Chronic Kidney Disease-Associated Pruritus: A Review

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Keywords

Chronic kidney disease-associated pruritus · Uraemic pruritus · Chronic kidney disease

Abstract

Background: Chronic kidney disease-associated pruritus (CKD-aP), also known as uraemic pruritus, is a disabling symptom for patients and a challenging condition for clinicians. Despite being common amongst end-stage kidney disease (ESKD) patients, it remains underestimated and underdiagnosed. The exact pathogenesis remains largely elusive, which hampers the synthesis of a definite treatment approach. **Summary:** Chronic pruritus (lasting 6 weeks or more in duration) is a common and potentially disabling symptom in patients with advanced CKD. A unified hypothesis of pathogenesis has not yet been concluded. Studies have shown changes in the immunochemical milieu of the skin in patients with CKD-aP with several inciting stimuli identified. However, other unrecognized factors are likely to be involved. This article will review the current observations and understanding of the postulated pathogenesis of CKD-aP, as well as the evidence for current management strategies. **Key Messages:** CKD-aP is a common and troubling symptom amongst ESKD patients that is associated with decreased quality of life and poor prognosis. Its exact pathogenesis, at

the time of writing, is not well-understood. A stepwise approach is recommended for management. Systematic reviews show the largest body of evidence was found for the effectiveness of gabapentin. Comparison is needed between newly emerging pharmacological agents such as kappa-opioid receptor agonists and more established agents, such as the gabapentinoids. Finally, renal transplantation should be considered in severe and refractory cases who are suitable transplant candidates as it has shown an excellent outcome in most cases.

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Published by S. Karger AG, Basel

Introduction

Pruritus, or itch, is defined as “an unpleasant sensation associated with a desire to scratch” [1]. Pruritus may be acute or chronic (lasting 6 weeks or more in duration). Chronic pruritus is a common and potentially disabling symptom in patients with advanced chronic kidney disease (CKD), especially in those with end-stage kidney disease (ESKD). In contrast to dermatologic causes of chronic pruritus, it does not present with primary skin alterations, although, over time, secondary skin changes such as excoriations occur as a result of intense scratching [2].

Epidemiology

Worldwide, the prevalence of CKD-associated pruritus (CKD-aP) in haemodialysis (HD) patients ranges from 10 to 77%. Regional differences and the irregular pattern of itch in HD patients may explain why it remains underdiagnosed and underestimated in such patients [3]. A meta-analysis of cross-sectional studies reported an overall prevalence of CKD-aP amongst adult dialysis patients of 55% [4]. In terms of the severity of CKD-aP, the international Dialysis Outcomes and Practice Patterns Study (DOPPS) of 35,452 patients revealed that 18% of HD patients reported they were troubled by CKD-aP “very much” or “extremely” [5]. That study showed that CKD-aP remains largely underestimated, with up to 18% receiving no treatment and 17% not reporting itching to health-care staff. Moreover, 69% of medical directors underestimated the prevalence of pruritus in their unit.

Clinical Characteristics and Natural History

CKD-aP can present variably. It tends to affect large, discontinuous, but symmetric, areas of skin and to be most symptomatic at night [6]. It does not exhibit a dermatomal pattern and there is no associated primary skin lesion, although over time, there are often signs of chronic scratching [7]. The spatial distribution of CKD-aP varies, and 25–50% complain of generalized itch [8]. Pruritus is most frequently reported on the legs, back, and scalp [9]. There is no known gender difference. Despite being the most common cause of pruritus in patient with ESKD, it is a clinical truism that not all patients with ESKD experiencing pruritus have CKD-aP. A variety of alternative non-uraemic systemic or dermatologic causes of pruritus should be considered, especially in patients with asymmetric pruritus, other atypical features or in patients with pruritus refractory to therapy [6].

In CKD-aP, statistically significant associations were found amongst itching severity and health-related quality-of-life domains such as mood, social relations, and sleep [10]. Those with CKD-aP may also be more likely to suffer restless leg syndrome [11]. In addition, patients with severe CKD-aP have a significantly worse prognosis than patients with less severe CKD-aP, with severe CKD-aP being independently associated with mortality even after adjusting for other clinical factors including diabetes mellitus, age, β 2-microglobulin, and albumin [12].

