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REVIEW

Chronic kidney disease-associated pruritus: impact on quality of life and current management challenges

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Abstract: Chronic kidney disease-associated pruritus (CKD-aP) is a distressing, often overlooked condition in patients with CKD and end-stage renal disease. It affects ~40% of patients with end-stage renal disease and has been associated with poor quality of life, poor sleep, depression, and mortality. Prevalence estimates vary based on the instruments used to diagnose CKD-aP, and standardized diagnostic instruments are sorely needed. Treatment studies have often yielded conflicting results. This is likely related to studies that are limited by small sample size, flawed designs, and nonstandardized diagnostic instruments. Several large well-designed treatment trials have recently been completed and may soon influence CKD-aP management.

Keywords: pruritus, chronic kidney disease, uremia, end-stage renal disease, itching, depression

Introduction

Pruritus is a highly prevalent condition in patients with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD) on dialysis. Despite being an annoyance, CKD-associated pruritus (CKD-aP) can adversely affect the quality of life (QOL) and medical outcomes. Several challenges have prevented significant advances in the treatment of CKD-aP despite >40 years of research in the field. These challenges include the protean manifestations of CKD-aP, a poor understanding of the underlying pathogenesis, nonstandardized diagnostic tools, and poorly designed treatment trials. This review examines current data on the diagnosis, epidemiology, outcomes, and treatment of CKD-aP. In addition, it also explores some of the challenges to successful treatment suggesting ways to overcome these challenges. Finally, it presents the findings from several recently completed trials that may soon affect CKD-aP treatment.

Diagnosis

CKD-aP has been defined as itching that is directly related to kidney disease, without another comorbid condition such as a comorbid liver or skin condition that includes itching. Because of the high prevalence of this condition in patients with advanced CKD and ESRD, providers should consider any itching in these patients to be related to CKD-aP unless there is a clear alternative explanation.[1]

There is no one specific profile that characterizes a patient with CKD-aP.[1] Severity of pruritus may vary over time from barely noticeable to itching that causes constant restlessness, and these symptoms can occur intermittently or be persistent.[1] Itching can also occur at any time in relation to dialysis, that is, before, during, or after.[2]

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The distribution of itching in CKD-AP is often symmetrical[3] but can be localized or generalized.[3] When localized, it often occurs in the back, face, and shunt arm.[2] Finally, CKD-aP can occur without any skin manifestations, can coexist with xerosis (dry skin) in between 50% and 85% of patients,[4] or can occur with superimposed complications of excoriation including impetigo, linear crusts, papules, ulcerations, and prurigo nodularis.[1]

Severity and QOL instruments

Several validated scales are used in studies that define the prevalence, outcomes, and treatment of CKD-aP. These scales can be divided into unidimensional (those that measure only CKD-aP severity), multidimensional (those that measure severity and other characteristics of pruritus), and scales that focus predominantly on QOL.[5] Commonly used unidimensional scales include the visual analog scale (VAS), the numeric rating scale (NRS), and the verbal rating scale (VRS).

The VAS is the most commonly used scale to measure CKD-aP severity.[6] The VAS, which was first developed to measure pain,[7] is a graphic depiction of a 100-mm horizontal line with the left end marked "no itch" and the right end marked "worst imaginable itch." Patients are asked to draw a vertical line along the marked scale to indicate where their itching severity lies along this spectrum. The length of the line created from the left end to the vertical mark is then measured in millimeters (separates itch severity by 1 mm units), and this length quantifies itch severity. Similarly, the NRS grades itch severity from 0 to 10 with 0 depicting no itch and 10 depicting the worst imaginable itch, and the VRS allows patients to choose between 4 itching severities: no, low, moderate, or severe itch. The VAS, NRS, and VRS seem to have similar reliability and validity.[5]

Multidimensional pruritus scales evaluate severity and other itch-related characteristics. Two common examples of multidimensional scales used in studies of patients with CKD-aP include the 5-D itch scale and the itch severity scale (ISS). The 5-D itch scale, designed as an outcome measure for clinical trials, measures the intensity of itch, how long it has lasted, whether it is improving or worsening, its effect on QOL, and its distribution. This scale correlates closely with VAS and is a reliable measure of change in itching severity over time.[8] Similarly, the ISS measures duration, frequency, pattern, distribution intensity, treatment, accompanying symptoms, and sensation of itching and effect of itching on QOL. This scale has been extensively validated and has good validity and reliability.[9]

Several scales have been developed and validated which measure the impact of skin disease on QOL. The dermatology QOL index (DLQI) and the Skindex have been used in patients with CKD-aP for this purpose. The DLQI, developed in 120 patients with various skin diseases, consists of 10 questions that can be grouped into 6 categories: symptoms/feelings, daily activities, leisure, work/school, personal relationships, and treatment.[10] It has been found to be a valid and reliable measure of pruritus in several skin conditions.[11] The Skindex consists of 61 items designed to capture the subjective effects of skin disease on QOL along with 5 major dimensions (psychosocial effects that are cognitive, social, or emotional and physical effects that are related to physical discomfort or limitations).[12] The original scale was found to be internally reliable, reproducible, and valid.[12] Since its development, several shorter modified versions have been validated and used in different dermatological conditions including CKD-aP.[3,13]

Sleep disruption is an important complication of itching. The Itch MOS was developed from the Medical Outcomes Study sleep questionnaire and validated in CKD-aP.[3] This instrument includes 10 questions evaluating the effect of itching on sleep latency, disruption, and daytime somnolence.

Finally, the majority of studies examining the effect of CKD-aP on QOL have used the 36-item short form health survey (SF-36), the 12-item short form healthy survey (SF-12) or a kidney-specific version, Kidney Disease QOL (KDQOL-SF). In its current version, the KDQOL-SF includes 43 kidney disease-specific questions and 36 SF core items.[14] The SF-36 core items measure physical functioning, role-physical, pain, general health perceptions, emotional well-being, role-emotional, social functioning, and energy/fatigue. The KDQOL-SF also includes a question about the extent to which patients were bothered by itchy skin over the past 4 weeks. All the versions of the SF are well validated and universally used.[15–17]

Challenges in diagnosis

Currently, there are no universally accepted scales for measuring CKD-aP severity, characteristics, or its effect on QOL. In addition, there is no one particular itching profile that defines patients with CKD-aP. This has undoubtedly resulted in heterogeneous patient populations in studies examining the prevalence, outcomes, and treatment of CKD-aP. These heterogeneous populations, in part, explain the large range of CKD-aP prevalence that has been observed and the mixed results of treatment studies. Universally accepted scales and definitions for CKD-aP are critical given the highly subjective

nature of this disease, so that treatment effects and decisions about efficacy can be standardized across studies. Universal scales should evaluate pruritus severity, duration, distribution, and its effect on QOL including sleep and mood. In the ITCH trial, Mathur et al developed and validated 4 scales that measure these attributes (Skindex-10, Itch MOS, Brief Itch Inventory, and the Patient Assessed Disease Severity) and also evaluated the NRS for worst itching intensity in the dialysis population for the first time.[3] These scales if universally used may help standardize the definitions of CKD-aP across studies.

Prevalence

CKD-aP is highly prevalent in CKD and ESRD populations worldwide and is estimated to occur in 20%–90% of dialysis patients. This wide range of prevalence rates is likely related to varying characteristics of studied populations, the era when studies were performed, and the diagnostic instruments used to define CKD-aP. Interestingly, the prevalence of CKD-aP may be improving over time, with rates declining from as high as 85% in the early 1970s, to between 20% and 40% in studies performed over the past 10 years.[1] Recent large studies defining prevalence rates of CKD-aP in hemodialysis (HD), peritoneal dialysis (PD), and CKD patients are summarized in Table 1.

HD

The largest international study of CKD-aP prevalence in HD patients was an analysis of the Dialysis Outcomes and Practice Patterns Study (DOPPS).[18] In this study, pruritus data

Table 1 Recent studies examining the prevalence, characteristics and outcomes of CKD-aP

Author, year	Study design and population	Itching and outcome tools	Prevalence	Characteristics	Outcome
Hemodialysis					
Pisoni et al, 2006[18]	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 adjusted odds of moderate to extreme pruritus: male, lung disease, CHF, neuro disease, ascites, hepatitis C; higher Ca, phos, WBC count, and lower albumin Lower adjusted odds: high serum ferritin, ESRD vintage ≤3 months or lived with ESRD >10 years	Patients with moderate to extreme pruritus compared to none: 1. 13% higher adjusted mortality risk in DOPPs I, 21% higher in DOPPS II 2. Feeling drained (AOR = 2.3–5.3) 3. Depression (AOR = 1.3–1.7) 4. Poor sleep (AOR = 1.4–4.0) 5. Worse QOL. No itch had MCS/PCS scores 8.6/6.4 points higher than those with extreme itchiness
Narita et al, 2006[30]	1,773 adult Japanese HD patients followed for 2 years 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, 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, >70% complained of grade 2–4 sleep disturbance (unadjusted)
Mathur et al, 2010[3]	103 US adult HD patients followed for 3.5 months	Itching severity: VAS, and NRS QOL: Skindex-10, BII, self-assessed Sleep disturbance: SSMOS, Itch MOS Depression: BDI	Daily or nearly daily itching in 84%; ongoing (>1 year) in 59%	Younger age associated with more severe pruritus	Changes in itching severity ≥20% associated with reduced HR-QOL Severity associated with sleep loss Severity was associated with higher BDI total scores (10.8 for <50 mm, 12.7 for 51–70 mm, and 17.7 for >71 mm)
Ramakrishnan et al, 2014[20]	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: 1. Decrease in QOL 2. Increased medication use: (IV antibiotic, IV ESA, and IV iron) 3. Increase in missed HD sessions

