erythropoiesis-stimulating agents; ESRD, end-stage renal disease; HD, hemodialysis; Hgb, hemoglobin; JDOPPS, Japanese Dialysis Outcomes and Practice Patterns Study; KDQOL, Kidney Disease quality of life; HTN, hypertension; MCS, Mental Component Summary; MCS; Mental Component Summary; NRS, Numeric Rating Scale; PCS, Physical Component Summary; PD, peritoneal dialysis; PCS, Physical Component Summary; Phos, phosphorus; PSQI, Pittsburgh Sleep Quality Index; PTH, parathyroid hormone; QOL, quality of life; SF-12, 12-item short-form health survey; SF-36, 36-item short-form health survey; VAS, visual analog scale; VRS, verbal rating scale; WBC, white blood cell.

directors estimated that <5% of their patients had severe pruritus, and overall, they underestimated the prevalence of pruritus in 69% of facilities.<sup>3</sup>

Patients similarly underreport itching. In phase V of DOPPS, 17% of patients who were nearly always or always bothered by itching did not report their symptoms to a clinician.<sup>3</sup> This varied from a low of 8% in Italy to a high of 33% in the US. They were most likely to report itching to a nephrologist (42%), a nurse or other dialysis staff member (32%), a dermatologist (18%), or a primary care doctor (16%).

In a study from the UK, face-to-face, semi-structured individual interviews were performed with 25 CKD patients who self-reported itching (61% of those approached), 10 nephrologists, and 12 nurses.<sup>36</sup> Reasons for underreporting and undertreating itching included a lack of knowledge of causes and treatment, ambivalent attitudes toward itching as an important health issue, and the need for prompts to assess itching during consultations.

### Characteristics of CKD-aP

Data are mixed regarding variables that associate with CKD-aP. Although markers of mineral metabolism<sup>13,22,23,37</sup> and dialysis efficiency<sup>13,23,24,26,38</sup> have historically been thought to associate with CKD-aP, many studies, including the most recent study of DOPPS, have challenged these findings.<sup>3,39</sup> A multivariate analysis of 6256 patients from DOPPS found no association between CKD-aP and phosphorus, calcium, calcium-phosphorus product, parathyroid hormone (PTH), Kt/V, or hemodiafiltration.<sup>3</sup> Older age, higher c-reactive protein, low serum albumin, and presence of hepatitis B or C were found to associate with CKD-aP.<sup>3</sup> Other studies have also found an association between comorbid conditions and CKD-aP.<sup>13,21,22</sup> Variables associated with CKD-aP from recent large prevalence studies are listed in Table 1.

### Outcomes

CKD-aP is associated with adverse medical and psychosocial outcomes. Recent studies examining CKD-aP outcomes are summarized in Table 1.

#### Medical Outcomes

Data from DOPPS phases I and II showed that hemodialysis patients with moderate to extreme pruritus had significantly higher mortality than those not bothered by pruritus, even after adjustment for demographic and clinical variables.<sup>13</sup> Adjusted mortality had a 13% higher risk in DOPPS I, and a 21% higher risk in DOPPS II. This mortality difference, however, was attenuated and became nonsignificant by the addition of 3 sleep variables (awake at night, sleepy during the day, and not enough sleep), suggesting that sleep

disturbances may explain increased mortality. Similarly, a prospective analysis of 6480 Japanese HD patients with moderate to extreme pruritus showed a 37% higher adjusted mortality risk when compared to patients with mild/no pruritus.<sup>22</sup>

Increasing pruritus severity has also been shown to increase both rates of medication use, including intravenous antibiotics, erythropoiesis-stimulating agents, and iron, and the number of missed HD sessions.<sup>21</sup> This may, in part, explain the higher mortality rates in patients with CKD-aP.

#### Quality of Life

In DOPPS I and II, increasing pruritus intensity was associated with lower KDQOL mental component summary and PCS scores in adjusted models, and patients not bothered by pruritus had mental component summary and PCS scores 8.6 and 6.4 points higher than those patients extremely bothered by pruritus.<sup>13</sup> Furthermore, pruritus was associated with symptoms that may negatively affect QOL. Moderate to extreme pruritus was associated with 2.3–5.2-fold higher adjusted odds of feeling drained.<sup>13</sup> In combined data from DOPPS I–V, patients who were nearly always or always bothered by itching were more often bothered by pruritus' effects on the appearance of their skin, social interactions, and their ability to work.<sup>3</sup>

QOL data from DOPPS has been corroborated in 103 HD patients with CKD-aP from the ITCH Registry study.<sup>4</sup> In this cohort, itching severity was significantly associated with lower health-related QOL. Additionally, longitudinal changes in itching intensity were associated with changes in QOL.

In patients on PD, pruritus is associated with worse QOL.<sup>26</sup> In a cross-sectional study of 362 continuous ambulatory PD patients from China, patients with severe pruritus had lower SF-36 PCS scores than those with mild or moderate pruritus.<sup>26</sup>

#### Sleep Disturbances

In DOPPS I, 72% of patients with pruritus were moderately to extremely bothered by either being awake at night, being sleepy during the day, or not getting enough sleep, and 45% of those with moderate to severe pruritus had poor sleep quality.<sup>13</sup> Additionally, HD patients with moderate to extreme itching had 1.4–4.0 times higher adjusted odds of being awake at night, feeling sleepy during the day, or not having enough sleep than patients not bothered by itching.

