Clinical Kidney Journal, 2021, vol. 14, Suppl 3, i16–i22

doi: 10.1093/ckj/sfab167
CKJ Review

CKJ REVIEW

Clinical management of chronic kidney disease-associated pruritus: current treatment options and future approaches

Zoe M. Lipman[1], Vijayakumar Paramasivam[2], Gil Yosipovitch[1] and Michael J. Germain [2]

[1]Dr Phillip Frost Department of Dermatology and Miami Itch Center, University of Miami, Miami, FL, USA and and [2]Division of Nephrology, Renal Transplant Associates of New England, Baystate Medical Center U Mass Medical School, Springfield, MA, USA

Correspondence to: Michael J. Germain; E-mail: Michael.Germain@baystatehealth.org

ABSTRACT

Chronic kidney disease (CKD)-associated pruritus (CKD-aP) is an underdiagnosed yet severely distressing condition that impacts 60% of patients on dialysis and many nondialysis patients with Stages 3–5 CKD. However, despite its high prevalence, there are currently limited treatment options available for these patients and a lack of treatment guidelines for clinicians. In this manuscript, we reviewed the available literature in order to evaluate the current management and treatment options for CKD-aP, including dialysis management, topical treatments, gabapentinoids, opioids and alternative medicine. We also review the available data on CKD-aP treatments in development and propose new guidelines for managing patients with CKD-aP.

Keywords: CKD, CKD-aP, ESRD, itch, pruritus, uremic pruritus

INTRODUCTION

Itch lasting 6 weeks or more is categorized as chronic pruritus [1]. Stemming from a wide variety of causes ranging from primary dermatologic to secondary effects of underlying medical conditions, chronic pruritus can be a debilitating condition that can greatly impact patients' quality of life as it can impact their mood, sleep, personal relationships and self-esteem [2]. Chronic kidney disease-associated pruritus (CKD-aP), or uremic pruritus, is a frequently underdiagnosed but severely distressing condition that occurs in 60% of patients undergoing dialysis [3–6]. In addition, pruritus has been found to also occur in nondialysis patients with Stages 3–5 CKD, with an increasing prevalence with worsening kidney function, age and medical comorbidities [7]. With between 20% and 40% of patients reporting intense, generalized systemic itching in the moderate-to-severe range, CKD-aP has been associated with depression, worsened sleep quality, increased risk of infection, decreased quality of life and an increased risk of death [3, 4, 8–11].

Four major hypotheses exist for the pathogenesis of CKD-aP, and it is likely that the true pathogenesis is multifactorial [12]. These four main hypotheses are: (i) uremic toxins' (such as vitamin A, aluminum, calcium, phosphorus and magnesium) deposition in the subcutaneous tissue [13]; (ii) peripheral neuropathy secondary to dysautonomia as well as central neuropathy in brain [14]; (iii) immune system dysregulation [15]; and (iv) Mu-opioid receptor (MOR) to kappa-opioid receptor (KOR) activation imbalance [15]. While there are currently no standardized guidelines for the treatment of CKD-aP, the currently available

Received: 27.4.2021; Editorial decision: 6.9.2021

and in-development treatments target CKD-aP from one or more of these angles.

OPTIMIZATION OF DIALYSIS

For patients experiencing CKD-aP while on dialysis, the first step in management should always be dialysis optimization in order to remove uremic toxins using the generally accepted *Kt/V* targets. Pruritus persists in many patients that have already achieved adequate *Kt/V* targets. If this is the case, a trial increase of the dialysis dose should be considered. Increasing the dose of hemodialysis or peritoneal dialysis has been shown to reduce itch in several studies [16–18], including a 5-year prospective study that showed patients with a $Kt/V < 1.5$ were more likely to have pruritus, while those with $Kt/V > 1.5$ were less likely to have pruritus [18]. A *Kt/V* target of 1.5–1.7 for 1–2 months has been recommended. The use of high-flux dialyzers has also been shown to alleviate symptoms further [19]. In addition, for the rare patient being dialyzed with a bioincompatible membrane, switching to a biocompatible dialysis membrane (e.g. polymethylmethacrylate) may be beneficial [20–22]. More frequent dialysis and increased dialysis time may provide benefits. In addition, changing to peritoneal dialysis may also be beneficial, as CKD-aP presents more frequently and with greater intensity in patients undergoing hemodialysis compared with peritoneal dialysis [23]. However, more research is required to determine whether switching from one dialysis form to another actually improves pruritus.