(*Continued*)

Table 1 (*Continued*)

Author, year	Study design and population	Itching and outcome tools	Prevalence	Characteristics	Outcome
Kimata et al, 2014[19]	6,480 Japanese HD patients from JDOPPS (1996–2008); 60–65 facilities followed for a median of 1.9 years	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 adjusted odds of moderate to extreme pruritus: older, male, smoking, HTN, AVG, ascites, hepatitis C, Ca, phos, or PTH levels; lower albumin, aluminum levels Lower odds: ESRD ≤1 year	Patients with moderate to extreme pruritus compared to no/mild pruritus: 1. Feel drained (AOR =2.2–5.8) 2. Poor sleep (AOR =1.9–3.7) 3. Lower QOL mental and physical composite scores (adjusted) Pruritus in HD patients associated with a 23% higher adjusted mortality (p=0.09)
Pre-dialysis CKD					
Solak et al, 2016[99]	402 Turkish patients with CKD 2–5	Presence of itching: Previously defined by Zucker et al[113] Itching severity: VAS	18.9%	Pruritus associated with furosemide, lower Hgb, eosinophils and xerosis cutis. ACEi or ARB not associated (unadjusted)	Itching severity not associated with CKD stage
Khanna et al, 2010[27]	150 Indian CKD 3–5 patients, and 50 on dialysis	Itching severity: VAS, and by 2 dermatologists	28.7%, pre-dialysis; 58%, dialysis	Pruritus associated with dialysis vintage, xerosis, and high Ca and phos	Increased prevalence of pruritus with worsening kidney disease
Peritoneal dialysis					
Min et al, 2016[22]	425 HD and 223 PD patients from Korea	Itching intensity: VAS, Modified Pauli-Magnus scale[90]	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 et al, 2015[21]	362 Chinese PD patients	Itching intensity: VAS (no =0, mild to moderate =1–5, severe >5) Sleep quality: PSQI Depression: BDI QOL: SF-36	No =34.8%, mild to 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 1. PSQI, BDI (adjusted) 2. lower SF-36 PCS scores – (unadjusted)

Abbreviations: CKD-aP, chronic kidney disease-associated pruritus; HD, hemodialysis; DOPPS, dialysis outcomes and practice patterns study; VRS, verbal rating scale; QOL, quality of life; SF, short form; CHF, congestive heart failure; Ca, calcium; phos, phosphorus; WBC, white blood cell; ESRD, end-stage renal disease; AOR, adjusted odds ratio; MCS, mental component summary; PCS, physical component summary; VAS, visual analog scale, BUN, blood urea nitrogen; PTH, parathyroid hormone; NRS, numeric rating scale; BII, brief itching inventory; SSMOS, sleep survey medical outcomes survey; MOS, medical outcomes survey; BDI, Beck's depression inventory; KDQOL, kidney disease QOL; DM, diabetes mellitus; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index; Hgb, hemoglobin; HTN, hypertension; AVG, arteriovenous graft; CKD, chronic kidney disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; PD peritoneal dialysis; PSQI, pittsburgh sleep quality index; HR, health related; IV, intravenous; ESA, erythropoietin.

were collected from 18,801 prevalent HD patients in 12 different countries. Participants were asked the extent to which they were bothered by itchy skin during a 4-week period and to categorize this itching into one of 5 grades: not at all bothered, somewhat bothered, moderately bothered, very much bothered, or extremely bothered. The prevalence of moderate to severe itching was 42% in DOPPS II (2002–2004) compared to 45% in DOPPS I (1996–2001). The prevalence of patients at least somewhat bothered by itching was 71% in DOPPS II and 74% in DOPPS I.

Similar prevalence rates of pruritus were found in 2 other large HD cohorts. In an analysis of 6,480 Japanese HD patients from the Japanese Dialysis Outcomes and Practice Patterns study (JDOPPS) (1996–2008), the prevalence of moderate to severe pruritus, defined using a 5-grade modified VRS scale, was 44%.[19] In the largest study of US HD patients (~40% African-Americans), the prevalence of any itching, defined using the 5-grade VRS scale from the KDQOL SF-36 survey was 60%.[20] In addition, 14.5% of these patients reported being very much or extremely bothered by itching and 30% being at least moderately bothered by itching.

PD

The prevalence of at least mild pruritus in PD patients seems to be ~50%. In a cross-sectional, single-center study of 362 Chinese PD patients, the prevalence of mild

to moderate pruritus was 52.5%, whereas the prevalence of severe pruritus was 12.7%.[21] In a cross-sectional study of 223 PD and 425 HD patients from Korea, the prevalence of at least mild pruritus was 62.5% in HD patients and 48.3% in PD patients.[22]

Several studies have compared CKD-aP prevalence rates in HD and PD patients with mixed results. Two studies found no difference in pruritus rates,[23,24] whereas one study found higher rates of pruritus in PD patients,[22] and one found higher rates of pruritus in HD patients.[25] These mixed results are likely due to the varied study populations and the different instruments used to measure CKD-aP in these studies.

CKD

Few studies have evaluated CKD-aP prevalence in patients with CKD not yet on dialysis. In a cross-sectional study of 402 patients with stage 2–5 CKD, the prevalence of CKD-aP was 18.9%.[26] In this study, pruritus was not affected by the stage of CKD. In a cross-sectional study of skin manifestations in 200 Indian CKD and ESRD patients (50 each in stages 3, 4, and 5 CKD and 50 patients with ESRD on dialysis), the prevalence of pruritus was 36%.[27] The authors found an increasing prevalence of skin manifestations with worsening kidney disease.

Two studies of advanced CKD patients (stages 4 and 5) referred to renal palliative care clinics and not initiated on dialysis found that pruritus prevalence is high in this population. In one study, pruritus occurred in 56% of 55 patients with stage 4 and 5 CKD (eGFR 3–30),[28] and in the other study, it occurred in 74% of 66 patients with stage 5 CKD (mean eGFR 11).[29]

Characteristics of CKD-aP

There are conflicting data regarding variables that associate with CKD-aP. There are, however, several groups of risk factors that show more consistent associations. These risk factors include gender, markers of bone and mineral metabolism, inadequate dialysis, and comorbid conditions. Variables associated with CKD-aP from recent large studies of prevalence are listed in Table 1.

Gender

Male gender has been found to be associated with CKD-aP in several large studies. In a study of the DOPPS database, male gender was associated with a 1.1 greater adjusted odds of having moderate to severe pruritus.[18] In 2 Japanese cohorts, male gender was associated with ~1.5 greater adjusted odds of moderate or severe pruritus.[19,30] In smaller and unadjusted analyses, however, gender has not been consistently associated with more severe pruritus.[3,20]

Mineral and bone metabolism

Markers of mineral and bone metabolism have been found to be associated with CKD-aP. In a prospective analysis of 1,173 Japanese HD patients, Narita et al found that hypercalcemia and hyperphosphatemia are associated with severe pruritus and that lower calcium and PTH reduced the risk of pruritus.[30] In the DOPPS, patients with a calcium phosphorus product >80 had a 1.5 times greater odds of pruritus compared with those having a product of 50–60.[18] In the Japanese DOPPS, a multivariate analysis showed higher calcium, phosphorus, and PTH were associated with greater adjusted odds of having moderate to severe pruritus.[19] Other small studies, however, have not found a consistent association with these markers and itching.[31,32]

Dialysis vintage and efficiency

Several studies have found an association between shorter dialysis vintage and pruritus. In the DOPPS, dialysis vintage ≤3months was associated with moderate to severe pruritus, and those on dialysis for >10 years were less likely to have pruritus in adjusted analyses.[18] In addition, in a study by Narita et al, dialysis vintage <12 months was associated with severe pruritus.[30] This association between dialysis vintage and pruritus has also been found in patients on PD.[21,22]

Early studies of CKD-aP reported higher prevalence rates, up to 85%, than those currently seen, suggesting a connection between dialysis efficiency and pruritus,[1] but these studies were limited by small sample sizes. Follow-up studies have shown an inconsistent relationship between dialysis efficiency and pruritus. In a study by Narita et al, higher BUN and β2 microglobulin (a maker of middle molecule clearance) were associated with more severe pruritus.[30] In a 5-year prospective study of 111 HD patients, Kt/V ≥1.5 and use of high-flux dialyzers were associated with a decreased intensity of pruritus.[33] The majority of studies, however, have not found an association between Kt/V and pruritus.[3,20,30]

Comorbid conditions

Comorbid conditions and inflammatory states are associated with pruritus in patients with ESRD. In several large studies, diabetes mellitus, lung disease, cardiovascular disease, neurological disease, liver disease, smoking, hypertension, higher body mass index, elevated white blood cell count, lower hemoglobin, and lower serum albumin were found to be associated with pruritus (Table 1).[18–20]

Outcomes

CKD-aP has been associated with adverse medical outcomes and poor QOL. Recent large studies examining the effect of CKD-aP on outcomes are summarized in Table 1.

Medical outcomes

ESRD patients with CKD-aP have higher mortality rates than those without. HD patients with moderate to extreme pruritus had a 13% higher adjusted mortality risk than those not bothered by pruritus in DOPPS I and a 21% higher risk in DOPPS II.[18] In a prospective study of 1,773 Japanese HD patients, followed for 24 months, of which 453 had severe pruritus, severe pruritus was independently associated with death.[30] Finally in an analysis of 6,480 Japanese HD patients from JDOPPS (1996–2008), followed for a median of 1.9 years, patients with moderate to extreme pruritus had a 37% higher adjusted mortality risk than patients with mild/no pruritus.[19]

In addition to affecting mortality, patients with CKD-aP have higher rates of medication use. In a cohort of 71,000 HD and PD patients, Ramakirshnan et al found that intravenous antibiotic, erythropoiesis-stimulating agent (ESA), and iron use increased as pruritus severity worsened. In addition, the number of missed HD sessions increased as pruritus worsened. In this cohort, ~56% of patients without pruritus missed dialysis sessions, whereas 63% of patients extremely affected by pruritus missed dialysis sessions. This increase in ESA use and missed HD sessions may, in part, explain the higher mortality rates in patients with CKD-aP.