Pathogenesis

The Challenge of Unifying Disparate Observations

The pathophysiology of CKD-aP remains unclear. There is no single overarching theory of mechanism. Without that clarity, a coherent approach to management is made more difficult. Currently, our understanding of the pathophysiology derives from multiple disparate sources, with many gaps and some contradictions. These sources include the epidemiological associations between CKD-aP and other features of advanced CKD, the multiple isolated observations of disturbance to the immunochemical milieu of the skin in CKD-aP and associated serum biomarkers, and inferences regarding pathophysiology based on our expanding knowledge of basic itch science and the pharmacological action of effective treatments of CKD-aP. These observations, from different fields, will, no doubt, eventually form a part of a unified hypothesis of mechanism. In the next sections, we will address these areas in detail by first summarizing the literature on the conventional associations made with CKD-aP, then synthesizing the diverse descriptions of immunochemical changes in the skin of patients with ESKD and CKD-aP compared to those without CKD-aP, and finally summarizing the evidence of management strategies.

Conventional Associations Revisited

Over time, conventional wisdom has focused on several purported associations with CKD-aP. A careful examination of these conventions reveals they are not supported by evidence or are inconsistent. In particular, it is often thought that CKD-aP is due to inadequate dialysis. In several large epidemiological studies, dialysis adequacy (as measured by Kt/V) did not consistently correlate with the frequency of CKD-aP [13, 14]. In addition, the associations between CKD-aP with the levels of serum parathyroid hormone [15, 16], serum calcium [14, 17], and phosphate [12, 15] are inconsistent between different studies. In the DOPPS II, the calcium x phosphate product was correlated with the frequency of CKD-aP but only when that product was at a remarkably high level (i.e., $>80 \text{ mg}^2/\text{dL}^2$) [13].

Historically, xerosis has been associated with CKD-aP [18, 19]. Yosipovitch et al. [20] however did not find an association. Szepletowski et al. [21] have, at least partially, eliminated xerosis as causative of CKD-aP. Xerosis therefore is more likely to be an exacerbating rather than a causative factor. Finally, histamine is commonly considered the principal, if not sole, mediator of itch regardless of cause.

Fig. 1. Partial representation of hypothesized CKD-aP pathophysiology at the level of the skin. Inciting stimuli for CKD-aP may involve (1) increased calcium ions or β 2-microglobulin deposition but unrecognized factors are likely to be important. Dermal mast cells release tryptase (2), activating PAR-2 receptors which (via sensitization of TRPV1 channels) activates both antegrade and retrograde signalling within the nerve (3). SP is released from nerve endings (4), causing cytokine release from both keratinocytes and dermal mast cells, adding to the pruritogenic environment. This pathway may be further amplified by release of cytokines from Th1 lymphocytes (5). Kappa-opioid receptors are present on multiple actors in this pathway and can dampen activity. Created with BioRender.com. PAR-2, proteinase-activated receptor-2; TRPV1, transient receptor potential vanilloid 1; CKD-aP, chronic kidney disease-associated pruritus; SP, substance P; κ -opioid, kappa-opioid.

Indeed, antihistamines are routinely prescribed for CKD-aP. Modern pruritus science however reveals that the sensation of pruritus is transmitted by dedicated itch fibres, on separate histaminergic and non-histaminergic pathways [22]. Papoiu et al. [23] demonstrated that CKD-aP is transmitted by a non-histaminergic pruritus pathway. Therefore, histamine is unlikely to be causative, and the role for antihistamines in management appears limited.