Once optimization is established, alternative approaches may be considered to further help in reduction of uremic toxins. These include reduction of protein (animal protein, in particular) intake [24], oral ingestion of activated charcoal [25], probiotics and prebiotics [26, 27], and antioxidants. While safe with minimal adverse effects, these interventions should be recommended with caution as there are limited controlled studies supporting their efficacy, specifically in the context of mitigating pruritus.

TREATMENT OF CKD-ASSOCIATED MINERAL AND BONE DISEASE

The data supporting the role of CKD-associated mineral and bone disease (CKD-MBD) in the pathogenesis of CKD-aP is still limited. Several small studies suggest that the treatment of hyperparathyroidism, hyperphosphatemia and an elevated calcium-phosphate product may reduce pruritus in CKD patients [28, 29]. In a case series of 37 hemodialysis patients who underwent parathyroidectomy for either pruritus, bone pain or both, visual analog scale itch intensity ratings decreased from 5.5 pre-operatively to 1.8 at 1 week post-operatively [29]. However, there is no evidence suggesting that parathyroidectomy is beneficial in the absence of elevated parathyroid hormone. Additionally, there is some evidence suggesting that nonsurgical treatment of hyperparathyroidism, such as the use of phosphate binders, activated vitamin D or cinacalcet may be effective in minimizing pruritus, but controlled studies are still necessary to determine the extent of this effect [30]. Conversely, some studies have found that managing CKD-MBD parameters has no effect on pruritus [31].

TOPICAL TREATMENTS FOR CKD-AP

Emollients

Topical emollients should be considered in all CKD patients experiencing pruritus, as xerosis (dry skin) is highly prevalent in CKD [32, 33]. In an uncontrolled trial, 21 out of 25 patients with uremic pruritus experienced at significant relief of itch with regular emollient use, with 9 of these patients reporting complete resolution [32]. A separate study involved 10 dialysis patients applying an emollient with a high water content twice daily; all patients reported decreased pruritus after 2 weeks of doing so [34]. While there have not been any trials comparing various emollients in CKD-aP, a randomized, double-blind, intraindividual trial found that patients were more responsive to an oil and water emulsion solution containing glycerol (15%) and paraffin (10%) than an oil and water emulsion alone [35]. In general, it is recommended to choose emollients with high water contents in order to reduce pruritic symptoms and improve quality of life [34].

Topical analgesics

Topical analgesics, such as pramoxine and capsaicin, may also be useful in reducing pruritus in CKD patients. Both of these compounds alleviate pruritus through blocking the conduction of nerve impulses from the skin, leading to decreased sensation, and numbness. A one-arm parallel study involving 28 patients found that twice-daily application of pramoxine resulted in a significantly greater reduction in itch compared with an emollient alone [36]. Pramoxine-containing emollients are available both over-the-counter and by prescription, making it an affordable option for patients with or without health insurance.

Capsaicin has been shown through various studies to effectively reduce pruritus symptoms in CKD patients with localized pruritus [37–39]; however, we still lack controlled trial data evaluating its effectiveness [40]. As common side effects of capsaicin are burning, stinging and erythema, it should not be used over large areas. Due to this limited efficacy data, as well as its impracticality for generalized pruritus, it is not recommended at this time as a first-line agent for CKD-aP.

Topical tacrolimus

While topical tacrolimus, an immunosuppressant, was initially thought to be an effective treatment for reducing more localized pruritus, a double-blind study has contradicted this, showing that there was no benefit in CKD-aP patients versus control patients [41]. Because of this, along with its black box warning from the US Food and Drug Administration (FDA) for extensive use due to potentially increasing the risk of dermatologic malignancies, we do not recommend the use of tacrolimus in treating CKD-aP.

Cannabinoids

Cannabinoids (such as tetrahydrocannabinol, cannabidiol and endogenous cannabinoids like *N*-palmitoylethanolamine and *N*-acetylethanolamine) and their use in treating various medical conditions has become a quickly growing field of research secondary to its growing legalization in the USA, Canada and worldwide. While current data on its use in CKD-aP are limited, one study of uremic pruritus found that 17 out of 21 patients experienced an improvement of their pruritic symptoms after 3 weeks of a topical cream containing endogenous cannabinoids, and 8 out of 21 experienced complete resolution [42]. The effect of systemic cannabinoids has not yet been studied in regards to mitigating CKD-aP or in CKD patients, in general; however, they have been shown to be successful in other pruritic conditions, such as cholestatic itch [43] and atopic dermatitis [44]. As the long-term effect of cannabinoids, specifically in

CKD patients, is currently unknown, recommendations involving cannabinoids should be made with caution until more, controlled research becomes available.