Additional cross-sectional studies have found a negative association between pruritus and sleep. In a study of 1773 Japanese HD patients, 34% with mild or moderate pruritus and 70% with severe pruritus complained of sleep disturbance.<sup>23</sup> In a study of 139 Italian HD patients and 30 PD patients, pruritus was

associated with an 8.4 times higher adjusted odds of poor sleep.<sup>30</sup>

### Depressive Symptoms

CKD-aP is associated with poor mood and depression, and additionally, depressive symptoms may lead to pruritus. In DOPPS I and II, itching severity was associated with 1.3–1.7 times higher odds of chart extracted, physician-diagnosed depression.<sup>13</sup> In DOPPS I–V, patients who were nearly always or always bothered by itching more often reported feeling frustrated, annoyed, and depressed.<sup>3</sup> In a prospective study of 1799 Japanese HD patients with mild to no pruritus, depressive symptoms significantly increased the adjusted odds of developing severe pruritus (adjusted odds ratio = 1.57).<sup>40</sup>

### Nondialysis CKD

Data from CKDopps showed that increasing pruritus severity was associated with worse KDQOL-36 mental component summary and PCS scores, even after adjustment for possible confounders, and patients with extreme pruritus had PCS and mental component summary scores that were 7 and 6 points lower than those in patients without pruritus.<sup>7</sup> Furthermore, patients with moderate and severe pruritus had adjusted prevalence ratios for depressive symptoms that were approximately 2 and 2.5 times higher, respectively, than those in patients without pruritus. Finally, in patients with moderate and extreme pruritus, the adjusted prevalence ratio of patient-reported restless sleep was 1.69 and 2.10 times higher, respectively, than that in patients without pruritus, and 48% self-reported restless sleep, at least 3 days out of the week, compared to 26% without pruritus.

### Pathogenesis

The pathophysiology of chronic itching is complex and incompletely understood. It is generally thought that pruritogens (itch-producing compounds like histamine, prostaglandins, cytokines, neuropeptides, and proteases) are released by keratinocytes, immune cells, or neighboring neurons in the skin<sup>8,41</sup> (Figure 2a). These pruritogens activate histamine dependent or independent primary afferent sensory neurons with cell bodies in the dorsal root and trigeminal ganglia through G protein-coupled, Toll-like, or interleukin receptors. These sensory neurons then propagate the itch signal to secondary neurons in the dorsal horn of the spinal cord. Spinal interneurons then modulate itching through specific neurotransmitters (e.g., natriuretic polypeptide B)<sup>42</sup> and ultimately activate projection neurons that transmit the signal up the spinothalamic tract to the cerebral cortex.<sup>43</sup>

Many different pruritogens, receptors, neurons, and neurotransmitters have been implicated in the pathophysiology of itching, and it is likely that different itch syndromes have unique sets of cells and molecules that transmit itch sensations. Few studies have examined the unique pathophysiologic mechanisms of itch generation in CKD-aP; however, based on the existing literature, 4 general theories have emerged: toxin deposition, peripheral neuropathy, immune system dysregulation, and opioid imbalance (Figure 2b).

