# Managing itch in patients receiving haemodialysis: a practical guide

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Prescribing information and adverse event reporting can be found on page S8.

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Itching (pruritus) is a common and impactful symptom in patients with chronic kidney disease (CKD). This guide presents of an overview of how to diagnose and treat CKD-associated pruritus.

Patients receiving haemodialysis experience a high symptom burden. Alongside the key outcomes of fatigue, cardiovascular disease and mortality, those undergoing haemodialysis have been shown to also prioritise food enjoyment, sleep and itching (Standardised Outcomes in Nephology, 2019).

## SYMPTOM BURDEN AND COMPLICATIONS

Itching (pruritus) is highly prevalent amongst haemodialysis recipients (Sukul and Rayner, 2022). Out of 34 526 participants in the 2020 Dialysis Outcomes and Practice Patterns Study, 23% reported serial data on pruritus symptoms, while 51% reported being 'at least moderately bothered' and 11% 'extremely bothered' by itchy skin. Beyond the immediate discomfort and aesthetic distress of scratching, patients who were at least moderately bothered by itch reported more adverse mental health, sleep disturbance and fatigue, as well as longer time to recover after a dialysis session (Sukul et al, 2023).

Moreover, analyses adjusted for confounding comorbidity, demographic data and dialysis adequacy identified a significant association between itch severity and both hospitalisation and mortality. Compared to people who were not at all bothered, patients extremely bothered by itching had an adjusted mortality hazard ratio of 1.24 (95% CI, 1.08–1.41) (Sukul et al, 2021).

Why patients with end-stage kidney disease (ESKD) should be prone to itching is unclear, but recent evidence suggests a multifactorial interaction of biochemical, inflammatory and neuropsychological factors. The neurological basis of itch is closely related to pain, in that signals are conducted from skin to brain via sensory C-fibres (Cevikbas and Lerner, 2020). In patients with advanced chronic kidney disease (CKD), the histamine-independent itch pathway, stimulated by cowhage, is abnormal (Papoiu et al, 2014). Cutaneous inflammation (at a micro- or macro-scale) may be more common in advanced CKD, for the following reasons:

- Dry skin
- Increased mast-cell proliferation and activity
- Cutaneous phosphate and calcium deposition
- Increased systemic proinflammatory cytokines.

Peripheral nerve dysfunction and over-stimulation may also contribute to itch. ESKD-associated peripheral neuropathy is presumed to be a result of direct toxicity from the uraemic milieu, which is a result of peripheral nerve damage and attempted re-growth. Paraesthesia, pain and pruritus can develop due to over-excitation of disordered peripheral nerves (Johansson et al, 1989).

Opioid receptors modulate C-fibre activity. Opioid receptors include the mu-opioid receptor (MOR), kappa-opioid receptor (KOR) and delta-opioid receptor (DOR). Endogenous agonists (endorphins, enkephalins and dynorphins) have different binding profiles and activation patterns across these receptors. It is postulated that

MOR activation is pro-pruritic, and KOR activation ameliorates this response. Patients with advanced CKD demonstrate down-regulation of KOR in cutaneous tissue, as well as up-regulation of MOR leading to propagation of pruritic signalling (Martin et al, 2020).

Depression is highly prevalent among patients with advanced CKD, and it exacerbates the impact of altered itch sensation on the functional effects of this unpleasant sensation (Brown et al, 2021).

## DIAGNOSIS

When a patient with CKD presents with itching, it is important to initially consider other causes of itch beyond kidney disease. Specific and effective treatments may be available, particularly for primary dermatological diseases (*Table 1*).

CKD-aP is a diagnosis of exclusion characterised by persistent itching. Unlike dermatological conditions such as eczema that present as primary lesions, CKD-aP presents with lesions secondary to the damage done by scratching the skin. There are no specific clinical signs or laboratory tests that confirm CKD-aP.

Excluding other potential causes of itching is neither onerous nor complex, but it does require a comprehensive assessment of medical and medication history, alongside a clinical examination that includes the skin.