Topical steroids

Although immune system dysregulation may be part of the pathophysiology of CKD-aP, there is little to no evidence supporting the use of topical steroids in reducing pruritus in these patients. Unless a comorbid inflammatory dermatosis is diagnosed with visible skin lesions, use of topical steroids should be avoided.

SYSTEMIC TREATMENTS FOR CKD-AP

Antihistamines

While the most frequently prescribed treatment for pruritus, oral antihistamines have displayed limited efficacy within the CKD-aP population [45]. One study compared hydroxyzine, an H1 antagonist, versus Avena sativa (oat) extract and diluted vinegar and found that there was no statistically significant difference in the relief of itch between these treatments [46]. Several other studies have found that oral antihistamines provided no extra benefit toward pruritic relief than emollients alone [33, 47]. While antihistamines may not be very effective in treating itch, they may still be useful to patients who experience nocturnal exacerbations of pruritus and require sedation in order to sleep more comfortably. In these circumstances, hydroxyzine or diphenhydramine can be used.

Gabapentinoids

The most widely studied agents in CKD-aP, gabapentin and pregabalin have shown efficacy in treating this condition. The mechanism by which these drugs work involves modulation of the alpha-2-delta subunit of voltage-gated calcium channels and/or inhibition of calcitonin gene-related peptide release (a mediator of itch) from sensory neurons and reduction of neural sensitization [45, 48, 49]. In five studies, there was a statistically significant benefit of gabapentin or pregabalin when compared with placebo [50–54]. A systematic review of 44 studies evaluating the effectiveness of CKD-aP treatments found that gabapentin/pregabalin had the largest body of evidence supporting its effectiveness [55]. A randomized, prospective crossover trial involving 29 patients found that there was no significant difference in effectiveness between the two, and both significantly improved pruritus [56]. However, if one of these medications is found ineffective, patients may experience benefit when switched to the other [5].

The preferred initiating dose for gabapentin is 100 mg after each dialysis session, and can be increased to up to 300 mg daily. Pregabalin can be initiated at 25 mg daily and increased up to 75 mg daily. Doses of 300 mg and 75 mg for gabapentin and pregabalin, respectively, should not be surpassed in dialysis patients [57]. A recent study showed increased complications in dialysis patients at higher doses [58]. These patients should also be monitored closely for dizziness and somnolence, as these side effects of the drugs may be perpetuated by CKD.

Opioids

The use of opioids in the treatment of CKD-aP is a growing field as more evidence becomes available supporting the role of opioid receptors in the pathogenesis of chronic pruritus in general, and in CKD-aP. While a detailed discussion of this mechanism is beyond the scope of this review, chronic pruritus of systemic diseases is induced through an imbalance of activation between the pro-pruritic MOR and the anti-pruritic KOR. As such, opioid treatments that antagonize the MOR and/or agonize the KOR are extremely promising in the treatment of CKD-aP [4]. Currently available-on-the-market treatments, such as naloxone, naltrexone (MOR antagonists), nalbuphine and butorphanol (mixed MOR antagonist/KOR agonists) have been studied and have shown some success in treating CKD-aP in small, uncontrolled studies. A beneficial effect of intranasal butorphanol was seen in a case series of five patients [59], and several short-term studies have shown effectiveness of naltrexone [60–63]; however, a randomized, double-blind crossover study did not show naltrexone to be more beneficial compared with placebo [64]. In a large multicenter randomized controlled trial, 373 patients on hemodialysis, nalbuphine 120 mg tablets lead to significant reductions in itch compared with placebo [65].