Towards Pathogenesis

Our current understanding of the pathogenesis of CKD-aP currently relies on studies comparing the immunochemical milieu of the skin in patients with ESKD with CKD-aP with those without CKD-aP. The observed differences are then aligned with the known actions of the differing substances or cells, which are often gleaned from general pruritus research (i.e., without the confounding factor of CKD). As such, important assumptions must be made to infer causation. With this limitation in mind, we know the following:

- In CKD-aP, there is an increase in dermal mast cells [24] and dermal cell tryptase [25].
- Tryptase activates proteinase-activated receptor-2 (PAR-2) on itch nerve afferent fibres [26].
- The activation of PAR-2 sensitises the transient receptor potential vanilloid 1 (TRPV1) ion channels (a target of capsaicin) downstream in nerve afferents and

the transmission of an itch signal to the dorsal root ganglion and onto the dorsal horn in the spinal cord [27].

- The sensitisation of TRPV1 causes the retrograde release of substance P (SP) from nerve endings. SP, in turn, activates dermal mast cells and keratinocytes to release more cytokines.
- In the skin of patients with CKD-aP, there is an up-regulation of kappa-opioid receptors and that increase is statistically correlated with the severity of CKD-aP [28].
- The activation of kappa-opioid receptors has an anti-pruritic effect. These receptors appear on the surface of dermal mast cells, keratinocytes, and in the dorsal horn.
- In CKD-aP, there is a significant shift in expression of uncommitted Th lymphocytes to Th1 lymphocytes [29].
- In CKD-aP, there is an increase in the cytokines produced by Th1 lymphocytes including interferon- γ (IFN- γ), interleukin-6 (IL-6), and tumour necrosis factor- α (TNF- α) [29].
- TNF- α enhances the expression of Th1 lymphocytes.
- IL-6 sets off a cascade known as the IL-6/pBRK/p-ERK signalling-induced pruritus [30].
- In CKD-aP, there is an increase in interleukin-31 (IL-31), a Th2 lymphocyte pruritogenic cytokine [31, 32].

Table 1. Medications and interventions used in the management of CKD-aP and their known or proposed mechanism of action

Medication/intervention	Known or proposed mechanism of action
Moisturisers	Helps restore skin permeability barrier
Gabapentin/pregabalin	Uncertain. Likely inhibition of $\alpha 2\delta$ subunit of calcium channels at the dorsal horn [34, 35]. Despite their name, do not act on GABA receptors [36]
Kappa-Opioid agonists	Activation of kappa-opioid receptors has an antipruritic effect. Peripherally, kappa-opioid receptors are on the surface of dermal mast cells and keratinocytes, and centrally in the dorsal horn. The efficacy of a peripherally acting kappa-opioid agonist, indicates the mechanism of action in CKD-aP, is peripheral [37]
Capsaicin	Acts on TRPV1 channels on nerve afferents to denude SP, an important neurotransmitter in pruritus [38, 39]
Evening primrose oil (active constituent: gamma linolenic acid)	Supplements the early part of the omega-6 essential fatty acid cascade in the epidermis. This reduces production of arachidonic acid, leading, in turn, to a reduced production of pro-inflammatory cytokines leukotriene B4 and prostaglandin E2 [40, 41]. In murine studies, evening primrose oil reduces the levels of serum IL-6 and TNF- α
Sertraline	Selective serotonin reuptake inhibitor. Enhances the natural inhibitory pathway for itch. Also, reduces circulating levels of IL-6 and TNF- α [42]
Mirtazapine	Blocks certain adrenergic and serotonin receptors and histamine 1 receptors
Thalidomide	Reduces TNF- α , leading to a reduction in Th1 lymphocyte expression Reduces the synthesis of IL-6 [43]
UVB therapy	Apoptosis of keratinocytes and dermal mast cells [44]. Decreased expression of Th1 lymphocytes
Phytocannabinoids	The activation of endogenous cannabinoid receptors (CB1 and CB2) may have an antipruritic effect, in part mediated via action at TRPV1 receptors

CKD-aP, chronic kidney disease-associated pruritus; TRPV1, transient receptor potential vanilloid 1; SP, substance P; GABA, gamma-aminobutyric acid; UVB, ultraviolet B.