### Toxin Deposition

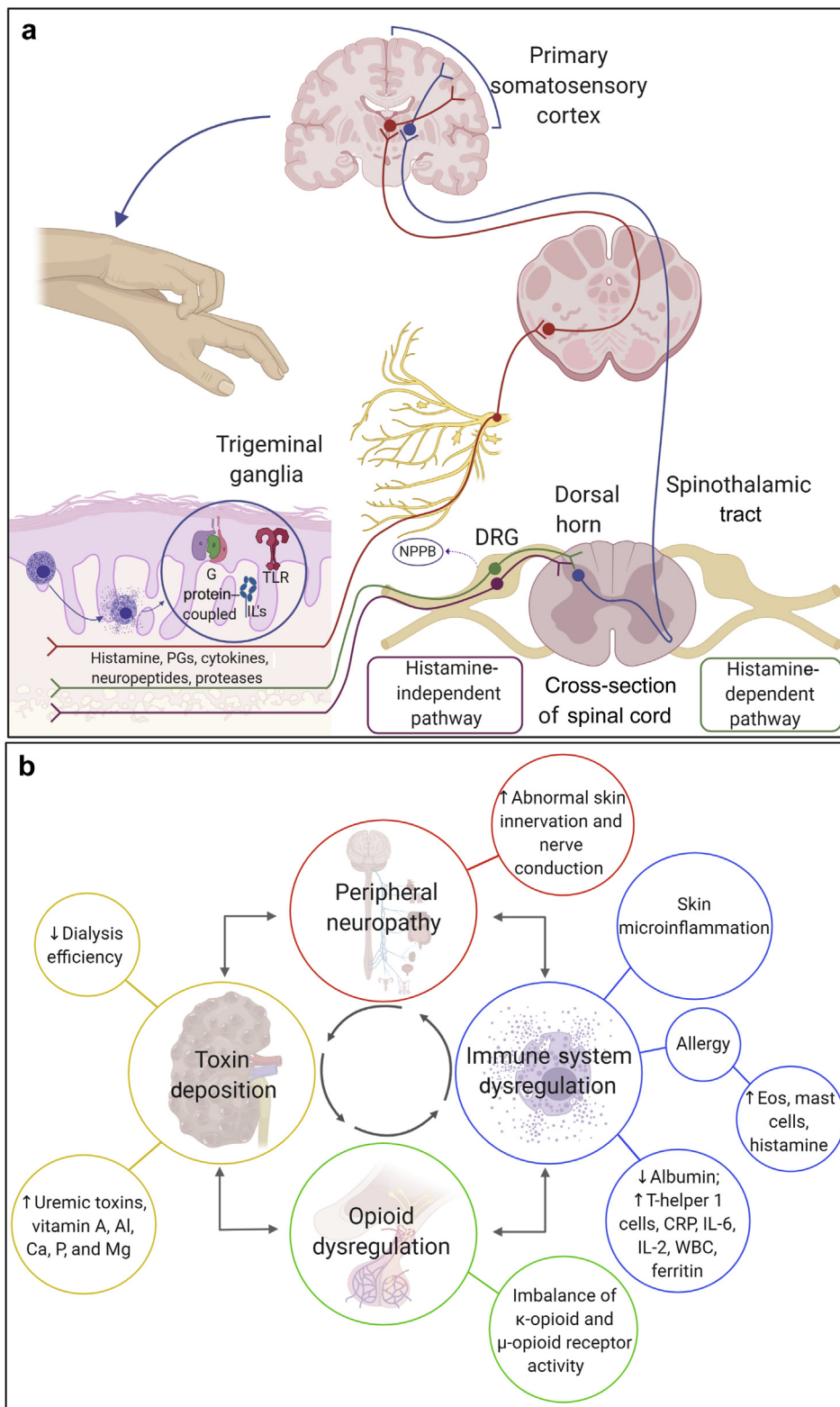
An initial theory of CKD-aP pathogenesis implicated toxins in the skin and subcutaneous tissue as potential pruritogens. Proposed toxins included “uremic toxins,” vitamin A, aluminum, calcium, phosphorus, and magnesium.<sup>1,22,44,45</sup> This theory was based on several early observations: (i) the association of CKD-aP with underdialysis<sup>1,23,46,47</sup> and with higher calcium, phosphorus, and PTH levels<sup>13,22,23,37</sup>; (ii) the improvement in CKD-aP prevalence rates over time<sup>1</sup>; and (iii) improvements in pruritus after treatment of high calcium, PTH, and phosphorus levels, including with parathyroidectomy.<sup>1,22,44,45,48</sup> Subsequent studies, however, have not confirmed these associations.<sup>3,39</sup> Furthermore, apart from 1 early prospective study showing a decrease in itching with increasing Kt/V,<sup>46</sup> subsequent studies have not shown improvement in CKD-aP with increasing dialysis efficiency.<sup>38,49</sup> It is currently thought that underdialysis and toxin deposition may cause CKD-aP in a subset of patients, and that itching in this subset should resolve with achievement of Kidney Disease: Improving Global Outcomes (KDIGO) goals for Kt/V, calcium, phosphorus, and PTH.<sup>5</sup>

### Peripheral Neuropathy

Neuropathic itching is thought to result when diseased primary afferent sensory neurons or diseased interneurons are activated out of proportion to or independent of any pruritogens.<sup>8</sup> A high prevalence of peripheral sensorimotor neuropathy and dysautonomia has been found in dialysis patients, and this may explain their itching.<sup>50</sup> Furthermore, dialysis patients with paresthesia and restless leg syndrome more frequently have CKD-aP.<sup>50–52</sup>

### Immune System Dysregulation

One theory of CKD-aP suggests that microinflammation in the skin and possibly systemic inflammation stimulate itching. Higher levels of inflammatory markers are seen in dialysis patients, including T-helper 1 cells, c-reactive protein, interleukin-6, and interleukin-2, supporting this hypothesis.<sup>53,54</sup> Furthermore, CKD-aP is associated with high white blood cell counts, low albumin and high ferritin levels (Table 1); anti-



**Figure 2.** Pathophysiology of chronic pruritus. (a) Histamine, prostaglandins (PGs), cytokines, neuropeptides, and proteases in the skin activate primary afferent sensory neurons with cell bodies in the dorsal root ganglia (DRG) and trigeminal ganglia through G protein–coupled, Toll-like, or interleukin receptors. These sensory neurons then activate secondary neurons in the dorsal horn of the spinal cord through itch-specific neurotransmitters and ultimately activate projection neurons that transmit the itch signal up the spinothalamic tract to the brain. (b) Multifactorial pathophysiology of chronic kidney disease–associated pruritus. Al, aluminum; Ca, calcium; CRP, C-reactive protein; Eos, eosinophils; IL, interleukin; Mg, magnesium; NPPB, natriuretic polypeptide B; P, phosphorus; TLR, Toll-like receptor; WBC, white blood cell.



inflammatory medication has been associated with a reduction in itching.

The allergic response may also be dysregulated in CKD-aP. Increased levels of eosinophils, mast cells, and the known pruritogens, histamine and tryptase, have been found in patients with CKD-aP.<sup>55,56</sup> However, classic histamine-specific skin changes such as wheals are absent in CKD-aP, and trials designed to decrease histamine release in CKD-aP generally have been negative.<sup>1</sup>

### Opioid Imbalance

Neuronal circuits that transmit pain and itch sensations overlap considerably.<sup>8</sup> Opioids, compounds that block pain, are also known to cause itching, and the opioid pathway, with receptors on the brain, peripheral nerves, keratinocytes, melanocytes, hair follicles, and immune cells, has been increasingly recognized as an important modulator of itching.<sup>57</sup> For example, endogenous opioid overstimulation has been implicated in the pathogenesis of cholestatic pruritus.<sup>58</sup>

One theory of CKD-aP suggests that overstimulation of central mu-opioid receptors, antagonism of peripheral kappa-opioid receptors, or an imbalance of stimulation and antagonism of mu- and kappa-opioid receptors causes itching.<sup>59,60</sup> This theory has been the basis of several recent trials of opioid receptor agonists and antagonists to treat CKD-aP.