QOL

The effect of pruritus on QOL in dialysis patients is readily apparent. These patients often appear unable to find a comfortable position and can scratch to the point of causing skin excoriations. When pruritus is severe and unrelenting despite treatment, sleep and social functioning can be affected. Finally, if left untreated long enough, these patients can develop depression. This relationship between pruritus and QOL may, in part, explain the higher mortality rates seen in patients with CKDaP compared to those without. Studies examining the relationship between CKDaP and QOL are summarized in Table 1.

The largest study to examine this relationship was from DOPPS. In this study, QOL was measured with generic, not CKD-aP-specific, scales: the SF-36 and SF-12.[18] The authors found that those with worse itching had worse QOL scores including mental and physical component summary scores (MCS and PCS).

In the prospective, longitudinal ITCH Registry study, Mathur et al measured QOL in 103 HD patients with CKD-aP over 12 weeks.[3] QOL was measured using the Skindex-10, Brief itching inventory (BII), and other author-developed instruments. The authors found that itching severity was significantly associated with lower health-related QOL in all measured domains across all instruments that were used. Furthermore, they found that longitudinal changes in itching intensity of ≥20% were associated with clinically significant changes in QOL.

In PD patients, pruritus is also associated with worse QOL.[21] Additional studies examining the effect of CKDA-aP on QOL are summarized in Table 1. The consistent association between CKD-aP and QOL is likely mediated, in part, through an effect of itching on sleep quality and mood.

CKD-aP has been associated with poor sleep quality. In the DOPPS, ~45% of patients with moderate to severe pruritus had poor sleep quality.[18] HD patients moderately to extremely affected by itching had a 1.4–4.0 higher adjusted odds of being awake at night, feeling sleepy during the day, or not having enough sleep than did patients not bothered by itchy skin. In the study by Narita et al, 70% of patients with severe pruritus complained of sleep disturbance, and 34% of patients with mild or moderate pruritus complained of sleep disturbance.[30] In a cross-sectional study of 139 Italian HD patients and 30 PD patients, 59.1% of patients with pruritus complained of difficulty sleeping.[24] By contrast, only 11.1% of patients without pruritus had difficulty sleeping. In addition, pruritus was associated with an 8.4 times higher adjusted odds of poor sleep.

Sleeping difficulties may also explain the link between pruritus and mortality. In the DOPPS, the significant relationship between pruritus and mortality became nonsignificant after adjustment for the 3 measured sleep variables.[18] This suggests that pruritus affects mortality through disrupted sleep.

CKD-aP has been associated with poor mood and depression. In several of the aforementioned studies, the mental component of the SF-36 and SF-12 QOL surveys were significantly affected by itching severity (Table 1). In the DOPPS, itching severity was associated with a 1.3–1.7 times higher odds of chart extracted, physician diagnosed depression.[18] In the ITCH study, itching severity was associated with higher total BDI scores (10.8 for VAS <50, 12.7 for VAS 51–70, and 17.7 for VAS >71).[3]

Furthermore, depressive symptoms may increase the future risk of developing pruritus. In a prospective study of 1,799 Japanese HD patients with mild to no pruritus followed

for between 0.5 and 2 years, depressive symptoms measured through the Mental Health Inventory significantly increased the adjusted odds of developing severe pruritus (adjusted odds ratio [OR] =1.57).[34]

In addition to the established strong correlations between the presence and severity of pruritus with negative effects on QOL, the causal effect of itching on QOL has also been examined in several treatment trials aimed at treating pruritus severity. For example, treatment with nalfurafine (vs placebo) significantly reduced itching intensity and also improved number of days of non-disturbing itching and number of nights of sound sleep.[35] Similarly, treatment with nalbuphine tablets (vs placebo) reduced itching and improved sleep quality[36] and pregabalin improved sleep and mental health (SF-12 mental health component) significantly compared with placebo.[37]

Pathogenesis

The pathogenesis of CKD-aP remains incompletely understood. Whereas inciting factors present in the uremic milieu (inflammatory mediators, electrolytes, altered endogenous opioids, etc) that trigger CKD-aP are unknown, the perception and perhaps perpetuation of itch seem to have a prominent central nervous system component. Local skin effects such as calcium phosphate deposition would be expected to result in generalized pruritus or pruritus that is randomly distributed; however, bilateral symmetry in discrete non-dermatomally distributed areas is characteristic of CKD-aP.[3,38,39] Over time, the location of itching in a patient can change, but bilateral symmetry is maintained.[3] This section briefly summarizes several theories that have been the basis of treatment studies (Figure 1). The treatment section will also contain a more in-depth review of these theories.

Immune-mediated hypothesis

The immune mediated hypothesis suggests that dysregulated systemic inflammation is the cause of CKD-aP.[1,40,41] This hypothesis is based on the high levels of systemic inflammation seen in patients with CKD-aP including high levels of T-helper 1 cells,[40] c-reactive protein, interleukin-6,[40] and interleukin-2,[41] and the association of CKD-aP with high white blood cell count, low albumin, and high ferritin levels (Table 1).

Xerosis hypothesis

This hypothesis suggests that dry skin is major contributor to CKD-aP. It is based on the high co-occurrence of xerosis with pruritus in advanced CKD and ESRD patients.[4] It is currently thought that xerosis is a significant contributor to CKD-aP severity but is not the only cause of itching.[4]

Histamine hypothesis

Increased levels of histamine, eosinophils, mast cells, and tryptase have been observed in patients with CKD-aP.[42,43] This

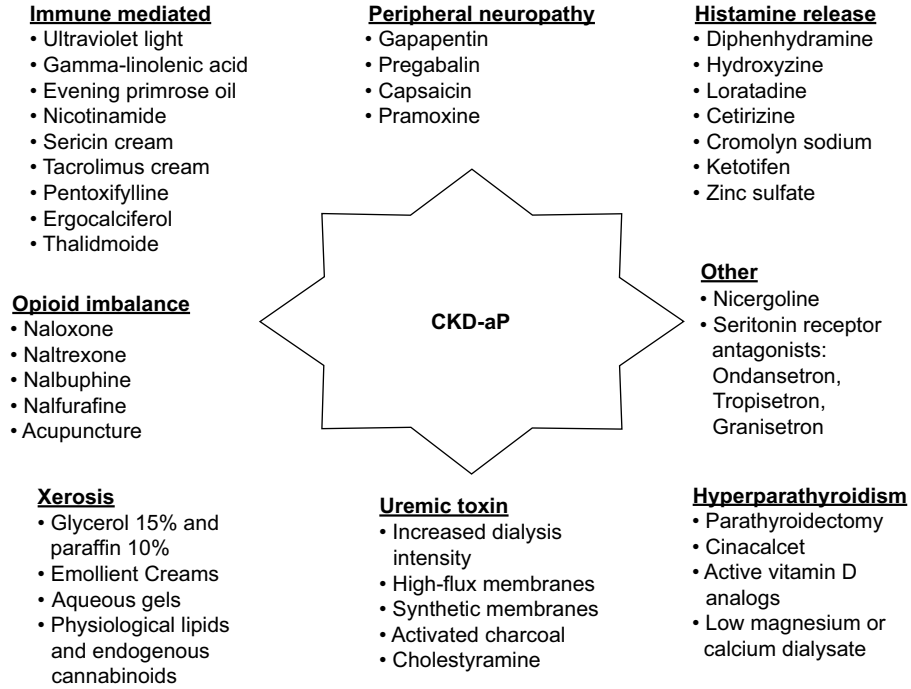

Figure 1 Prior treatments for chronic kidney disease-associated pruritus (CKD-aP) by proposed pathogenic mechanism.

hypothesis suggests that mast cell, histamine, and tryptase release may lead to CKD-aP.

Uremic toxin hypothesis

This hypothesis suggests that CKD-aP results from a buildup of uremic toxins. It is based on the improvement of CKD-aP prevalence rates over time that have been presumed to be related to improvements in dialysis efficiency,[1] the association of pruritus with markers of under-dialysis,[30] and the controversial association of increased dialysis efficiency with a decrease in itching severity.[44,45] Implicated toxins have included vitamin A, aluminum, calcium, phosphorus, and magnesium.[1,19,46,47]

Opioid imbalance hypothesis

Endogenous opioid over-stimulation has been implicated in the pathogenesis of cholestatic pruritus.[48] Similarly, it has been hypothesized that over-stimulation of endogenous opioid receptors causes CKD-aP.[49] Another similar hypothesis suggests that CKD-aP results from an imbalance of mu and kappa-opioid receptor activity with mu-receptor overactivation increasing itch and kappa receptor blockade also increasing itch.[50]

Peripheral neuropathy hypothesis

This hypothesis suggests that peripheral nervous system dysfunction leads to uremic itching. It is based on the abnormal skin innervation,[51–53] and abnormal nerve conduction studies seen in patients on dialysis, and the co-occurrence of CKD-aP with paraesthesia and restless leg syndrome.[51] CKD-aP, however, does not occur in a stocking-glove pattern characteristic of peripheral neuropathy.[3]

Hyperparathyroidism hypothesis

This hypothesis suggests that high levels of parathyroid hormone (PTH) lead to uremic itching. It is based on the consistent association of high PTH with CKD-aP (Table 1), and the improvement in pruritus seen in patients with CKD-aP after parathyroidectomy.[54]

Treatment

There have been many proposed treatments for CKD-aP. However, studies examining these treatments have been limited by non-controlled designs at single centers, small samples sizes, and non-uniform definitions of CKD-aP. To date, there has only been one published, large, double-blind, randomized controlled trial (RCT) testing a treatment for CKD-aP.[55] We present prior treatments for CKD-aP, categorizing then by proposed pathogenic targets. In addition, we have listed prior double-blind, RCT for CKD-aP in Table 2. We chose to include both positive and negative trials so that readers will not attempt to duplicate prior negative trials.