It is important to note that unlike MOR agonists, KOR agonists do not promote euphoria and therefore, have minimal addictive potential [66]; however, the MOR antagonist component of the above drugs can produce significant adverse effects, such as gastrointestinal symptoms. That is why selective KOR agonist drugs, such as difelikefalin (intravenous formulation recently approved by the FDA, with trials for an oral formulation underway) [67–69] and nalfurafine (approved only in Japan) [70–72] are very promising. In the published results from difelikefalin's phase 3 trial, given intravenously during the dialysis session, 51.9% of patients given the drug were observed to have a decrease in itch intensity numerical rating scale (NRS) score by at least 3 points at the end of 12 weeks compared with baseline, a significantly larger percentage than the placebo (27.9%) [67]. Additionally, difelikefalin seems to have a rapid action, as improvement in itch NRS scores was evident within 1 week of treatment. The treatment group was also reported to have a significant improvement in quality of life via several validated measures.

ANTI-DEPRESSANTS

While anti-depressants have been used for the treatment of pruritus in general, sertraline specifically has shown some efficacy in the treatment of uremic pruritus. In an uncontrolled study, 20 nondialysis CKD-aP patients who failed prior treatment with antihistamines were given sertraline; 17 noted a reduction in itch at an average duration of 5.1 weeks after treatment initiation [73]. In a double-blind, randomized controlled study with 50 patients, those administered sertraline experienced a greater reduction in their pruritus compared with placebo, at an average duration of 4 weeks after beginning treatment [74]. While the duration of time between treatment and drug efficacy makes the use of sertraline less practical, it may be worth consideration in patients with comorbid depression.

NONPHARMACOLOGIC TREATMENTS FOR CKD-AP

Phototherapy

UV-B light therapy acts on CKD-aP by immunomodulation, inhibiting T-helper 1- and 2-mediated immune responses, decreasing proinflammatory cytokines and induction of mast

cell apoptosis [75]. It has been shown to be effective in several small and/or uncontrolled studies, with significantly greater efficacy and reduction in CKD-aP compared with UV-A therapy [76–79]. While effective, UV-B therapy is associated with increased risk of carcinogenesis and was previously recommended to not be used in immunosuppressed patients [10]; however, a recent systematic review did not find any significant evidence of increased risk of skin cancer secondary to phototherapy in any skin type [80]. While it may be recommended to still stay away from this treatment in immunosuppressed patients, UV-B phototherapy may be an effective treatment option for those who do not want, or did not respond to, pharmacologic therapy.

Acupuncture/acupressure

While the mechanism of acupuncture's effect on pruritus is far from well-understood, it has been hypothesized to act via parasympathetic innervation and positive functional connectivity of the putamen-posterior midcingulate cortex [81]. Two studies to date have looked at the effect of acupressure on pruritus in CKD. The first study compared the effects of acupressure at the L1–L11 spots versus transcutaneous electrical acupoint stimulation and a control in 77 patients; it found that both acupressure and transcutaneous electrical acupoint stimulation were more effective at reducing itch than the control [82]. Another study of 71 patients compared the effects of auricular acupressure using a vaccaria seed with a control (tape placed at the same acupressure points) and also found that acupressure significantly decreased itch intensity more than the control [83].

Fatty acid supplementation

Omega-3 fatty acid supplementation has been hypothesized to decrease CKD-aP by treating an underlying essential fatty acid deficiency and reducing inflammation [84]. One study showed that supplementation of omega-3 fatty acids decreased pruritus by 40% more compared with controls [85].

CONCLUSION AND RECOMMENDATIONS

Although the number of treatments for CKD-aP is growing and more targeted treatments are being developed, it is still an understudied condition in light of the large number of patients it impacts. Many of the treatments discussed above lack sufficient evidence obtained through randomized, controlled, blinded studies, and to date, there have been very few studies comparing the different treatment options with one another. Based on the currently available evidence, we propose the following treatment recommendations in order to better manage these patients:

- All patients with CKD-aP should be dialyzed optimally according to *Kt/V* targets. If pruritus persists, a trial of an increased dialysis dose with a new *Kt/V* target of 1.5–1.7 for 1–2 months may be considered. This can be accomplished with increasing dialysis time and/or frequency. Converting to peritoneal dialysis can be considered.
- Comorbid medical conditions, both independent and associated with CKD (e.g. hyperparathyroidism), should be controlled.
- High water content emollients should be recommended for all patients. The addition of pramoxine to an emollient regiment may be recommended for extra relief.
- Topical therapies should be first-line in mild and/or localized CKD-aP.
- In generalized, moderate-to-severe and/or refractory CKD-aP, systemic therapies should be pursued. Until now, gabapentinoids (gabapentin and pregabalin) had the most evidence supporting their safety and efficacy in these patients, and have therefore been considered first-line, with caution required regarding dosing (see above section: Gabapentinoids).
- With the recent FDA approval, the selective KOR agonists difelikefalin may be considered a safe and effective alternative to gabapentinoids. Physicians should follow the progress of new drugs like this closely.
- Alternative and adjuvant treatments, such as fatty acid supplementation, phototherapy, activated charcoal, cannabinoids and acupuncture/acupressure should be considered on a patient-by-patient basis according to accessibility, practicality, financial status and other comorbidities.