**Table 1. Potential causes of itch in chronic kidney disease (CKD)**

| Aetiology type | Aetiology | Clinical features |
|---|---|---|
| Dermatological disease | Eczema/atopic dermatitis | Erythematous patches with dry flaky skin |
| | Psoriasis | Plaques of dry silver scales, typically on elbows and knees (may be associated with inflammatory arthritis) |
| | Infections (scabies, fungal, lice) | Typical localised rashes, nits, lice, burrows |
| | Autoimmune disease | Urticaria, hives |
| | Xerosis | Dry flaky skin |
| Non-renal disease | Cholestasis | Jaundice, other signs of liver disease, pregnancy |
| | Lymphoma | No rash; lymphadenopathy |
| Medication | Opioids | |
| | Angiotensin-converting enzyme (ACE) inhibitors | |
| CKD | Iron deficiency | Anaemia, reduced serum iron indices, history of blood loss |
| | Hyperphosphataemia | Severely elevated serum phosphate (>3.0 mmol/l) |
| | CKD-associated pruritis | Advanced kidney disease; absence of other cause of pruritus |

## SCREENING

Given the high prevalence of itch reported by patients with ESKD, the impact of itch on patients' lives should be included in all routine assessments. Most clinicians involved in the management of patients with ESKD underestimate the prevalence of pruritus, and consequently CKD-aP is underdiagnosed (Rayner et al, 2017).

Validated clinical assessment tools are available to quantify the severity and impact of pruritus on patients' lives and have been used as primary outcome measures in clinical trials. Of these, the Worst Itching Intensity Numerical Rating Scale (WI-NRS) is the most widely used, and it is simple to use in routine clinical care (*Box 1*). Patients with weekly mean scores of 4 or more have been defined as having moderate-to-severe pruritus (Fishbane et al, 2020), and a reduction in score of 3 or more with an intervention has been defined to be 'meaningful' (Vernon et al, 2021).

Validated tools for measuring pruritus, such as the WI-NRS, are subjective and time-limited. The severity and impact of pruritus on an individual's functional status can vary considerably over time, and so it is as important to include a narrative approach in assessing CKD-aP. For example, it is worth asking how itching has affected sleep, social activities, employment and relationships over recent months.

## TREATMENT OPTIONS

Historically, clinicians involved in the management of patients with CKD-aP have recommended a sequential treatment approach, including the following interventions (not all of which are supported by evidence):

- Topical treatments (emollients with or without levomenthol)
- Increased dialysis intensity
- Enhanced serum phosphate control
- Reduction in parathyroid hormone, antihistamines and gabapentinoids such as gabapentin/ pregabalin (Eusebio-Alpapara et al, 2020).

Patients whose everyday life and relationships are affected by itching may benefit from psychological intervention (Schut et al, 2016; Bonchak and Lio, 2020). Cognitive behavioural therapy (CBT) encourages people to notice and alter the negative thought processes and patterns that accompany the itch–scratch cycle. Mindfulness-based stress reduction increases awareness of bodily sensations and thoughts and encourages an acceptance and tolerance of them, reducing the level of distress and intensity and frequency of itching (Alipour et al, 2014).

### DIALYSIS, PARATHYROID HORMONE AND SERUM PHOSPHATE OPTIMISATION

In haemodialysis recipients who are not achieving recommended urea clearance (Kt/V >1.2 per session), CKD-aP

**Box 1. Worst Itching Intensity Numerical Rating Scale (WI-NRS)**

Over the past 24 hours, indicate the intensity of the worst itching you have experienced, where 0 is no itching and 10 is the worst itching imaginable

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

symptoms may improve with increased dialysis intensity (Hiroshige et al, 1995), although this association has not been replicated in large trials. However, intensifying therapy beyond this has not been shown to ease symptoms.

Severe hyperphosphataemia (>3.0 mmol/l) may directly increase cutaneous inflammation via the IL-6/p-BTK/p-ERK pathway (Keshari et al, 2019). However, systematic reviews suggest that confounding factors, including inflammation and under-dialysis, are more dominant contributors to a link between phosphate and pruritus in clinical practice (Shirazian et al, 2013). Recent studies did not find correlation between itch severity and either serum phosphate or phosphate binder pill burden (Colombijn et al, 2022), nor consistent associations between itch severity and serum parathyroid hormone levels (Sukul et al, 2023).