Immunomodulatory treatment

Immunomodulatory medications that have been studied to treat CKD-aP include ultraviolet-B (UVB) light therapy, gamma-linolenic acid (GLA), thalidomide, turmeric, nicotinamide, sericin cream, pentoxifylline, tacrolimus cream, and ergocalciferol. Of these treatments, UVB light therapy and GLA have shown the most promise for treating CKD-aP.

UVB light therapy inhibits T helper 1 and 2-mediated immune responses and modulates interleukin production. In the first trial of UV therapy to treat CKD-aP, 18 HD patients with severe pruritus were randomized to time-matched exposures of UVB or UVA therapy.[56] Nine of 10 participants in the UVB group experienced a dramatic improvement in pruritus compared to 2 participants in UVA group after 4 weeks. Subsequent trials confirmed the effectiveness of broadband UVB light therapy in reducing CKD-aP.[1,57,58] However, the side effects of this therapy, including possible skin carcinogenesis, have limited its use.[1] Recent trials of narrowband UVB therapy, designed to deliver a smaller range of UV light and reduce side effects, have yielded mixed results.[59,60]

GLA is an essential fatty acid that is metabolized to a prostaglandin precursor with known anti-inflammatory properties. It has been hypothesized that GLA and other essential fatty acids can improve itching by decreasing inflammation.[61] In a randomized controlled, crossover trial of 17 HD or PD patients with refractory pruritus, GLA 2.2% cream significantly improved pruritus compared to placebo over 2 weeks.[61] Similarly in a study of 16 HD patients randomized to oral evening primrose oil, which is GLA-rich, versus linolenic acid, evening primrose oil showed a trend toward improved pruritus compared to linolenic acid after 6 weeks of therapy ($0.05<p<0.1$). However, this study was not placebo controlled.[62]

Several additional RCT have shown promising results for anti-inflammatory agents as treatment for CKD-aP. In a double blind, randomized, controlled, crossover trial, thalidomide, a medication known to decrease systemic inflammation by suppressing tumor necrosis factor-alpha, significantly reduced pruritus compared to placebo over a 1-week treatment period.[63] However, only 62% of participants were able to complete the trial, and because of its side effects and potential for teratogenicity, subsequent trials of thalidomide to treat CKD-aP have not been performed.[63] In a double-blind, RCT of 100 patients on HD, turmeric, a

Table 2 Selected double-blind randomized-controlled treatment trials in patients with CKD-aP

Author, year	Study design and population	Intervention	Mechanism of action	Itching severity tool	Results
Silva et al, 1994[63]	DB, crossover RCT, of 29 HD patients (18 completed)	Thalidomide vs placebo treated for 2 weeks	Immunomodulator	UP score =NRS (4-grade) Response =50% reduction in UP score	56% responded with 78% reduction in UP score. Placebo with no response. (p<0.05 vs placebo)
Cho et al, 1997[101]	DB, crossover, RCT of 22 HD patients	Capsaicin 0.025% cream vs placebo base cream treated for 8 weeks	Analgesic	Patient self-assessment = modified VRS: none, mild, moderate, or severe	19/22 with relief of the itching. Significantly more effective at reducing itch than placebo (p<0.01)
Pauli-Magnus et al, 2000[90]	DB, crossover, RCT of 23 dialysis patients	Naltrexone vs placebo treated for 8 weeks	Mu-opioid antagonist	Detailed score: severity, distribution, sleep disturbance; VAS	VAS decreased 29.2% on naltrexone and 16.9% on placebo. Not significant, (p=0.1). No power analysis and incomplete washout
Gunal et al, 2004[53]	DB, crossover, RCT of 25 HD patients	Gabapentin vs placebo treated for 8 weeks	Analgesic	VAS	Gabapentin significantly improved itch severity compared to placebo. Unknown if washout complete
Duque et al, 2005[67]	DB, RCT of 22 HD patients	Tacrolimus 0.1% ointment vs placebo treated for 4 weeks	Immunomodulator	VAS	Tacrolimus 0.1% ointment similar to placebo (p=0.5). No power analysis
Chen et al, 2006[61]	DB, crossover, RCT of 17 dialysis patients	GLA 2.2% cream vs placebo-based cream treated for 4 weeks	Immunomodulator	VAS and a modified questionnaire	GLA-based cream significantly improved pruritus compared to placebo (p<0.01)
Young et al, 2009[104]	DB, RCT of 28 HD patients	Pramoxine 1% lotion vs control lotion treated for 4 weeks	Analgesic	VAS	61% decrease in itch intensity versus 12% in control group
Kumagai et al, 2010[55]	Multicenter, DB, RCT of 337 HD patients	Nalfurafine 5 vs 2.5 μg vs placebo randomized 1:1:1 and treated for 2 weeks	Kappa-opioid agonist	VAS	Both 5 and 2.5 μg nalfurafine significantly reduced VAS score compared to placebo (p<0.01)
Balaska et al, 2011[72]	DB, RCT of 100 dialysis patients treated for 1 week and followed for 56 days	Glycerol 15% and paraffin 10% in an oil-in-water emulsion vs emulsion	Rehydrating dry skin	El Gamma score (xerosis severity) and VAS	Treatment response (xerosis) in 73% of the patients compared to 44% in control (p<0.01). 75% improvement in pruritus during open-label period
Feily et al, 2012[82]	DB, RCT of 60 dialysis patients	Cromolyn sodium 4% cream vs placebo treated for 4 weeks	Mast-cell stabilizer	VAS scale	Cromolyn sodium 4% improved itching severity compared to placebo (p<0.04)
Shirazian et al, 2013[70]	DB, RCT of 50 HD patients	Ergocalciferol 50,000 IU vs placebo treated for 12 weeks	Immunomodulator	Pruritus severity questionnaire	Percent change in itch 38.9% with treatment vs 47.5% with placebo (p=0.34) + Power analysis
Yue et al, 2015[37]	DB, RCT of 188 HD or PD patients	Pregabalin vs ondansetron vs placebo treated for 12 weeks	Analgesic or serotonin receptor antagonist	VAS and modified Duo's VAG Scale	Pregabalin significantly improved pruritus compared to ondansetron and placebo (p<0.05)
Vandana et al, 2015[36] (abstract only)	Multicenter (46 US and EU sites), DB RCT of 373 HD patients	Nalbuphine ER tablets (2 doses) vs placebo treated for 8 weeks	Kappa-opioid agonist, mu-opioid antagonist	NRS, Skindex-10, Itch MOS, HADS	Itching intensity (primary endpoint) was significantly improved vs placebo

Abbreviations: CKD-aP, chronic kidney disease-associated pruritus; DB, double-blind; RCT, randomized controlled trial; HD, hemodialysis; UP, uremic pruritus; NRS, numerical rating scale; VRS, verbal rating scale; VAS, visual analog scale; GLA, gamma-linolenic acid; IU, international units; EU, European union, ER, extended release; MOS, medical outcomes survey; HADS, Hospital Anxiety and Depression Scale.

dietary spice with anti-inflammatory properties, significantly improved pruritus and high-sensitivity C-reactive protein compared to placebo.[64] In a 4-week RCT of 50 HD patients, oral nicotinamide significantly improved pruritus compared to placebo.[65] Two non-controlled trials showed that pentoxyfilline and sericin cream improved CKD-aP; however, these results have not been confirmed with a subsequent RCT.[62,66]

There have also been negative treatment studies of immunomodulators in patients with CKD-aP. Tacrolimus cream was postulated to be an effective treatment for CKD-aP because

of its minimal systemic absorption and anti-inflammatory properties.[67] Although initially showing promise as a therapy for CKD-aP in 2 non-controlled trials,[68,69] a double-blind, randomized, and vehicle-controlled study of 22 HD patients found that 0.1% tacrolimus cream was no more effective than placebo in reducing pruritus after 4 weeks.[67] However, both tacrolimus and placebo cream improved itching severity by ~80% (this finding in the placebo group was unexpected). In an RCT of 50 patients on HD by Shirazian et al, oral high-dose ergocalciferol, which was postulated to have immunomodulatory effects in the skin, did not improve pruritus compared to placebo.[70] However, again both the groups had large improvements in pruritus severity, 38.9% in the treatment group and 47.5% in the placebo group.

Xerosis treatment

Xerosis (dry skin) occurs in up to 85% of HD and PD patients and predisposes patients to pruritus and poor wound healing.[4] It has been postulated that creams that rehydrate dry skin (emollients) may improve itching.[71] Several different formulations of emollient creams have been studied in patients with CKD-aP.