- There is indirect evidence that leukotriene B4, a highly pruritogenic cytokine, is involved in CKD-aP [33].
- In patients with ESKD, there is an increased concentration of $\beta 2$ -microglobulin in the serum and skin [12, 34]. $\beta 2$ -microglobulin is pruritogenic [35].
- In CKD-aP patients, there is an increased level of extracellular free calcium ions in the basal layer of the epidermis compared to ESKD patients without CKD-aP [36].

This complex pathophysiology is summarized, in part, in Figure 1. Much remains to be explained, but our current understanding emphasizes the role of crosstalk between dermal mast cells, epidermal keratinocytes, Th-1 lymphocytes, and nerve fibres.

In contrast to the peripheral mechanisms, little information is available concerning the central pathways involved in transmission of pruritus in patients with kidney disease. The pathophysiology of CKD-aP may extend to the CNS, with a functional CNS imaging study finding different areas of activity in patients with ESKD and healthy controls exposed to a pruritogenic stimulus [23]. In addition to its expression on keratinocytes, kappa-opioid receptors are widely expressed in the CNS [37]. The

relative importance of central versus peripheral kappa-opioid receptors in the pathophysiology of CKD-aP remains unclear. While the 2 kappa agonists with demonstrated efficacy (nalfurafine and difelikefalin) have limited CNS penetration, it may be that some central action does contribute to their effect. Overall, the exact CNS pathways mediating CKD-aP remain to be elucidated.

The next section summarises the management of CKD-aP. To assist readers in linking the above elements of pathogenesis with management, Table 1 lists each therapy and intervention with its proposed mechanism of action.

Measurement of CKD-aP

CKD-aP is most commonly measured on a numeric rating scale from 0 to 10, as is found in multidimensional symptom scoring tools such as the Edmonton Symptom Assessment System revised: Renal. Other tools include a visual analogue scale (where the itch intensity is indicated on a continuous line from 0 to 10), a 5-point Likert scale (as in the Integrated Patient Outcome Scale [Renal])[IP-

OS-Renal]), and multidimensional scores such as Duo or 5-D itch scale, which permit description of itch frequency and distribution in addition to severity. Although the multidimensional tools are validated in a general pruritus population [38], these instruments are not well validated in the CKD population. Information on minimal clinically important differences is sparse in both the general and CKD population. This must be borne in mind when comparing results between studies.

Management

The optimal management for CKD-aP is not yet well-defined. At least in part, this reflects the lack of clear pathogenic mechanisms, as discussed. Several reviews have recommended a stepwise approach to management depending on patient's response to initial therapy [32, 39].

Initial Management Strategies

Topical Emollients

Given the high incidence of xerosis in patients with CKD-aP, regular skin care is important for alleviating pruritus. A randomized, double-blind intraindividual (left vs. right comparison), multicentre clinical study followed by an open-labelled use of the test product on all of the xerotic areas, showed that the use of glycerol and paraffin containing emulsion compared to emulsion alone is highly effective in patients with moderate-to-severe uraemic xerosis with a substantial improvement of the uraemic pruritus (75% of patients) and quality of life at study end [40]. In another study, the regular use of an aqueous gel with higher water content was shown to reduce itching and improve xerosis in patients with mild uraemic pruritus [41].

Specific Topical Agents

For CKD-aP not responding to initial management, topical agents could be trialed as a next step. The following topical agents have been studied for efficacy in managing CKD-aP:

Topical Capsaicin

A randomized, double-blinded, crossover placebo-controlled trial of capsaicin 0.03% showed a significant reduction in the mean pruritus score on weeks 1–4 of capsaicin treatment ($p < 0.001$) compared to placebo [42]. Other preceding trials were criticized for design flaws and insufficiency of data that hindered their evaluation [43].

The main clinical difficulty with capsaicin is that its topical application is invariably followed by a transient burning sensation which many patients find intolerable.

Topical Pramoxine

A randomized, double-blind, controlled comparative trial, where topical 1% pramoxine was applied twice daily for 4 weeks compared to an emollient, showed a 61% decrease in itch intensity in the treatment group versus 12% reduction in the control group [44]. Pramoxine is a topical anaesthetic which decreases the permeability of neuronal membranes to sodium ions, blocking both the initiation and conduction of nerve impulses.