### Treatment

There have been many prior studies of CKD-aP treatments. Unfortunately, studies examining these treatments have been limited by noncontrolled designs at single centers, small samples sizes, and varying methods of pruritus assessment. These flaws have limited the clinical relevance of the majority of CKD-aP studies. We present here only select trials of more commonly used treatments and prior double-blind randomized controlled trials (RCTs), categorizing them by proposed pathogenic targets (Table 2).

### Xerosis

Xerosis (dry skin) occurs in up to 85% of dialysis patients,<sup>6,7</sup> and although not thought to be the cause of CKD-aP,<sup>1</sup> it likely contributes to its severity.<sup>6</sup> Trials of emollient creams that rehydrate dry skin have decreased itching.<sup>5,76-79</sup> In a 7-day, multicenter, double-blind RCT of 100 dialysis patients with moderate to severe uremic xerosis randomized to glycerol 15% and paraffin 10% in an oil-in-water emulsion versus an oil-in-water emulsion alone, 73% of the group receiving the glycerol-paraffin emulsion had a treatment response, compared to only 44% of the

comparator group. At the end of a 49-day, unblinded, follow-up treatment period, pruritus severity decreased by 75%.<sup>75</sup> Given its low risk of side effects, we agree with recommendations to treat patients with CKD-aP, and evidence of xerosis, with emollient creams first, and to consider additional treatments if pruritus persists.<sup>1,5</sup>

### Toxin Removal

Toxin removal may improve CKD-aP by clearing pruritogens or improving the function of diseased neurons. In addition to uremic toxins, attempts have also been made to decrease calcium and phosphorus deposition in the skin.

There has been only 1 randomized trial to examine the effect of dialysis intensity on CKD-aP.<sup>46</sup> In a 3-month, randomized trial of 22 HD patients with severe pruritus, increased dialysis dose (mean Kt/V, 1.28) led to a significant decrease in itching compared to unchanged dialysis (mean Kt/V, 1.09). Unfortunately, these Kt/V values are below the current standards, making this study less relevant to current practice. Subsequent nonrandomized studies have yielded mixed results showing decreased itching,<sup>38</sup> and increased itching,<sup>49</sup> with increasing dialysis dose (Table 1).

Gut binding of uremic toxins has been studied to treat CKD-aP. In an 8-week, crossover RCT of 20 HD patients with resistant itching, 6 grams daily of activated charcoal, significantly decreased itching compared to placebo.<sup>62</sup> Unfortunately, the validity of this study is questionable due to a high drop-out rate (11 of 20 participants), and 1-sided statistical testing. Similarly, a small 4-week RCT of cholestyramine, a binding resin, resulted in modest improvements in CKD-aP.<sup>80</sup> In a recent review, Cupisti *et al.* summarize existing data and conclude that, although the evidence is limited, both oral activated charcoal and HD or hemoperfusion with an activated charcoal cartridge may have a role in the treatment of CKDaP.<sup>81</sup>

Hyperparathyroidism and high calcium, magnesium, and phosphorus levels have been associated with CKD-aP, and a few small studies suggest that decreasing the levels of these potential pruritogens may decrease itching.<sup>61,82</sup> A prospective, uncontrolled study of 37 dialysis patients with secondary hyperparathyroidism (mean PTH level, 1473 pg/ml), of which 22 had pruritus, found that parathyroidectomy significantly decreased itching.<sup>61</sup>

### Peripheral Neuropathy

Medications that treat peripheral neuropathy by blunting peripheral C-fiber nerve transmission have been used to treat itching.<sup>52,83-85</sup> In a crossover RCT of 25 HD patients, 300 mg gabapentin after dialysis