In a multicenter, double-blind, RCT, 100 HD or PD patients with moderate to severe uremic xerosis were randomized to glycerol 15% and paraffin 10% in an oil-in-water emulsion versus an oil-in-water emulsion alone. The authors hypothesized that glycerol would have a hydrating and soothing effect and paraffin would protect the skin against irritants. At the end of 7 days of the double-blind therapy, the group receiving the glycerol–paraffin emulsion experienced a 73% reduction in El Gamma score by 2 grades (the El Gamma score is a measure of xerosis severity). In addition, at the end of a 49-week follow-up, unblinded treatment period where all patients received the glycerol–paraffin emulsion, pruritus severity decreased by 75%.[72] Several additional non-controlled trials have also shown the beneficial effects of compounds containing emollient creams in patients with xerosis and CKD-aP.[71,73–76] In a prospective clinical trial, 200 g of a aqueous cream applied twice daily significantly improved pruritus severity in 16 out of 21 recruited dialysis patients and resulted in the abatement of itching in 9 patients.[75] In a prospective study of 21 HD patients, all treated with structured physiological lipids and endogenous cannabinoids twice daily for 3 weeks, pruritus severity was significantly reduced at the end of the treatment period and pruritus completely abated in 8 of 21 participants.[76]

However, despite the proven effectiveness of emollient creams in treating xerosis, no trials have tested its effect on pruritus in a double-blind, placebo-controlled fashion. In addition, no trials have compared different emollient creams for uremic pruritus to one another. Because of the low risk of side effects with these medications, we agree with current recommendations to treat patients with CKD-aP and evidence of xerosis on examination with emollient creams and then to consider additional treatments if pruritus persists.[1,71]

Antihistamine treatment

Antihistamines are a widely used medication to treat itching. They can be classified into 2 categories: histamine receptor antagonists such as diphenhydramine, hydroxyzine, loratidine, or cetirizine and medications that prevent the release of histamine such as the mast cell stabilizers cromolyn sodium and ketotifen.

Studies examining the antipruritic properties of histamine receptor antagonists have been generally unsucessful.[2,77–79] Because of the potential for dangerous side effects related to over-sedation, especially in the elderly, these medications cannot be recommended as first line for the treatment of CKD-aP.

Several recent trials have shown that CKD-aP can be successfully treated with mast cell stabilizers. In a small, non-controlled trial of 5 patients with CKD-aP, 8 weeks of ketotifen therapy resulted in a significant reduction in itching severity.[43] In a recent, double-blind, RCT of 52 HD patients comparing ketotifen to gabapentin, participants treated with ketotifen had a 76.9% reduction in pruritus severity after a 2-week treatment period.[80] However, there was no difference in efficacy between the gabapentin- and ketotifen-treated groups. Cromolyn sodium was found to improve pruritus in a case study of 2 HD patients.[81] In a subsequent RCT of 60 HD patients, twice daily cromolyn sodium cream 4% significantly reduced pruritus severity compared to placebo over 4 weeks.[82] In a double-blind, RCT of 40 HD patients, zinc sulfate, a medication shown to prevent histamine release from mast cells,[83] given for 2 months led to a significant improvement in CKD-aP compared to placebo.[84] However, a subsequent RCT of 36 patients did not confirm these findings.[85]

Uremic toxin removal

The only randomized trial to examine the effect of increased dialysis intensity on CKD-aP was by Hiroshige et al.[44] In this trial, 22 HD patients with severe prolonged pruritus were randomly assigned either to increased dialysis or unchanged dialysis. After 3 months, there was a significantly higher percentage of patients with improved pruritus in the group

randomized to increased dialysis. Importantly, Kt/V values that improved pruritus in this study were below the current standards, making this study less relevant to current practice. Subsequent non-randomized studies have yielded mixed results. One showed that a Kt/V ≥1.5 and high flux dialyzers reduced pruritus intensity,[33] whereas another study has shown an association of higher Kt/V with CKD-aP,[38] or no association between the 2 variables (Table 1). Trials examining pruritus intensity or CKD-aP prevalence in patients undergoing daily or nocturnal dialysis have not yet been performed.

In addition to increased uremic toxin removal from the blood, gut binding of uremic toxins has also been studied as a potential way to treat CKD-aP.[86] In a crossover, double-blind placebo-controlled study of 20 HD patients with resistant CKD-aP, 6 g of activated charcoal daily, for 8 weeks, significantly improved pruritus intensity compared to placebo.[87] However, several statistical problems marred this study including a high dropout rate (11/20 participants) and the use of one-sided statistical testing. A similar double-blind, placebo-controlled trial of cholestyramine, a binding resin, in 10 HD patients showed that 4/5 participants treated with 5 g of cholestyramine twice daily over 4 weeks showed an improvement in pruritus, whereas only 1 of 5 placebo treated patients showed an improvement in pruritus.[88]

Opioid imbalance treatment

The opioid imbalance theory of uremic pruritus proposes that CKD-aP can be caused by either over-stimulation of central mu-opioid receptors or antagonism of kappa-opioid receptors. An imbalance between stimulation and antagonism of these receptor systems can also cause itching. Accordingly, central mu-opioid receptors antagonists and kappa-opioid receptor agonists have been studied to treat CKD-aP.

The first studies of medications to modulate the opioid pathway in patients with CKD-aP were of naloxone and naltrexone, both mu-opioid receptor antagonists. These studies yielded mixed results.[89–91] In a randomized, controlled, crossover study of 15 HD patients, 1 week of naltrexone treatment significantly improved pruritus severity compared to placebo.[49] Two subsequent trials, however, failed to confirm this effect. In a randomized, double-blind, controlled, crossover study of 23 HD patients by Pauli-Magnus et al, naltrexone did not significantly improve pruritus intensity compared to placebo over a 4-week treatment period.[90] In another randomized trial, naltrexone did not significantly improve pruritus compared to loratidine over a 2-week treatment period.[91]

Subsequently, peripheral kappa-opioid receptor agonists showed more promising results to treat CKD-aP. The most widely studied kappa-opioid receptor agonist is nalfurafine.[35] In a meta-analysis of RCT, nalfurafine was found to significantly improve pruritus in 144 HD patients compared to placebo over 2 and 4 weeks.[35] In a large study of 337 patients on HD with CKD-aP, participants were randomized 1:1:1 to 5 μg of nalfurafine, 2.5 μg of nalfurafine or placebo and followed for 2 weeks.[55] Both 5 and 2.5 μg of nalfurafine significantly improved pruritus intensity compared to placebo. Based on these results, oral nalfurafine was approved to treat resistant pruritus in Japanese HD patients.[92]

Studies of nalbuphine hydrochloride extended-release (ER) tablets, a mu-opioid receptor antagonist and kappa-opioid receptor agonist, have also shown promising results in the treatment of CKD-aP. In a prospective observational study conducted by Hawi et al, nalbuphine at both 60 and 120 mg twice daily was found to improve CKD-aP in 15 HD patients over 2 weeks; however, significance was not reported because of the small sample size.[93] A subsequent large randomized, double-blind placebo-controlled trial of nalbuphine ER tablets in 373 HD patients confirmed the efficacy of this medication in treating CKD-aP;[36] however, to date, the results of this study have only been published in abstract form.

Finally, acupuncture, which is thought to block spinal cord release of opioid-like substances, has been studied to treat CKD-aP.[94] In a trial of 40 HD patients with refractory pruritus randomized to correct acupuncture or sham acupuncture 3 times weekly for 1 month, participants randomized to the correct acupuncture had a significant reduction of pruritus at 4 and 12 weeks compared to sham.[94] In 2010, a review of 3 RCT and 3 uncontrolled observational studies using acupuncture to treat CKD-aP was published.[95] Although the authors found that all trials reported benefits of acupuncture, they concluded there was insufficient evidence to recommend acupuncture treatment for CKD-aP because of the high risk of bias in these studies.

Peripheral neuropathy treatment

Medications that blunt peripheral C-fiber nerve transmission and modulate pain and itching have been used to treat CKD-aP including gabapentin, pregabalin, capsaicin, and pramoxine.

Several studies have shown beneficial effects of gabapentin in treating CKD-aP.[53,96–98] In a double-blind, crossover, RCT of 25 HD patients assigned to gabapentin 300 mg by mouth after dialysis or placebo, pruritus intensity significantly improved with gabapentin but not with placebo.[53] Similarly, in a double-blind, placebo-controlled trial of 34 HD

patients, gabapentin treatment (400 mg twice weekly) over 4 weeks significantly improved pruritus intensity compared to placebo.[98] A recent qualitative systematic review of 7 studies evaluating gabapentin (179 participants) supported a trial of gabapentin for the treatment of CKD-aP refractory to antihistamines and/or emollients.[97]

Pregabalin, a medication similar to gabapentin, may also improve CKD-aP[37,99] and may be particularly useful when patients are not able to tolerate gabapentin.[1,100] In a randomized, crossover trial, 50 HD patients were assigned to gabapentin 300 mg or pregabalin 75 mg daily. After a 6-week treatment period, both the medications significantly improved pruritus intensity.[98] In a double-blind trial of 188 HD or PD patients, randomized to 75 mg of pregabalin twice weekly or 8 mg/day of ondansetron or placebo, only pregabalin significantly improved pruritus severity over the 12-week treatment period.[99] In a study of 71 patients (stage 4 and 5 CKD and dialysis) treated with gabapentin or pregabalin, both the medications significantly improved pruritus intensity. In addition, pregabalin relieved itching in 13 of 16 patients who were unable to tolerate gabapentin after a median treatment period of 2.5 months. However, the side effects of gabapentin and pregabalin such as somnolence, confusion, dry mouth, visual changes, weight gain, angioedema, and increased suicide risk may limit their use.