Topical Cromolyn Sodium

Cromolyn sodium is a mast cell membrane stabiliser which was initially reported as an effective oral therapy in 2 patients with refractory CKD-aP [45]. A randomized, double-blind, prospective, 4-week study of 60 HD patients showed a significant reduction in CKD-aP in favour of topical cromolyn sodium 4% ($p < 0.04$) compared to placebo at the end of week 4 [46].

Topical Gamma-Linolenic Acid

One randomized, double-blind, placebo-controlled, crossover study showed the efficacy of a gamma-linolenic acid (GLA)-rich cream, which was statistically significant compared to placebo cream for alleviating CKD-aP [47].

Topical Sericin

One randomised, double-blind, placebo-controlled study showed a significant improvement in itching and quality of life in the group treated by sericin compared to placebo. Sericin possibly works by suppressing the release of pro-inflammatory cytokines [48].

Topical Vitamin D

One open-label pilot study that assessed the efficacy and safety of topical vitamin D on 23 patients with CKD-aP showed skin dryness and itching were significantly decreased after 2 and 4 weeks of the topical vitamin D treatment compared with the vehicle ($p < 0.05$) [49].

Other Agents

Several other topical agents, targeting specific receptors, have been used or proposed. Cold receptor agonists, such as menthol (activating cold receptors in the skin has an antipruritic effect) [50] and topical cannabinoids (activating endocannabinoid receptors in the skin has an antipruritic effect) [51]. Lack of efficacy was demonstrated

for the following agents in regard to management of CKD-aP: topical calcineurin inhibitors tacrolimus 0.1% [52] and pimecrolimus 1% [53], and dead sea mineral-enriched body lotion [54].

Systemic Agents

For patients with resistant CKD-aP, not rapidly responding to initial management and specific topical agents, therapy should then be escalated to systemic pharmacologic agents.

Gabapentin and Pregabalin

Both gabapentinoids have been used in the management of CKD-aP. Multiple double-blind placebo-controlled trials have shown a statistically significant benefit of gabapentin compared to placebo in the management of CKD-aP and a recent meta-analysis found these agents to be effective (mean reduction in the itch score compared with placebo of 4.95, 95% confidence interval [CI] 4.44–5.46; based on 5 trials including 297 participants) and safe [55]. A starting dose of 100 mg gabapentin or 25 mg pregabalin in the evening is recommended to minimize adverse events in this population [56]. Both drugs are dialysable, and severe toxicity can be managed with dialysis [57]. In usual practice, supplemental doses post-dialysis are rarely required.

Few studies have compared gabapentinoids to other active agents. A randomised single-blind clinical trial comparing pregabalin (50 mg every other day) versus doxepin (10 mg daily) showed pregabalin to be more effective than doxepin in reducing the severity of CKD-aP and improving the quality of life of patients [58]. A 12-week randomized, double-blind, placebo-controlled study that included 179 HD patients compared pregabalin (75 mg twice per week) versus ondansetron (8 mg daily) or placebo, showed pregabalin to be superior [59], which is consistent with meta-analysis of 3 randomised studies showing ondansetron to be equivalent to placebo in the treatment of CKD-aP [55].

There is no evidence to suggest that one gabapentinoid should be preferred to another. A 14-week randomised, prospective, crossover trial of HD patients who were randomly assigned to receive gabapentin (300 mg post HD) or pregabalin (75 mg daily) showed both gabapentin and pregabalin improved pruritus significantly with no difference in their efficacy [60]. Another study used gabapentin (starting dose 100 mg after dialysis or daily) or pregabalin (starting dose 25 mg after dialysis or daily) in 71 consecutive patients with CKD-aP. Patients' intolerant of gabapentin were offered pregabalin. In to-

tal, gabapentin or pregabalin relieved itching in 85% of patients [61].