**Table 2.** Select treatment trials in patients with chronic kidney disease–associated pruritus (CKD-aP)

Author, yr	Study design and population	Intervention	Mechanism of action	Itching severity tool	Results
<b>Toxin removal</b>					
Ko <i>et al.</i> , 2013 <sup>38</sup>	Prospective cohort, unicenter study including 111 HD patients with milder pruritus	Increase Kt/V $\geq 1.5$ with use of high-flux dialyzer for 5 yr	More-efficient clearance of toxins that are pruritogenic	VAS	15.3% with aggravated pruritus, 33.3% unchanged, and 51.4% improved
Chou <i>et al.</i> , 2000 <sup>51</sup>	Retrospective cohort, 37 HD patients with secondary hyperparathyroidism, of which 22 had pruritus	Parathyroidectomy	Increase of Mg, Ca, and Phos might increase pruritus by metastatic cutaneous calcification (Ca x Phos) and stimulation of itch receptors	VAS and BRS	VAS decreased from $5.4 \pm 3.2$ to $1.8 \pm 1.5$ ( $P < 0.001$ )
Pederson <i>et al.</i> , 1980 <sup>62</sup>	Placebo-controlled, crossover, double-blind trial including 20 HD patients	Oral charcoal 6 g daily compared to placebo dextrose for 8 wk	Reduce GI absorption of uremic toxins that are pruritogenic	Uremic pruritus score	Reduction in uremic pruritus score (33% $\pm$ 15%) ( $P = 0.01$ )
<b>Peripheral neuropathy</b>					
Gabapentin or pregabalin					
Gunal <i>et al.</i> , 2004 <sup>52</sup>	Randomized, placebo-controlled, double-blind crossover trial including 25 HD patients	Gabapentin 300 mg or placebo thrice weekly for 4 wk at the end of HD	Mimics the neurotransmitter GABA	VAS	Pruritus decreased to $1.2 \pm 1.8$ (gabapentin; $P < 0.01$ ) and to $7.6 \pm 2.6$ (placebo; $P = 0.01$ ) from a mean of $8.4 \pm 0.94$
Yue <i>et al.</i> , 2015 <sup>63</sup>	Randomized, prospective, double-blind study including 188 HD or PD patients	Pregabalin 75 mg twice weekly (PD) or daily (after HD), ondansetron 8 mg/d, or placebo for 12 wk	Suppresses release of presynaptic glutamate	VAS and modified Duo's VAG scale	Pruritus improved in pregabalin group compared to ondansetron or placebo ( $P < 0.05$ )
Rayner <i>et al.</i> , 2012 <sup>64</sup>	Randomized trial including 71 CKD stage IV–V, HD, and PD patients with uremic pruritus	Gabapentin 100 mg or pregabalin 25 mg daily for 2 mo	As above	Pruritus scale (0–10)	Gabapentin relieved itching in 66% and pregabalin in 81%
<b>Topical capsaicin</b>					
Cho <i>et al.</i> , 1997 <sup>65</sup>	Randomized, double-blind, placebo-controlled, crossover study including 22 HD patients with moderate to severe refractory pruritus	2 subgroups with low PTH ( $\leq 35$ pg/ml) or high PTH ( $\geq 35$ pg/ml) assigned to capsaicin 0.025% cream or placebo-based cream for 8 wk	Depletes substance P, a potential pruritogen, from peripheral neurons	Pruritus score (mild, moderate, or severe)	Capsaicin cream was significantly more effective in improving the itching score ( $P < 0.001$ ). 7 patients had complete resolution and 12 obtained significant relief ( $P < 0.01$ )
<b>Serotonin antagonists</b>					
Murphy <i>et al.</i> , 2003 <sup>66</sup>	Randomized, placebo-controlled, double-blind trial including 24 HD patients	Ondansetron 8 mg or placebo 3 times/d for 2 wk	5-HT <sub>3</sub> , a potential pruritogen, receptor antagonist	VAS	Pruritus decreased by 16% during active treatment and 25% during placebo
<b>Immunomodulatory treatment</b>					
Ultraviolet-B phototherapy					
Ko <i>et al.</i> , 2011 <sup>67</sup>	Single-blind, randomized, controlled trial for refractory uremic pruritus including 28 CKD stage III–V, HD, or PD patients	NB UV-B phototherapy 3 $\times$ per wk for 6 wk or placebo with 10% incremental increase each session	UVB modulates T helper 1 and 2 lymphocyte differentiation and decreases production of IL-2	VAS, sleep quality, and short-form McGill pain questionnaire	NB-UVB showed a significant improvement in VAS ( $P < 0.01$ ) but not sleep quality
Gilchrest <i>et al.</i> , 1977 <sup>68</sup>	Randomized trial of 18 HD patients with severe pruritus	Exposure of UV A or B light therapy twice a wk for 4 wk	As above	Visual examination and severity of itching (none, mild, moderate, or severe)	9 of 10 in the UVB group experienced dramatic improvement in pruritus ( $P < 0.01$ )
<b>Gamma-linolenic acid</b>					
Chen <i>et al.</i> , 2006 <sup>69</sup>	Prospective, randomized, double-blind, placebo-controlled, crossover study including 17 HD and PD patients in a single center with refractory uremic pruritus	GLA 2.2% cream or placebo once a day to entire body and to pruritic sites 3 $\times$ /d for 2 wk with crossover after	GLA is an essential fatty acid associated with immune modulation of T lymphocytes and lymphokines	VAS and modified PS	Greater antipruritic effect with GLA than placebo with means of VAS (change ratio %)—( $51.23\% \pm 29.41\%$ vs. $14.97\% \pm 14.73\%$ ) and means of PS (change ratio %)—( $40.36\% \pm 21.34\%$ vs. $9.92\% \pm 11.62\%$ ; $P < 0.01$ )

(Continued on next page)