More research investigating the pathophysiology of CKD-aP, comparing the different available and in-development treatments with one another, and analyzing patient outcomes are all necessary in order to successfully tackle this pressing, debilitating and understudied condition. We encourage those able to design larger-scale, well-controlled studies to further advance our understanding of CKD-aP, and are optimistic about future advancements in this field.

FUNDING

This article is part of a supplement supported by Vifor Pharma without any influence on its content.

CONFLICT OF INTEREST STATEMENT

M.J.G. is a consultant for Cara Therapeutics and Trevi Pharmaceuticals. G.Y. is a Scientific Board Member of Menlo, Trevi, Sienna, Sanofi, Regeneron, Galderma, Pfizer, Novartis, Bayer, Kiniksa, Eli Lilly, Bellus and AbbVie; research supported by Pfizer, Sun Pharma, Leo, Menlo and Kiniksa. The other authors have no conflicts of interest to disclose. The results presented in this article have not been previously published elsewhere.

REFERENCES

1. Yosipovitch G, Bernhard JD. Chronic pruritus. *N Engl J Med* 2013; 368: 1625–1634
2. Zachariae R, Lei U, Hædersdal M *et al*. Itch severity and quality of life in patients with pruritus: preliminary validity of a Danish adaptation of the itch severity scale. *Acta Derm Venerol* 2012; 92: 508–514
3. 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 Transplant* 2006; 21: 3495–3505
4. Shirazian S, Aina O, Park Y *et al*. Chronic kidney disease-associated pruritus: impact on quality of life and current