Kappa-Opioid Agonists

The studies of the kappa-opioid agonists have consistently shown statistically significant efficacy in the management of CKD-aP although the magnitude of this effect (mean reduction in the itch score compared with placebo of 1.05, 95% CI 0.70–1.40; based on 5 trials including 661 participants) may be less than observed with gabapentinoids [55]. Difelikefalin is a peripherally specific, highly selective agonist of kappa-opioid receptors. A recent phase 3 clinical trial for CKD-aP in HD patients showed a significant reduction in itch intensity and improved itch-related quality of life in patients treated with difelikefalin compared to placebo [62]. Nalfurafine, a kappa-opioid agonist has been studied in 2 multicentre, randomized, double-blind, placebo-controlled studies of patients with CKD-aP, who were randomized to receive post-dialysis intravenous treatment with either nalfurafine or placebo for 2–4 weeks. Statistically significant reductions in CKD-aP were found in favour of nalfurafine compared to placebo [63, 64]. Studies comparing these agents to gabapentinoids are lacking.

Mu-Receptor Antagonists

While kappa-opioid agonists have an antipruritic effect, the activation of mu-opioid receptors has, especially in the dorsal horn, a pruritic effect. Naltrexone is a mu-opioid antagonist. The studies on the efficacy of naloxone in CKD-aP are inconsistent and it is not recommended [55, 65, 66].

Antihistamines

As stated above, CKD-aP is not histaminergic in origin. Nevertheless, antihistamines are used commonly. Studies on antihistamines have shown no or modest benefit [67] or are flawed methodologically [55, 68]. We do not recommend antihistamines in the management of CKD-aP.

Sertraline

There have been 3 studies on the use of sertraline in CKD-aP. They varied in methodology: an open-label trial [69], a retrospective cohort study [70], and a double-blind, placebo-controlled trial [71]. The latter demonstrated a significantly lower itch score with sertraline but was limited by uncertainties in methodology [55, 71].

Fig. 2. Stepwise approach to the management of CKD-aP guided by severity and/or resistance of pruritus. A stepwise approach is recommended in the management of CKD-aP. Initial management strategies including moisturisers and other topical agents should be trialed first. Low-dose gabapentinoids should be considered as an initial systemic agent for patients with resistant CKD-aP. In refractory cases, other agents, such as kappa-opioid receptor agonists, sertraline, and UVB therapy are recommended. UVB, ultraviolet B; CKD-aP, chronic kidney disease-associated pruritus; kappa-opioid, kappa-opioid.

Mast Cell Stabilisers

Oral cromolyn sodium (135 mg 3 times daily) [72] and oral zinc sulphate (440 mg/day) [73] were shown to be more effective than placebo in relieving CKD-aP. Oral nicotinamide however was no more effective than placebo [74].

Gamma-Linolenic Acid

This is a constituent of evening primrose oil. The efficacy of oral GLA was studied in a randomized trial, where the control was linolenic acid. GLA-rich evening primrose oil improved overall skin symptoms, including pruritus, significantly compared to those who received linolenic acid alone ($p < 0.05$) [75].

Montelukast

Montelukast is a leukotriene receptor antagonist. Two randomized placebo-controlled trials have shown montelukast to be significantly more effective than placebo in alleviating CKD-aP [76, 77].

Thalidomide

There is one double-blind, placebo-controlled RCT on the use of thalidomide in CKD-aP that showed statistically significant benefit [78].

Turmeric

A single study, randomizing 100 participants to 3 turmeric capsules daily or placebo found a significant improvement in itch with turmeric (mean difference [on a 40-point scale] 6.4, 95% CI 5.4–7.4) [79].

Other Agents

Several other agents have shown promise, including aprepitant (an antagonist of neurokinin-1 receptor, which mediates SP signalling) [80], mirtazapine [81], and parenteral lidocaine [82].

Phototherapy

Ultraviolet B (UVB) irradiation has been shown to be effective in a number of trials and should be considered in patients with refractory CKD-aP [83–86]. A relatively small total dose of 2.11 J/cm² proved effective in the majority of treated patients [83]. Durability of treatment has been variable. Remissions were reported to be long-lasting in many patients, sometimes >2 years [84]; however, for other patients, recurrence of symptoms following cessation of therapy may be a problem [85]. By contrast, UVA light was shown to have no significant effect and is not recommended in the treatment of CKD-aP [86].