**Table 2.** (Continued) Select treatment trials in patients with chronic kidney disease–associated pruritus (CKD-aP)

Author, yr	Study design and population	Intervention	Mechanism of action	Itching severity tool	Results
Yoshimoto-Furuie <i>et al.</i> , 1999 <sup>70</sup>	Double-blind, randomized trial including 16 HD patients with uremic pruritus	Oral supplementation with either $\gamma$ -linolenic acid rich evening primrose oil (EPO) or linolenic acid (2 g/each) for 6 wk	As above	Questionnaire and visual inspection assessing dryness, pruritus, and erythema in a double-blind matter (5-grade)	EPO-exposed patients had significant improvement in the skin scores for the 3 different uremic skin symptoms and had increased levels of dihomo- $\gamma$ -linolenic acid (precursor of PGE <sub>1</sub> )
<b>Topical tacrolimus</b>					
Duque <i>et al.</i> , 2005 <sup>71</sup>	Randomized, double-blind, vehicle-controlled study in a single US center including 22 HD patients with severe uremic pruritus	Topical tacrolimus ointment 0.1% 3× weekly or placebo for 4 wk only on pruritic areas	Prevents transcription of messenger RNA for various inflammatory cytokines (IL-2) in Th1 and Th2	VAS and 3-point Likert scale	No difference in severity between groups
<b>Opioid</b>					
<b>Difelikefalin</b>					
Fishbane <i>et al.</i> , 2020 <sup>19</sup>	Double-blind, randomized placebo-controlled study including 378 HD patients with moderate to severe pruritus at 56 US sites	2 groups: i.v. difelikefalin (CR845) (0.5 $\mu$ g/kg of dry BWT) or placebo 3× per wk for 12 wk	Peripherally restricted, selective kappa opioid receptor agonist	24-hour WI-NRS, 5-D itch scale, and Skindex-10 scale	Primary: improvement of $\geq 3$ points from baseline at wk 12 in weekly mean 24-h WI-NRS (51.9% vs. 30.9%, $P < 0.01$ ) Secondary: improvement of 5-D itch scale ( $-5 \pm 0.3$ vs. $-3.7 \pm 0.3$ ) and the Skindex-10 scale ( $-17.2 \pm 1.3$ vs. $12 \pm 1.2$ )
<b>Naltrexone</b>					
Pauli-Magnus <i>et al.</i> , 2000 <sup>25</sup>	Randomized, double-blind, placebo-controlled crossover study including 23 HD and PD patients with persistent pruritus	Naltrexone sequence (50 mg/d) or matched placebo with crossover for 4 wk	$\mu$ -opioid receptor antagonist	VAS, modified Pauli-Magnus scale	Pruritus decreased by 29.2% vs. 16.9% (placebo) on the VAS ( $P = 0.1$ ) and by 17.6% vs. 22.3% (placebo) on the detailed score ( $P = 0.6$ )
<b>Nalfurafine</b>					
Kumagai <i>et al.</i> , 2010 <sup>72</sup>	Randomized, double-blind, placebo-controlled study including 337 HD patients with CKD-aP	Randomized 1:1:1 to 5 $\mu$ g, 2.5 $\mu$ g of nalfurafine or placebo for 2 wk	Peripheral $\kappa$ -opioid receptor agonist that inhibits substance P, suppresses CNS $\mu$	VAS	5 and 2.5 $\mu$ g of nalfurafine significantly improved pruritus intensity compared to placebo ( $P < 0.01$ )
<b>Nalbuphine hydrochloride extended release</b>					
Mathur <i>et al.</i> , 2017 <sup>73</sup>	Multicenter, randomized, double-blind, placebo-controlled trial including 373 HD patients with moderate to severe pruritus	Randomized 1:1:1 to nalbuphine 120 mg, 60 mg, or placebo for 8 wk	$\mu$ -opioid receptor antagonist and $\kappa$ -opioid receptor agonist	Numerical rating scale (0–10)	The mean NRS declined by 3.5 (nalbuphine 120 mg) vs. 2.8 (placebo; $P = 0.02$ ), no significant difference between nalbuphine 60 mg and placebo
<b>Acupuncture</b>					
Che-Yi <i>et al.</i> , 2005 <sup>74</sup>	Randomized controlled trial including 40 HD patients with refractory pruritus	Acupuncture 3 times weekly or sham control for 1 and 3 mo	Block spinal cord release of opioid-like substances	Pruritus score questionnaire	Acupuncture had a significant reduction of pruritus at 4 and 12 wk vs. sham ( $P < 0.01$ )
<b>Other</b>					
<b>Xerosis treatment</b>					
Balaskas <i>et al.</i> , 2011 <sup>75</sup>	Randomized, double-blind, intraindividual, multicentric clinical study including 100 HD patients with moderate to severe CKD-aP	Applied twice/d an emulsion with glycerol 15%/paraffin 10% on 1 leg and the emulsion alone on the other leg for 7 d	Moisturizing and emollient therapy with high hydrating and covering properties	EI Gammal Score	73% reduction in EI Gammal score in the treatment group vs. 44% in the comparator ( $P < 0.01$ ) Pruritus severity decreased by 75% with treatment

BWT, body weight; BRS, behavior rating scale; Ca, Calcium; CNS, central nervous system; EPO, erythropoietin; EI Gammal, clinical score to grade pruritus; GI, gastrointestinal; GLA, gamma-linolenic acid; HD, hemodialysis; IL, interleukin; Mg, magnesium; NB, narrowband; NRS, numerical rating scale; PD, peritoneal dialysis; PGE<sub>1</sub>, prostaglandin E<sub>1</sub>; Phos, phosphorus; PTH, parathyroid hormone; PS, pruritus score; QOL, quality of life; UV, ultraviolet; WI-NRS, Worst Itching Intensity Numerical Rating Scale; VAS, visual analog scale.

significantly decreased itching intensity compared to placebo.<sup>52</sup> A qualitative systematic review of 7 studies with 179 patients with CKD-aP, the majority of which were refractory to antihistamines and topical emollients, found that gabapentin significantly decreased itching in 6 of 7 studies.<sup>84</sup> In 5 studies that used the 10-point VAS to measure itching, a decrease of 5.7 to 9.4 points from baseline was found on average by 3–8 weeks of treatment. Another recent systematic review and meta-analysis of 7 RCTs with 315 patients with CKD-aP found that gabapentin significantly reduced CKD-aP severity compared to placebo, but it had a nonsignificantly higher incidence of adverse drug events, including dizziness, drowsiness, and somnolence.<sup>86</sup> Other side effects of gabapentin include confusion, dry mouth, visual changes, weight gain, angioedema, and increased suicide risk. Unfortunately, these side effects often limit the use of gabapentin for CKD-aP.