Analgesics for neuropathic pain, which desensitize peripheral C-fiber nerves, have been used to treat CKD-aP. Several studies examining capsaicin have shown mixed results.[101–103] Finally, in a systemic review that included 3 RCT of patients with CKD-aP, capsaicin could not be supported as a medication to treat pruritus related to any medical condition because of design flaws in current studies and insufficient evidence to support its use.[103] Pramoxine, a topical analgesic, has also been used to treat CKD-aP. In an RCT of 28 HD patients randomized to twice daily pramoxine versus control lotion and followed for 4 weeks, pramoxine led to greater degree of reduction in pruritus severity than control (61% vs 12%).[104]

Hyperparathyroidism treatment

Hyperparathyroidism and high calcium, magnesium, and phosphorus levels have been consistently associated with CKD-aP (Table 1); however, few studies have examined the effect of treating these parameters on CKD-aP.[105,106] In a uncontrolled study of 37 dialysis patients with secondary hyperparathyroidism (mean PTH level 1,473 pg/mL) of which 22 had pruritus, parathyroidectomy resulted in a significant improvement in pruritus.[106] In addition, 2 small, case studies have also shown an improvement in pruritus with low magnesium or calcium dialysate.[106,107] Finally, the improvement of pruritus in dialysis patients over time suggests treating mineral and bone disease may also treat CKD-aP.

The best current advice is to ensure that patients with CKD-aP are meeting kidney disease improving global outcome (KDIGO) guideline defined PTH, calcium, and phosphorus goals with phosphate binders, low calcium dialysate, active vitamin D analogs, cinacalcet, and parathyroidectomy, as treatment for CKD-aP.[68]

Other medications

Other medications used to treat pruritus include nicergoline and serotonin receptor antagonists (SRA).

Nicergoline is an arterial vasodilator with alpha-adrenergic blocker activity. In a crossover, double-blind trial of nicergoline in oral and intravenous formulations versus placebo, nicergoline reduced pruritus in 13 of 15 HD patients, with 8 patients showing complete abatement of itching after 6 HD sessions.[108]

Several studies of SRA have been undertaken with generally negative results.[75,99,109,110] In a non-controlled, unblinded trial of 14 HD patients, granisetron, an anti-emetic and SRA, significantly improved pruritus severity over 4 weeks of therapy.[111] However, in a double-blind, crossover RCT of 24 patients on HD, 8 mg of ondansetron 3 times daily over 2 weeks did not significantly improve CKD-aP compared to placebo.[110] In a small, non-controlled trial of 11 HD patients, the SRA tropisetron and ondansetron and the anti-histamine cetirizine did not sufficiently improve itching.[75] Finally, a systematic review that included 2 RCT of patients with CKD-aP concluded that ondansetron had a negligible effect on pruritus.[109]

Challenges of treatment

Flaws in trial design, analysis, and reporting have confounded treatment studies for CKD-aP. In particular, the evaluation of treatment efficacy from non-controlled, non-blinded, and/or underpowered trials is problematic. First, the importance of control groups in pruritus studies is illustrated by the dramatic improvements in itching in these groups in CKD-aP trials, up to 80% in a study by Duque et al.[64,67] Second, double-blinding participants and investigators are important given the subjective nature of pruritus. There is a potential for bias when participants or investigators are aware of assigned groups, as this may influence pruritus assessments. In addition, studies that report blinding often do not specify whether treatments were, in fact, matched so that they are indistinguishable. Third, the majority of studies examining

treatments for CKDaP are underpowered. This is particularly problematic for negative studies, as the possibility of treatment efficacy cannot be excluded. Fourth, many studies were from single centers. Although multiple centers is not a requirement for all clinical trials, historically, multicenter studies find lesser effect sizes than single-site studies.[112] Fifth, trials involving crossover design often do not have sufficient washout; therefore, carryover effects from prior treatments may affect the interpretation of results. Sixth, most of the studies do not clearly report the pre-specified analytic population, endpoints, and statistical methodology, making interpretation of the validity of reported *p*-values challenging. Finally, a number of studies are of short duration (1–2 week treatment periods). Because CKDaP is a chronic condition, an evaluation of durability of efficacy of any intervention is very important. Whereas trials of short duration are useful as proof-of-concept, longer studies provide greater confidence in the generalizability of the findings.

Recommendations

Based on the current literature, we propose a multifaceted approach to treat CKD-aP.[1,68,83] First, we ensure that patients are meeting KDIGO-defined goals for dialysis efficiency and mineral bone disease treatment, and if not, we help patients achieve the goals. Next, if, after a thorough examination xerosis is present, we treat patients with a trial of emollient cream. However, if patients have refractory pruritus despite this initial management, treatment remains less clearly defined. We do not feel the evidence is strong enough to recommend any medication over another for refractory pruritus. However, there is new hope. Both nalfurafine, a kappa opioid receptor agonist, and oral nalbuphine hydrochloride, a mu-opioid receptor antagonist and kappa-opioid receptor agonist have shown promising results in large, double-blind, randomized controlled clinical trials. At this time, nalfurafine is currently approved for use only in Japan and nalbuphine is under investigation for the treatment of CKD-aP. These medications may become effective future treatment options for patients afflicted with refractory pruritus worldwide.

Disclosure

Dr Vandana Mathur is currently a consultant to Trevi Therapeutics and Cara Therapeutics, and, formerly to Patara Pharmaceuticals. The other authors report no conflicts of interest in this work.

References

1. Mettang T, Kremer AE. Uremic pruritus. *Kidney Int.* 2015;87(4):685–691.
2. Gilchrest BA, Stern RS, Steinman TI, Brown RS, Arndt KA, Anderson WW. Clinical features of pruritus among patients undergoing maintenance hemodialysis. *Arch Dermatol.* 1982;118(3):154–156.
3. Mathur VS, Lindberg J, Germain M, et al. A longitudinal study of uremic pruritus in hemodialysis patients. *Clin J Am Soc Nephrol.* 2010;5(8):1410–1419.
4. Szepietowski JC, Reich A, Schwartz RA. Uraemic xerosis. *Nephrol Dial Transpl.* 2004;19(11):2709–2712.
5. Phan NQ, Blome C, Fritz F, et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. *Acta Derm Venereol.* 2012;92(5):502–507.
6. Pereira MP, Stander S. Assessment of severity and burden of pruritus. *Allergol Int.* 2016 Epub Sep 12.
7. Olsen S, Nolan MF, Kori S. Pain measurement. An overview of two commonly used methods. *Anesthesiol Rev.* 1992;19(6):11–15.
8. Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. *Br J Dermatol.* 2010;162(3):587–593.
9. Majeski CJ, Johnson JA, Davison SN, Lauzon CJ. Itch Severity scale: a self-report instrument for the measurement of pruritus severity. *Br J Dermatol.* 2007;156(4):667–673.
10. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol.* 1994;19(3):210–216.
11. Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol.* 2008;159(5):997–1035.
12. Chren MM, Lasek RJ, Quinn LM, Mostow EN, Zyzanski SJ. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. *J Invest Dermatol.* 1996;107(5):707–713.
13. Chren MM. The Skindex instruments to measure the effects of skin disease on quality of life. *Dermatol Clin.* 2012;30(2):231–236, xiii.
14. Hays RD, Kallich JD, Mapes DL, et al. *Kidney Disease Quality of Life Short Form (KDQOL-SF™), Version 1.3: A Manual for Using and Scoring.* Santa Monica, CA: RAND; 1995: P-7994.
15. Ware JE Jr, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *J Clin Epidemiol.* 1998;51(11):903–912.
16. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol.* 1998;51(11):1171–1178.
17. Hays RD, Kallich JD, Mapes DL, Coons SJ, Carter WB. Development of the kidney disease quality of life (KDQOL) instrument. *Qual Life Res.* 1994;3(5):329–338.
18. Pisoni RL, Wikstrom B, Elder SJ, et al. Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transpl.* 2006;21(12):3495–3505.
19. Kimata N, Fuller DS, Saito A, et al. Pruritus in hemodialysis patients: results from the Japanese Dialysis Outcomes and Practice Patterns Study (JDOPPS). *Hemodial Int.* 2014;18(3):657–667.
20. Ramakrishnan K, Bond TC, Claxton A, et al. Clinical characteristics and outcomes of end-stage renal disease patients with self-reported pruritus symptoms. *Int J Nephrol Renovasc Dis.* 2013;7:1–12.
21. Li J, Guo Q, Lin J, Yi C, Yang X, Yu X. Prevalence and associated factors of uraemic pruritus in continuous ambulatory peritoneal dialysis patients. *Intern Med.* 2015;54(22):2827–2833.
22. Min JW, Kim SH, Kim YO, et al. Comparison of uremic pruritus between patients undergoing hemodialysis and peritoneal dialysis. *Kidney Res Clin Pract.* 2016;35(2):107–113.
23. Mettang T, Fritz P, Weber J, Machleidt C, Hubel E, Kuhlmann U. Uremic pruritus in patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). The role of plasma histamine and skin mast cells. *Clin Nephrol.* 1990;34(3):136–141.
24. Tessari G, Dalle Vedove C, Loschiavo C, et al. The impact of pruritus on the quality of life of patients undergoing dialysis: a single centre cohort study. *J Nephrol.* 2009;22(2):241–248.