management challenges. *Int J Nephrol Renovasc Dis* 2017; 10: 11–26
5. Rayner HC, Larkina M, Wang M *et al.* International comparisons of prevalence, awareness, and treatment of pruritus in people on hemodialysis. *Clin J Am Soc Nephrol* 2017; 12: 2000–2007
6. Patel TS, Freedman BI, Yosipovitch G. An update on pruritus associated with CKD. *Am J Kidney Dis* 2007; 50: 11–20
7. Sukul N, Speyer E, Tu C *et al.*; CKDopps and CKD-REIN Investigators. Pruritus and patient reported outcomes in non-dialysis CKD. *Clin J Am Soc Nephrol* 2019; 14: 673–681
8. Mathur VS, Lindberg J, Germain M *et al.*; ITCH National Registry Investigators. A longitudinal study of uremic pruritus in hemodialysis patients. *Clin J Am Soc Nephrol* 2010; 5: 1410–1419
9. Narita I, Alchi B, Omori K *et al.* Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. *Kidney Int* 2006; 69: 1626–1632
10. Kuypers DR. Skin problems in chronic kidney disease. *Nat Clin Pract Nephrol* 2009; 5: 157–170
11. 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: 657–667
12. Hashimoto T, Yosipovitch G. Itching as a systemic disease. *J Allergy Clin Immunol* 2019; 144: 375–380
13. Yamamoto S. Molecular mechanisms underlying uremic toxin-related systemic disorders in chronic kidney disease: focused on β(2)-microglobulin-related amyloidosis and indoxyl sulfate-induced atherosclerosis-Oshima Award Address 2016. *Clin Exp Nephrol* 2019; 23: 151–157
14. Papoiu ADP, Emerson NM, Patel TS *et al.* Voxel-based morphometry and arterial spin labeling fMRI reveal neuropathic and neuroplastic features of brain processing of itch in end-stage renal disease. *J Neurophysiol* 2014; 112: 1729–1738
15. Verduzco HA, Shirazian S. CKD-associated pruritus: new insights into diagnosis, pathogenesis, and management. *Kidney Int Rep* 2020; 5: 1387–1402
16. Hiroshige K, Kabashima N, Takasugi M *et al.* Optimal dialysis improves uremic pruritus. *Am J Kidney Dis* 1995; 25: 413–419
17. Liakopoulos V, Krishnan M, Stefanidis I *et al.* Improvement in uremic symptoms after increasing daily dialysate volume in patients on chronic peritoneal dialysis with declining renal function. *Int Urol Nephrol* 2004; 36: 437–443
18. 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: e71404
19. Chen ZJ, Cao G, Tang WX *et al.* A randomized controlled trial of high-permeability haemodialysis against conventional haemodialysis in the treatment of uraemic pruritus. *Clin Exp Dermatol* 2009; 34: 679–683
20. Aucella F, Vigilante M, Gesuete A *et al.* Uraemic itching: do polymethylmethacrylate dialysis membranes play a role? *Nephrol Dial Transplant* 2007; 22: v8–v12
21. Kato A, Takita T, Furuhashi M *et al.* Polymethylmethacrylate efficacy in reduction of renal itching in hemodialysis patients: crossover study and role of tumor necrosis factor-alpha. *Artif Organs* 2001; 25: 441–447
22. Lin HH, Liu YL, Liu JH *et al.* Uremic pruritus, cytokines, and polymethylmethacrylate artificial kidney. *Artif Organs* 2008; 32: 468–472
23. Wu HY, Peng YS, Chen HY *et al.* A comparison of uremic pruritus in patients receiving peritoneal dialysis and hemodialysis. *Medicine (Baltimore)* 2016; 95: e2935
24. Marzocco S, Dal Piaz F, Di Micco L *et al.* Very low protein diet reduces indoxyl sulfate levels in chronic kidney disease. *Blood Purif* 2013; 35: 196–201
25. Cupisti A, Piccoli GB, Gallieni M. Charcoal for the management of pruritus and uremic toxins in patients with chronic kidney disease. *Curr Opin Nephrol Hypertens* 2020; 29: 71–79
26. Mafra D, Borges N, Alvarenga L *et al.* Dietary components that may influence the disturbed gut microbiota in chronic kidney disease. *Nutrients* 2019; 11: 496
27. Neirynck N, Vanholder R, Schepers E *et al.* An update on uremic toxins. *Int Urol Nephrol* 2013; 45: 139–150
28. Massry SG, Popovtzer MM, Coburn JW *et al.* Intractable pruritus as a manifestation of secondary hyperparathyroidism in uremia. Disappearance of itching after subtotal parathyroidectomy. *N Engl J Med* 1968; 279: 697–700
29. Chou FF, Ho JC, Huang SC *et al.* A study on pruritus after parathyroidectomy for secondary hyperparathyroidism. *J Am Coll Surg* 2000; 190: 65–70
30. Levy AR, Xing S, Brunelli SM *et al.* Symptoms of secondary hyperparathyroidism in patients receiving maintenance hemodialysis: a prospective cohort study. *Am J Kidney Dis* 2020; 75: 373–383
31. Shirazian S, Kline M, Sakhiya V *et al.* Longitudinal predictors of uremic pruritus. *J Ren Nutr* 2013; 23: 428–431
32. Morton CA, Lafferty M, Hau C *et al.* Pruritus and skin hydration during dialysis. *Nephrol Dial Transplant* 1996; 11: 2031–2036
33. Gilchrest BA, Stern RS, Steinman TI *et al.* Clinical features of pruritus among patients undergoing maintenance hemodialysis. *Arch Dermatol* 1982; 118: 154–156
34. Okada K, Matsumoto K. Effect of skin care with an emollient containing a high water content on mild uremic pruritus. *Therapher Dial* 2004; 8: 419–422
35. 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: 748–752
36. 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 Dermatolog Treat* 2009; 20: 76–81
37. Tarng DC, Cho YL, Liu HN *et al.* Hemodialysis-related pruritus: a double-blind, placebo-controlled, crossover study of capsaicin 0.025% cream. *Nephron* 1996; 72: 617–622
38. Breneman DL, Cardone JS, Blumsack RF *et al.* Topical capsaicin for treatment of hemodialysis-related pruritus. *J Am Acad Dermatol* 1992; 26: 91–94
39. Cho YL, Liu HN, Huang TP *et al.* Uremic pruritus: roles of parathyroid hormone and substance P. *J Am Acad Dermatol* 1997; 36: 538–543
40. Gooding SM, Canter PH, Coelho HF *et al.* Systematic review of topical capsaicin in the treatment of pruritus. *Int J Dermatol* 2010; 49: 858–865
41. Duque MI, Yosipovitch G, Fleischer AB , Jr *et al.* 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: 519–521
42. 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: 97–103
43. Neff GW, O'Brien CB, Reddy KR *et al.* Preliminary observation with dronabinol in patients with intractable pruritus