Pregabalin has also improved CKD-aP,<sup>63,87</sup> including in patients who are not able to tolerate gabapentin.<sup>64</sup> In a 12-week double-blind trial of 188 HD or PD patients, randomized to 75-mg twice-weekly pregabalin, 8 mg/d ondansetron, or placebo, only pregabalin improved pruritus severity.<sup>63</sup> In a study of 71 stage 4 and 5 CKD and dialysis patients, both gabapentin and pregabalin significantly improved pruritus intensity.<sup>88</sup> Furthermore, in 13 of 16 patients unable to tolerate gabapentin, pregabalin improved itching intensity after a median treatment period of 2.5 months.

Additional medications that have been used to treat neuropathic pain and CKD-aP include analgesics like capsaicin and pramoxine, and serotonin receptor antagonists.<sup>65,89–91</sup> A systemic review that included 3 RCTs of patients with CKD-aP found that topical capsaicin could not be recommended to treat CKD-aP given design flaws in current studies and insufficient evidence to support its use.<sup>90</sup> A 4-week RCT of 28 HD patients randomized to twice-daily pramoxine cream versus control lotion found pramoxine decreased itch severity more than control (61% vs. 12%).<sup>91</sup> Studies of serotonin receptor antagonists, like granisetron, tropisetron, and ondansetron (all anti-emetics), for CKD-aP have been essentially negative.<sup>63,92–94</sup> A systematic review, which included 2 RCTs of patients with CKD-aP, found that ondansetron had minimal to no effect on pruritus.<sup>93</sup>

### Immunomodulatory

Many immunomodulatory treatments have been studied in patients with CKD-aP (Table 2). Of these treatments, ultraviolet B (UVB) light therapy, gamma-linolenic acid, and mast-cell stabilizers have shown the most promise in reducing itching.

UVB light therapy modulates the immune system by inhibiting T-helper 1- and 2-mediated immune responses and altering interleukin production. Several noncontrolled trials of UVB therapy have shown dramatic improvement in pruritus.<sup>55,56</sup> A 4-week trial of 18 HD patients with severe pruritus randomized to UVB or UVA therapy light found that 90% of the UVB group had reduced itching compared to 20% of the UVA group.<sup>68</sup> Unfortunately, side effects, including the risk of skin carcinogenesis, have limited its use.<sup>1</sup> Trials of narrowband UVB therapy, designed to deliver a smaller range of ultraviolet light and reduce side effects, have yielded mixed results.<sup>67,95</sup>

Gamma-linolenic acid is an essential fatty acid that is metabolized to a prostaglandin precursor with anti-inflammatory properties.<sup>69</sup> In a 2-week, randomized controlled, crossover trial of 17 dialysis patients with refractory pruritus, gamma-linolenic acid 2.2% cream significantly improved pruritus compared to placebo.<sup>69</sup> Similarly, in a 6-week study of 16 HD patients randomized to gamma-linolenic acid-rich oral evening primrose oil versus linolenic acid, primrose oil showed a trend toward decreased itching compared to linolenic acid.<sup>70</sup>

Antihistamines are a widely used medication to treat chronic itching. Current treatments can be divided into histamine receptor antagonists, such as diphenhydramine, hydroxyzine, loratidine, or cetirizine, and mast cell stabilizers such as cromolyn sodium, zinc sulfate, and ketotifen. Unfortunately, despite a clear mechanistic explanation for its proposed effects, studies of histamine receptor antagonists generally have been unsuccessful.<sup>2,92,96,97</sup> Disappointing trial results and the potential for dangerous side effects like oversedation, especially in the elderly, make histamine receptor antagonists less desirable medications for the treatment of CKD-aP.

Mast cell stabilizers have had positive results in treating CKD-aP.<sup>56,98,99</sup> In a 4-week RCT of 60 HD patients, twice-daily cromolyn sodium cream 4% significantly reduced itching severity compared to placebo.<sup>100</sup> In a 2-month, double-blind RCT of 40 HD patients, zinc sulfate significantly improved CKD-aP compared to placebo<sup>101</sup>; these findings, however, were not confirmed in a subsequent RCT.<sup>88</sup>

One of the best designed trials of immunomodulators in patients with CKD-aP was a negative RCT of tacrolimus cream. Tacrolimus cream is a locally applied calcineurin inhibitor that has anti-inflammatory properties with minimal systemic absorption.<sup>71</sup> Two noncontrolled trials showed decreases in itching with this medication<sup>102,103</sup>; however, a 4-week double-blind RCT of 22 HD patients found that despite an approximately 80% reduction in itching severity, 0.1%



tacrolimus cream was similar to placebo in reducing itching.<sup>71</sup> Unfortunately, itching severity decreased by approximately 80% in the placebo group, more than originally expected, complicating attempts to prove the superiority of tacrolimus cream.