25. Wu HY, Peng YS, Chen HY, et al. A comparison of uremic pruritus in patients receiving peritoneal dialysis and hemodialysis. *Medicine.* 2016;95(9):e2935.
26. Solak B, Acikgoz SB, Sipahi S, Erdem T. Epidemiology and determinants of pruritus in pre-dialysis chronic kidney disease patients. *Int Urol Nephrol.* 2016;48(4):585–591.
27. Khanna D, Singal A, Kalra OP. Comparison of cutaneous manifestations in chronic kidney disease with or without dialysis. *Postgrad Med J.* 2010;86(1021):641–647.
28. Murphy EL, Murtagh FE, Carey I, Sheerin NS. Understanding symptoms in patients with advanced chronic kidney disease managed without dialysis: use of a short patient-completed assessment tool. *Nephron Clin Pract.* 2009;111(1):c74–c80.
29. Murtagh FE, Addington-Hall JM, Edmonds PM, et al. Symptoms in advanced renal disease: a cross-sectional survey of symptom prevalence in stage 5 chronic kidney disease managed without dialysis. *J Palliat Med.* 2007;10(6):1266–1276.
30. Narita I, Alchi B, Omori K, et al. Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. *Kidney Int.* 2006;69(9):1626–1632.
31. Shirazian S, Kline M, Sakhiya V, et al. Longitudinal predictors of uremic pruritus. *J Renal Nutr.* 2013;23(6):428–431.
32. Welter Ede Q, Frainer RH, Maldotti A, Losekann A, Weber MB. Evaluating the association between alterations in mineral metabolism and pruritus in hemodialysis patients. *An Bras Dermatol.* 2011;86(1):31–36.
33. Ko MJ, Wu HY, Chen HY, et al. Uremic pruritus, dialysis adequacy, and metabolic profiles in hemodialysis patients: a prospective 5-year cohort study. *PLoS One.* 2013;8(8):e71404.
34. Yamamoto Y, Hayashino Y, Yamazaki S, et al. Depressive symptoms predict the future risk of severe pruritus in haemodialysis patients: Japan Dialysis Outcomes and Practice Patterns Study. *Br J Dermatol.* 2009;161(2):384–389.
35. Wikstrom B, Gellert R, Ladefoged SD, et al. Kappa-opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. *J Am Soc Nephrol.* 2005;16(12):3742–3747.
36. Vandana SM, Jayant K, Paul WC, Howard H, Thomas S. Randomized, double-blind, placebo-controlled, parallel, 3-arm study of safety and anti-pruritic efficacy of nalbuphine HCl ER tablets in hemodialysis patients with uremic pruritus [abstract]. *J Am Soc Nephrol*. 2015;26:B2 NCT02143648.
37. Yue J, Jiao S, Xiao Y, Ren W, Zhao T, Meng J. Comparison of pregabalin with ondansetron in treatment of uraemic pruritus in dialysis patients: a prospective, randomized, double-blind study. *Int Urol Nephrol.* 2015;47(1):161–167.
38. Duque MI, Thevarajah S, Chan YH, Tuttle AB, Freedman BI, Yosipovitch G. Uremic pruritus is associated with higher kt/V and serum calcium concentration. *Clin Nephrol.* 2006;66(3):184–191.
39. Yosipovitch G, Zucker I, Boner G, Gafter U, Shapira Y, David M. A questionnaire for the assessment of pruritus: validation in uremic patients. *Acta Derm Venereol.* 2001;81(2):108–111.
40. Kimmel M, Alscher DM, Dunst R, et al. The role of micro-inflammation in the pathogenesis of uraemic pruritus in haemodialysis patients. *Nephrol Dial Transpl.* 2006;21(3):749–755.
41. Fallahzadeh MK, Roozbeh J, Geramizadeh B, Namazi MR. Interleukin-2 serum levels are elevated in patients with uremic pruritus: a novel finding with practical implications. *Nephrol Dial Transpl.* 2011;26(10):3338–3344.
42. Dugas-Breit S, Schopf P, Dugas M, Schiffl H, Rueff F, Przybilla B. Baseline serum levels of mast cell tryptase are raised in hemodialysis patients and associated with severity of pruritus. *J Dtschn Dermatol Ges.* 2005;3(5):343–347.
43. Francos GC, Kauh YC, Gittlen SD, et al. Elevated plasma histamine in chronic uremia. Effects of ketotifen on pruritus. *Int J Dermatol.* 1991;30(12):884–889.
44. Hiroshige K, Kabashima N, Takasugi M, Kuroiwa A. Optimal dialysis improves uremic pruritus. *Am J Kidney Dis.* 1995;25(3):413–419.
45. Masi CM, Cohen EP. Dialysis efficacy and itching in renal failure. *Nephron.* 1992;62(3):257–261.
46. Blachley JD, Blankenship DM, Menter A, Parker TF 3rd, Knochel JP. Uremic pruritus: skin divalent ion content and response to ultraviolet phototherapy. *Am J Kidney Dis.* 1985;5(5):237–241.
47. Yatzidis H, Digenis P, Fountas P. Hypervitaminosis A accompanying advanced chronic renal failure. *Br Med J.* 1975;3(5979):352–353.
48. Bergasa NV, Alling DW, Talbot TL, et al. Effects of naloxone infusions in patients with the pruritus of cholestasis. A double-blind, randomized, controlled trial. *Ann Intern Med.* 1995;123(3):161–167.
49. Peer G, Kivity S, Agami O, et al. Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet.* 1996;348(9041):1552–1554.
50. Cowan A, Kehner GB, Inan S. Targeting itch with ligands selective for kappa opioid receptors. *Handb Exp Pharmacol.* 2015;226:291–314.
51. Zakrzewska-Pniewska B, Jedras M. Is pruritus in chronic uremic patients related to peripheral somatic and autonomic neuropathy? Study by R-R interval variation test (RRIV) and by sympathetic skin response (SSR). *Neurophysiol Clin.* 2001;31(3):181–193.
52. Johansson O, Hilliges M, Stahle-Backdahl M. Intraepidermal neuron-specific enolase (NSE)-immunoreactive nerve fibres: evidence for sprouting in uremic patients on maintenance hemodialysis. *Neurosci Lett.* 1989;99(3):281–286.
53. Gunal AI, Ozalp G, Yoldas TK, Gunal SY, Kirciman E, Celiker H. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. *Nephrol Dial Transpl.* 2004;19(12):3137–3139.
54. Hampers CL, Katz AI, Wilson RE, Merrill JP. Disappearance of "uremic" itching after subtotal parathyroidectomy. *N Engl J Med.* 1968;279(13):695–697.
55. Kumagai H, Ebata T, Takamori K, Muramatsu T, Nakamoto H, Suzuki H. Effect of a novel kappa-receptor agonist, nalfurafine hydrochloride, on severe itch in 337 haemodialysis patients: a phase III, randomized, double-blind, placebo-controlled study. *Nephrol Dial Transpl.* 2010;25(4):1251–1257.
56. Gilchrest BA, Rowe JW, Brown RS, Steinman TI, Arndt KA. Relief of uremic pruritus with ultraviolet phototherapy. *N Engl J Med.* 1977;297(3):136–138.
57. Tan JK, Haberman HF, Coldman AJ. Identifying effective treatments for uremic pruritus. *J Am Acad Dermatol.* 1991;25(5 Pt 1):811–818.
58. Gilchrest BA, Rowe JW, Brown RS, Steinman TI, Arndt KA. Ultraviolet phototherapy of uremic pruritus. Long-term results and possible mechanism of action. *Ann Intern Med.* 1979;91(1):17–21.
59. Ada S, Seckin D, Budakoglu I, Ozdemir FN. Treatment of uremic pruritus with narrowband ultraviolet B phototherapy: an open pilot study. *J Am Acad Dermatol.* 2005;53(1):149–151.
60. Ko MJ, Yang JY, Wu HY, et al. Narrowband ultraviolet B phototherapy for patients with refractory uraemic pruritus: a randomized controlled trial. *Br J Dermatol.* 2011;165(3):633–639.
61. Chen YC, Chiu WT, Wu MS. Therapeutic effect of topical gamma-linolenic acid on refractory uremic pruritus. *Am J Kidney Dis.* 2006;48(1):69–76.
62. Yoshimoto-Furuie K, Yoshimoto K, Tanaka T, et al. Effects of oral supplementation with evening primrose oil for six weeks on plasma essential fatty acids and uremic skin symptoms in hemodialysis patients. *Nephron.* 1999;81(2):151–159.
63. Silva SR, Viana PC, Lugon NV, Hoette M, Ruzany F, Lugon JR. Thalidomide for the treatment of uremic pruritus: a crossover randomized double-blind trial. *Nephron.* 1994;67(3):270–273.
64. Pakfetrat M, Basiri F, Malekmakan L, Roozbeh J. Effects of turmeric on uremic pruritus in end stage renal disease patients: a double-blind randomized clinical trial. *J Nephrol.* 2014;27(2):203–207.
65. Omidian M, Khazanee A, Yaghoobi R, et al. Therapeutic effect of oral nicotinamide on refractory uremic pruritus: a randomized, double-blind study. *Saudi J Kidney Dis Transpl.* 2013;24(5):995–999.
66. Aramwit P, Keongamaroon O, Siritientong T, Bang N, Supasyndh O. Sericin cream reduces pruritus in hemodialysis patients: a randomized, double-blind, placebo-controlled experimental study. *BMC Nephrol.* 2012;13:119.