secondary to cholestatic liver disease. *Am J Gastroenterol* 2002; 97: 2117–2119
44. Yuan C, Wang XM, Guichard A *et al.* N-palmitoylethanolamine and N-acetylethanolamine are effective in asteatotic eczema: results of a randomized, double-blind, controlled study in 60 patients. *Clin Interv Aging* 2014; 9: 1163–1169
45. Yosipovitch G, Rosen JD, Hashimoto T. Itch: from mechanism to (novel) therapeutic approaches. *J Allergy Clin Immunol* 2018; 142: 1375–1390
46. Nakhaee S, Nasiri A, Waghei Y *et al.* Comparison of Avena sativa, vinegar, and hydroxyzine for uremic pruritus of hemodialysis patients: a crossover randomized clinical trial. *Iran J Kidney Dis* 2015; 9: 316–322
47. Weisshaar E, Dunker N, Röhl FW *et al.* Antipruritic effects of two different 5-HT3 receptor antagonists and an antihistamine in haemodialysis patients. *Exp Dermatol* 2004; 13: 298–304
48. Fehrenbacher JC, Taylor CP, Vasko MR. Pregabalin and gabapentin reduce release of substance P and CGRP from rat spinal tissues only after inflammation or activation of protein kinase C. *Pain* 2003; 105: 133–141
49. Fowler E, Yosipovitch G. Chronic itch management: therapies beyond those targeting the immune system. *Ann Allergy Asthma Immunol* 2019; 123: 158–165
50. Gunal AI, Ozalp G, Yoldas TK *et al.* Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. *Nephrol Dial Transplant* 2004; 19: 3137–3139
51. Naini AE, Harandi AA, Khanbabapour S *et al.* Gabapentin: a promising drug for the treatment of uremic pruritus. *Saudi J Kidney Dis Transplant* 2007; 18: 378
52. Nofal E, Farag F, Nofal A *et al.* Gabapentin: a promising therapy for uremic pruritus in hemodialysis patients: a randomized-controlled trial and review of literature. *J Dermatol Treat* 2016; 27: 515–519
53. Tol H, Atalay H, Güney I et al. The effects of gabapentin therapy on pruritus, quality of life, depression and sleep quality in pruritic hemodialysis patients. *Trakya Univ Tip Fak Derg* 2010; 27: 1
54. Yue J, Jiao S, Xiao Y *et al.* Comparison of pregabalin with ondansetron in treatment of uraemic pruritus in dialysis patients: a prospective, randomized, double-blind study. *Int Urol Nephrol* 2015; 47: 161–167
55. Simonsen E, Komenda P, Lerner B *et al.* Treatment of uremic pruritus: a systematic review. *Am J Kidney Dis* 2017; 70: 638–655
56. 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 (Carlton)* 2012; 17: 710–717
57. Yoo L, Matalon D, Hoffman RS *et al.* Treatment of pregabalin toxicity by hemodialysis in a patient with kidney failure. *Am J Kidney Dis* 2009; 54: 1127–1130
58. Ishida JH, McCulloch CE, Steinman MA *et al.* Gabapentin and pregabalin use and association with adverse outcomes among hemodialysis patients. *J Am Soc Nephrol* 2018; 29: 1970–1978
59. Dawn A, Yosipovitch G. Butorphanol for treatment of intractable pruritus. *J Am Acad Dermatol* 2006; 54: 527–531
60. Bernstein JE, Swift R. Relief of intractable pruritus with naloxone. *Arch Dermatol* 1979; 115: 1366–1367
61. Andersen LW, Friedberg M, Lokkegaard N. Naloxone in the treatment of uremic pruritus: a case history. *Clin Nephrol* 1984; 21: 355–356
62. Legroux-Crespel E, Clèdes J, Misery L. A comparative study on the effects of naltrexone and loratadine on uremic pruritus. *Dermatology* 2004; 208: 326–330
63. Peer G, Kivity S, Agami O *et al.* Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet* 1996; 348: 1552–1554
64. 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: 514–519
65. Mathur VS, Kumar J, Crawford PW *et al.*; TR02 Study Investigators. A multicenter randomized, double-blind, placebo-controlled trial of nalbuphine ER tablets for uremic pruritus. *Am J Nephrol* 2017; 46: 450–458
66. Cowan A, Kehner GB, Inan S. Targeting itch with ligands selective for κ opioid receptors. *Handb Exp Pharmacol* 2015; 226: 291–314
67. Fishbane S, Jamal A, Munera C *et al.* A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. *N Engl J Med* 2020; 382: 222–232
68. Fishbane S, Mathur V, Germain MJ *et al.* Randomized controlled trial of difelikefalin for chronic pruritus in hemodialysis patients. *Kidney Int Rep* 2020; 5: 600–610
69. Fishbane S, Mathur V, Germain MJ *et al.*; Trial Investigators. Randomized controlled trial of difelikefalin for chronic pruritus in hemodialysis patients. *Kidney Int Rep* 2020; 5: 600–610
70. Kozono H, Yoshitani H, Nakano R. Post-marketing surveillance study of the safety and efficacy of nalfurafine hydrochloride (Remitch(®) capsules 2.5 μg) in 3,762 hemodialysis patients with intractable pruritus. *Int J Nephrol Renovasc Dis* 2018; 11: 9–24
71. Kumagai H, Ebata T, Takamori K *et al.* 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 Transplant* 2010; 25: 1251–1257
72. Wikström 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: 3742–3747
73. Chan KY, Li CW, Wong H *et al.* Use of sertraline for antihistamine-refractory uremic pruritus in renal palliative care patients. *J Palliat Med* 2013; 16: 966–970
74. Pakfetrat M, Malekmakan L, Hashemi N *et al.* Sertraline can reduce uremic pruritus in hemodialysis patient: a double blind randomized clinical trial from Southern Iran. *Hemodial Int* 2018; 22: 103–109
75. Szepietowski JC, Morita A, Tsuji T. Ultraviolet B induces mast cell apoptosis: a hypothetical mechanism of ultraviolet B treatment for uraemic pruritus. *Med Hypotheses* 2002; 58: 167–170
76. Gilchrest BA, Rowe JW, Brown RS *et al.* Ultraviolet phototherapy of uremic pruritus: long-term results and possible mechanism of action. *Ann Intern Med* 1979; 91: 17–21
77. Gilchrest BA, Rowe JW, Brown RS *et al.* Relief of uremic pruritus with ultraviolet phototherapy. *N Engl J Med* 1977; 297: 136–138
78. Ada S, Seçkin D, Budakoğlu I *et al.* Treatment of uremic pruritus with narrowband ultraviolet B phototherapy: an open pilot study. *J Am Acad Dermatol* 2005; 53: 149–151
79. Sherjeena PB, Binitha MP, Rajan U *et al.* A controlled trial of narrowband ultraviolet B phototherapy for the treatment of uremic pruritus. *Indian J Dermatol Venereol Leprol* 2017; 83: 247–249