Additional trials of anti-inflammatory medications to treat CKD-aP include positive RCTs of thalidomide and turmeric, a positive noncontrolled trial of sericin cream, and a negative RCT of ergocalciferol.<sup>104–107</sup>

### Opioid Imbalance

Mu-opioid receptor antagonists, kappa-opioid receptor agonists, and combined antagonists and agonists have been studied to treat CKD-aP. Initial studies of naloxone and naltrexone, both mu-opioid receptor antagonists, yielded underwhelming results.<sup>25,108,109</sup> After 1 small RCT of naltrexone significantly improved pruritus, 2 subsequent trials failed to confirm this effect.<sup>25,108–110</sup>

Nalfurafine, a peripheral kappa-opioid receptor agonist, has successfully treated CKD-aP.<sup>72,111</sup> In a meta-analysis of RCTs, nalfurafine significantly reduced itching in 144 HD patients compared to placebo over 2 and 4 weeks.<sup>111</sup> In a 2-week study of 337 HD patients with pruritus, randomized 1:1:1 to 5 µg of nalfurafine, 2.5 µg of nalfurafine, or placebo, both 5 and 2.5 µg of nalfurafine significantly decreased itching.<sup>72</sup> Oral nalfurafine is currently approved to treat resistant pruritus in Japanese HD patients.<sup>112</sup>

Nalbuphine hydrochloride, a mu-opioid receptor antagonist and kappa-opioid receptor agonist, has improved pruritus in HD patients. In a large, multicenter RCT, 373 HD patients with moderate or severe CKD-aP were randomized 1:1:1 to nalbuphine 60-mg tablets, nalbuphine 120-mg tablets, or placebo.<sup>73</sup> Nalbuphine 120 mg led to significant reductions in itching, as measured by the NRS, compared to placebo over 8 weeks, and trended to less sleep disruption ( $P = 0.06$ ). There were no significant differences between 60-mg nalbuphine and placebo in itch reduction, and no difference in serious adverse events between groups.

Difelikefalin, a peripheral kappa opioid receptor agonist, has also improved pruritus in HD patients.<sup>19</sup> In a recently published multicenter RCT, 378 HD patients with moderate or severe uremic pruritus (weekly mean score >4 points on the 24-hour worst itching intensity NRS) were randomized 1:1 to intravenous difelikefalin (at a dose of 0.5 µg/kg) or matched placebo three times per week for 12 weeks. 38% of patients in the difelikefalin group were on other anti-pruritic medications at study initiation and throughout the study. Difelikefalin significantly reduced worst itching intensity NRS compared to placebo (49.1% vs. 27.9%) and led to significant improvements in QOL compared to placebo.

To date, this is the largest RCT in CKD-aP. Side effects of difelikefalin included diarrhea, dizziness, and vomiting, but no dysphoria, hallucination, euphoria, or physical dependence was reported in the difelikefalin group.

Finally, acupuncture is thought to decrease itching by blocking spinal cord release of opioid-like substances.<sup>74</sup> A review of 3 RCTs and 3 uncontrolled observational trials found that acupuncture had beneficial effects on CKD-aP in all trials, but that there was a high risk of bias in these studies and ultimately there was insufficient evidence to recommend acupuncture to treat CKD-aP.<sup>113</sup>

### Treatment Patterns

Despite being nearly always or always bothered by itching, 18% of patients with CKD-aP in DOPPS phase V were not receiving treatment for this.<sup>3</sup> This is, in part, related to insufficient information and options provided to patients about these symptoms, and to inadequate treatment prescription.<sup>36</sup> Furthermore, in patients with CKD, not yet on dialysis, only 10% with moderate to extreme pruritus were being prescribed medications for itching.<sup>7</sup>

When dialysis medical directors do treat severe pruritus, they consider phosphorus control as the most important treatment, followed by increasing dialysis dose in patients with low Kt/V, increasing prescribed time in patients with short treatments, and lowering PTH levels when elevated. Prescribing medications was ranked the least important intervention. When medical directors did prescribe medication, 57% used oral antihistamines, 23% topical antihistamines, 9% topical corticosteroids, and 5% gabapentin therapy as first-line treatment. In terms of patient reporting, of patients nearly always or always bothered by itchy skin, 68% report using topical treatments, 28% oral medications, 18% no treatment, and 1% UV light therapy.<sup>3</sup>

### Future Directions

Recently, antagonists of neurotransmitters specific to the itch pathway have been studied in animal models of chronic itching. B-type natriuretic peptide (BNP, also called natriuretic polypeptide B) is a neurotransmitter involved in the murine itch response to multiple triggers, and blocking natriuretic peptide receptor 1 led to reductions in itching in animal models.<sup>42</sup> This is particularly relevant for dialysis patients, as higher levels of BNP have been found, and these higher levels correlate with increased itching.<sup>114</sup> Other potential receptor targets for itching include mas-related G-protein-coupled receptors, the protease-activated receptors 2 and 4, and histamine-4-receptor.<sup>115</sup>

## Recommendations

Our current approach to CKD-aP treatment is multifaceted and similar to recently published algorithms.<sup>1,5,43</sup> We first ensure that patients are meeting goals defined by Kidney Disease: Improving Global Outcomes for dialysis clearance and mineral and bone disease treatment, and if not, we bring patients to goal. Next, we treat xerosis if present, with a trial of emollient cream. For those patients with persistent pruritus despite this, we consider 300 mg gabapentin after dialysis, or 75 mg pregabalin twice weekly, depending on concurrent medical conditions and medications. If gabapentin or pregabalin are ineffective or unable to be used, the evidence is not strong enough to recommend any particular medication over another. There are, however, newer treatments that may be available to treat refractory pruritus in the near future. Nalfurafine, a kappa opioid receptor agonist; nalbuphine, a mu-opioid receptor antagonist and kappa-opioid receptor agonist; and difelikefalin, a peripheral kappa opioid receptor agonist, all showed positive results in large, double-blind RCTs, and nalfurafine is currently approved for use in Japan. These therapies may soon become treatment options for patients with CKD-aP.

## DISCLOSURE

SS has received consulting fees from CARA Therapeutics and Galderma within the past 5 years. Both companies have studied medications to treat chronic pruritus. SS was an investigator on a phase 2 trial of difelikefalin. The other author declared no competing interests.

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