67. Duque MI, Yosipovitch G, Fleischer AB Jr, Willard J, Freedman BI. Lack of efficacy of tacrolimus ointment 0.1% for treatment of hemodialysis-related pruritus: a randomized, double-blind, vehicle-controlled study. *J Am Acad Dermatol.* 2005;52(3 Pt 1):519–521.
68. Kuypers DR, Claes K, Evenepoel P, Maes B, Vanrenterghem Y. A prospective proof of concept study of the efficacy of tacrolimus ointment on uraemic pruritus (UP) in patients on chronic dialysis therapy. *Nephrol Dial Transpl.* 2004;19(7):1895–1901.
69. Pauli-Magnus C, Klumpp S, Alscher DM, Kuhlmann U, Mettang T. Short-term efficacy of tacrolimus ointment in severe uremic pruritus. *Perit Dial Int.* 2000;20(6):802–803.
70. Shirazian S, Schanler M, Shastry S, et al. The effect of ergocalciferol on uremic pruritus severity: a randomized controlled trial. *J Renal Nutr.* 2013;23(4):308–314.
71. Combs SA, Teixeira JP, Germain MJ. Pruritus in kidney disease. *Semin Nephrol.* 2015;35(4):383–391.
72. Balaskas E, Szepietowski JC, Bessis D, et al. Randomized, double-blind study with glycerol and paraffin in uremic xerosis. *Clin J Am Soc Nephrol.* 2011;6(4):748–752.
73. Castello M, Milani M. Efficacy of topical hydrating and emollient lotion containing 10% urea ISDIN(R) plus dexpanthenol (Ureadin Rx 10) in the treatment of skin xerosis and pruritus in hemodialyzed patients: an open prospective pilot trial. *G Ital Dermatol Venereol.* 2011;146(5):321–325.
74. Okada K, Matsumoto K. Effect of skin care with an emollient containing a high water content on mild uremic pruritus. *Ther Apher Dial.* 2004;8(5):419–422.
75. Morton CA, Lafferty M, Hau C, Henderson I, Jones M, Lowe JG. Pruritus and skin hydration during dialysis. *Nephrol Dial Transpl.* 1996;11(10):2031–2036.
76. Szepietowski JC, Szepietowski T, Reich A. Efficacy and tolerance of the cream containing structured physiological lipids with endocannabinoids in the treatment of uremic pruritus: a preliminary study. *Acta Dermatovenerol Croat.* 2005;13(2):97–103.
77. Russo GE, Spaziani M, Guidotti C, et al. [Pruritus in chronic uremic patients in periodic hemodialysis. Treatment with terfenadine (an antagonist of histamine H1 receptors)]. *Minerva Urol Nefrol.* 1986;38(4):443–447. Italian.
78. Weisshaar E, Dunker N, Rohl FW, Gollnick H. Antipruritic effects of two different 5-HT3 receptor antagonists and an antihistamine in haemodialysis patients. *Exp Dermatol.* 2004;13(5):298–304.
79. Matsui C, Ida M, Hamada M, Morohashi M, Hasegawa M. Effects of azelastin on pruritus and plasma histamine levels in hemodialysis patients. *Int J Dermatol.* 1994;33(12):868–871.
80. Amirkhanlou S, Rashedi A, Taherian J, Hafezi AA, Parsaei S. Comparison of gabapentin and ketotifen in treatment of uremic pruritus in hemodialysis patients. *Pak J Med Sci.* 2016;32(1):22–26.
81. Rosner MH. Cromolyn sodium: a potential therapy for uremic pruritus? *Hemodial Int.* 2006;10(2):189–192.
82. Feily A, Dormanesh B, Ghorbani AR, et al. Efficacy of topical cromolyn sodium 4% on pruritus in uremic nephrogenic patients: a randomized double-blind study in 60 patients. *Int J Clin Pharmacol Ther.* 2012;50(7):510–513.
83. Sanada S, Kuze M, Yoshida O. [Beneficial effect of zinc supplementation on pruritus in hemodialysis patients with special reference to changes in serum histamine levels]. *Hinyokika Kiyo.* 1987;33(12):1955–1960. Japanese.
84. Najafabadi MM, Faghihi G, Emami A, et al. Zinc sulfate for relief of pruritus in patients on maintenance hemodialysis. *Ther Apher Dial.* 2012;16(2):142–145.
85. Mapar MA, Pazyar N, Siahpoosh A, Latifi SM, Beladi Mousavi SS, Khazanee A. Comparison of the efficacy and safety of zinc sulfate vs. placebo in the treatment of pruritus of hemodialytic patients: a pilot randomized, triple-blind study. *G Ital Dermatol Venereol.* 2015;150(4):351–355.
86. Lugon JR. Uremic pruritus: a review. *Hemodial Int.* 2005;9(2):180–188.
87. Pederson JA, Matter BJ, Czerwinski AW, Llach F. Relief of idiopathic generalized pruritus in dialysis patients treated with activated oral charcoal. *Ann Intern Med.* 1980;93(3):446–448.
88. Silverberg DS, Iaina A, Reisin E, Rotzak R, Eliahou HE. Cholestyramine in uraemic pruritus. *Br Med J.* 1977;1(6063):752–753.
89. Andersen LW, Friedberg M, Lokkegaard N. Naloxone in the treatment of uremic pruritus: a case history. *Clin Nephrol.* 1984;21(6):355–356.
90. Pauli-Magnus C, Mikus G, Alscher DM, et al. Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol.* 2000;11(3):514–519.
91. Legroux-Crespel E, Cledes J, Misery L. A comparative study on the effects of naltrexone and loratadine on uremic pruritus. *Dermatology.* 2004;208(4):326–330.
92. Inui S. Nalfurafine hydrochloride to treat pruritus: a review. *Clin Cosmet Investig Dermatol.* 2015;8:249–255.
93. Hawi A, Alcorn H Jr, Berg J, Hines C, Hait H, Sciascia T. Pharmacokinetics of nalbuphine hydrochloride extended release tablets in hemodialysis patients with exploratory effect on pruritus. *BMC Nephrol.* 2015;16:47.
94. Che-Yi C, Wen CY, Min-Tsung K, Chiu-Ching H. Acupuncture in haemodialysis patients at the Quchi (LI11) acupoint for refractory uraemic pruritus. *Nephrol Dial Transpl.* 2005;20(9):1912–1915.
95. Kim KH, Lee MS, Choi SM. Acupuncture for treating uremic pruritus in patients with end-stage renal disease: a systematic review. *J Pain Sympt Manag.* 2010;40(1):117–125.
96. Razeghi E, Eskandari D, Ganji MR, Meysamie AP, Togha M, Khashayar P. Gabapentin and uremic pruritus in hemodialysis patients. *Ren Fail.* 2009;31(2):85–90.
97. Lau T, Leung S, Lau W. Gabapentin for uremic pruritus in hemodialysis patients: a qualitative systematic review. *Can J Kidney Health Dis.* 2016;3:14.
98. Naini AE, Harandi AA, Khanbabapour S, Shahidi S, Seirafiyan S, Mohseni M. Gabapentin: a promising drug for the treatment of uremic pruritus. *Saudi J Kidney Dis Transpl.* 2007;18(3):378–381.
99. Solak Y, Biyik Z, Atalay H, et al. Pregabalin versus gabapentin in the treatment of neuropathic pruritus in maintenance haemodialysis patients: a prospective, crossover study. *Nephrology.* 2012;17(8):710–717.
100. Rayner H, Baharani J, Smith S, Suresh V, Dasgupta I. Uraemic pruritus: relief of itching by gabapentin and pregabalin. *Nephron Clin Pract.* 2012;122(3–4):75–79.
101. Cho YL, Liu HN, Huang TP, Tarng DC. Uremic pruritus: roles of parathyroid hormone and substance P. *J Am Acad Dermatol.* 1997;36(4):538–543.
102. Weisshaar E, Dunker N, Gollnick H. Topical capsaicin therapy in humans with hemodialysis-related pruritus. *Neurosci Lett.* 2003;345(3):192–194.
103. Gooding SM, Canter PH, Coelho HF, Boddy K, Ernst E. Systematic review of topical capsaicin in the treatment of pruritus. *Int J Dermatol.* 2010;49(8):858–865.
104. Young TA, Patel TS, Camacho F, et al. A pramoxine-based anti-itch lotion is more effective than a control lotion for the treatment of uremic pruritus in adult hemodialysis patients. *J Dermatol Treat.* 2009;20(2):76–81.
105. Massry SG, Popovtzer MM, Coburn JW, Makoff DL, Maxwell MH, Kleeman CR. Intractable pruritus as a manifestation of secondary hyperparathyroidism in uremia. Disappearance of itching after subtotal parathyroidectomy. *N Engl J Med.* 1968;279(13):697–700.
106. Chou FF, Ho JC, Huang SC, Sheen-Chen SM. A study on pruritus after parathyroidectomy for secondary hyperparathyroidism. *J Am Coll Surg.* 2000;190(1):65–70.
107. Kyriazis J, Glotsos J. Dialysate calcium concentration of </=1.25 mmol/l: is it effective in suppressing uremic pruritus? *Nephron.* 2000;84(1):85–86.
108. Bousquet J, Rivory JP, Maheut M, Michel FB, Mion C. Double-blind, placebo-controlled study of nicergoline in the treatment of pruritus in patients receiving maintenance hemodialysis. *J Allergy Clin Immunol.* 1989;83(4):825–828.

109. To TH, Clark K, Lam L, Shelby-James T, Currow DC. The role of ondansetron in the management of cholestatic or uremic pruritus--a systematic review. *J Pain Sympt Manag.* 2012;44(5):725–730.
110. Murphy M, Reaich D, Pai P, Finn P, Carmichael AJ. A randomized, placebo-controlled, double-blind trial of ondansetron in renal itch. *Br J Dermatol.* 2003;148(2):314–317.
111. Layegh P, Mojahedi MJ, Malekshah PE, et al. Effect of oral granisetron in uremic pruritus. *Indian J Dermatol Venereol Leprol.* 2007;73(4):231–234.
112. Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. *Ann Intern Med.* 2011;155(1):39–51.
113. Zucker I, Yosipovitch G, David M, Gafter U, Boner G. Prevalence and characterization of uremic pruritus in patients undergoing hemodialysis: uremic pruritus is still a major problem for patients with end-stage renal disease. *J Am Acad Dermatol.* 2003;49(5):842–846.