Alteration of Dialytic Treatment

There is evidence from randomized studies to suggest that high-flux HD is superior to low-flux for CKD-aP [87] and that haemodiafiltration may be superior to high-flux HD [88]. The addition of haemoperfusion may also provide additional benefit [89]. Methodological flaws limit the strength of these observations but further study is warranted.

Renal Transplantation

In very severe and refractory cases, patients suitable for renal transplantation might be switched to “high ur-

gency” status, as successful renal transplantation dramatically reduces the prevalence of CKD-aP [39, 90]. This fact implies that the pathology underlying CKD-aP is at least partly reversible.

Other Therapies with Inconclusive Results

Studies of acupuncture [91, 92], ondansetron [93–95], and cholestyramine [96, 97] have been inconclusive and they do not presently have a role in the management of CKD-aP.

Evidence Summary

In their recent Cochrane systematic review, Hercz et al. [55] conclude that gabapentinoids are the most well-studied treatment and demonstrate the largest relative effect size, that kappa-opioid agonists are likely to have a modest effect, and that oral montelukast, turmeric, zinc sulphate, and topical capsaicin may also be effective. This review is notable for identifying a large number of small, heterogeneous studies, many of which were methodologically flawed, permitting few firm conclusions to be made about many potential therapies.

Clinical Recommendations

Several authors have published recommended treatment algorithms for CKD-aP [32, 39]. Similarly, we recommend a stepwise approach to management (see Fig. 2). First, before assuming that the cause of pruritus in a patient with CKD is CKD-aP, always consider other non-uraemic causes. Having concluded that the patient has CKD-aP, the initial management is topical moisturisers and gabapentinoids. Patients should be advised about side effects of the latter (e.g., dizziness, ataxia, and somnolence) and these medications should be initiated at low doses. For dialysis patients, commence gabapentin 100 mg or pregabalin 25 mg post-dialysis. For those ESKD patients on a conservative, non-dialysis pathway, commence gabapentin 100 mg or pregabalin 25 mg every alternate night. Patients’ intolerant of one may tolerate the other and a legitimate strategy is to rotate the gabapentinoids. It should also be noted that the gabapentinoids have efficacy in the management of two other symptoms commonly experienced by patients with ESKD – uraemic restless legs syndrome [98] and painful peripheral neuropathy [99] and that this one class of medicine may be used to simultaneously manage several symptoms. In refractory cases, other agents, such as kappa-opioid receptor agonists and UVB therapy are recommended. Regarding the kappa-opioid agonists, longer term safety and efficacy data, as well as comparative ef-

ficacy data with other medications such as the gabapentinoids, are needed.

Future

CKD-aP remains a challenging issue for both patients and physicians. Greater understanding of pathogenesis is crucial and will, no doubt, build upon the significant advances in the general pathophysiology of pruritus and assist in more targeted management. A large number of treatments have been considered for CKD-aP, with highly variable results. Comparison is needed between newly emerging pharmacological agents such as kappa-opioid receptor agonists and more established agents, such as the gabapentinoids.

Conclusion

CKD-aP is a common and troubling symptom amongst ESKD patients that is associated with decreased quality of life, sleep impairment, and poor prognosis. Its exact pathogenesis is not well-understood. A stepwise approach is recommended for management starting with topical agents then escalating to gabapentinoids for resistant pruritus. Systematic reviews highlight the uncertainty about the effect of other therapies. A trial of kappa-opioid receptor agonists, if available, or UVB phototherapy should then be considered in refractory cases. Multiple other therapeutic strategies have been tested and could be considered. Finally, renal transplantation should be considered in severe and refractory cases who are suitable transplant candidates as it has shown an excellent outcome in most cases.

Conflict of Interest Statement

There are no conflicts of interest to declare.

Funding Sources

This study did not receive any funding.

Author Contributions

The review was conceived by B.S., with research and manuscript drafting by M.M., and expert input from F.B. All authors collaborated on the writing of the manuscript.

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