80. Wang E, Sasaki J, Nakamura M *et al*. Cutaneous carcinogenic risk of phototherapy: an updated comprehensive review. *J Psoriasis Psoriatic Arthrit* 2015; 1: 44–51
81. Min S, Kim KW, Jung WM *et al*. Acupuncture for histamine-induced itch: association with increased parasympathetic tone and connectivity of putamen-midcingulate cortex. *Front Neurosci* 2019; 13: 215
82. Akça NK, Taşcı S. Acupressure and transcutaneous electrical acupoint stimulation for improving uremic pruritus: a randomized, controlled trial. *Alternat Ther Health Med* 2016; 22: 18–24
83. Yan CN, Yao WG, Bao YJ *et al*. Effect of auricular acupressure on uremic pruritus in patients receiving hemodialysis treatment: a randomized controlled trial. *Evid Based Complement Alternat Med* 2015; 2015: 1–8
84. Panahi Y, Dashti-Khavidaki S, Farnood F *et al*. Therapeutic effects of omega-3 fatty acids on chronic kidney disease-associated pruritus: a literature review. *Adv Pharm Bull* 2016; 6: 509–514
85. Ghanei E, Zeinali J, Borghei M *et al*. Efficacy of omega-3 fatty acids supplementation in treatment of uremic pruritus in hemodialysis patients: a double-blind randomized controlled trial. *Iran Red Crescent Med J* 2012; 14: 515–522