## ANTIHISTAMINES

Antihistamines have been the most common first-line pharmaceutical agent used for CKD-aP, despite the absence of reliable data to support their efficacy (Rayner et al., 2017).

Some patients with advanced CKD do report improvement in itch with antihistamines, which can be the result of primary dermatological disease, predominant mast-cell instability or the sedative properties of some agents. However, supportive evidence from randomised controlled trials (RCTs) is scarce. Two RCTs reported mixed results, with one showing a significant improvement in itch compared with placebo, the other not. Both were small unblinded studies (Hercz et al, 2020). Functional magnetic resonance imaging (fMRI) studies have shown that activity of the histamine-dependent itch pathway in brains of patients with CKD-aP is not different from controls (Papoiu et al, 2014).

## GABAPENTINOIDS

Gabapentin and pregabalin inhibit disordered nerve activity by decreasing neuronal calcium influx (Vila et al, 2008). Systematic reviews of RCTs of gabapentin and pregabalin report significantly improved itch severity for patients with CKD-aP; however, the trials involved a small number of participants, limiting the strength of the evidence. A non-significant increase in somnolence and dizziness was also reported. (Eusebio-Alpapara et al, 2020). In five studies with 297 participants, gabapentin and pregabalin led to a mean 4.95/10 greater reduction in itch severity than placebo (95% CI 5.46–4.44) . The risk ratio for pruritus with gabapentinoid compared with placebo was 0.18 (95% CI 0.09–0.33) (Hercz et al, 2020).

Gabapentinoids are excreted by kidneys, so patients with ESKD should have a reduced initial dose. Among more elderly and comorbid patients, neurological side effects can be particularly troublesome, making careful dose adjustment important. Although gabapentin and pregabalin are widely prescribed for CKD-aP, neither agent is licensed for this use.

## OPIOID-RECEPTOR MODULATION

Opioid-receptor modulation to counteract the up-regulation of MOR and down-regulation of KOR found with advanced CKD is an alternative treatment option for CKD-aP.

### NALTREXONE

The MOR antagonist naltrexone has been shown to be ineffective in reducing itch in CKD-aP in trials (Hercz et al, 2020).

## NALBUPHINE

The combined MOR antagonist and KOR agonist nalbuphine had a modest beneficial effect on itch amongst HD recipients, reducing WI-NRS score by 3.5 after 8 weeks of treatment vs 2.8 for placebo (p=0.017) (Mathur et al, 2017). However, nalbuphine is not licensed for treating CKD-aP, nor readily available.

## NALFURAFINE

The oral or intravenous KOR agonist nalfurafine has been studied in patients receiving haemodialysis with severe and refractory CKD-aP. Seven trials showed a beneficial effect. with statistically significant reductions in WI-NRS (or equivalent) of 2.2 to 3.3 vs 1.3 to 1.9 for placebo (Zhang et al, 2023). Nalfurafine is licensed for CKD-aP in Japan but not in continental Europe, the UK or the US.

## DIFELIKEFALIN▼

Difelikefalin (Kapruvia) is a kappa-opioid receptor (KOR) agonist with antipruritic and anti-inflammatory effects related to activation of KORs on peripheral sensory neurons and immune cells. It is given intravenously three times a week after each dialysis session in or after the rinse back. Difelikefalin was studied in two RCTs of haemodialysis recipients with moderate-to-severe CKD-aP. RCT trial data showed difelikefalin three times a week resulted in a greater proportion of patients achieving a ≥3.0 reduction in WI-NRS than placebo after 12 weeks of treatment (51.1% vs 35.2%, p<0.001), as well as a greater proportion of patients achieving complete resolution of itch symptoms (12.0% vs 6.7%, p=0.006) (Topf et al, 2022). Adverse events were similar between treatment and placebo groups other than marginal increase in diarrhoea and dizziness amongst difelikefalin recipients. Serious adverse events and treatment discontinuation rate were similar (Fishbane et al, 2020). Reduced itch was associated with improved quality of life indices and sleep quality (Weiner et al, 2024). Difelikefalin is the only treatment indicated for moderate-to-severe CKD-aP in adults on in-centre haemodialysis. It was recommended as a cost-effective use of NHS resources for treatment of moderate-to-severe CKD-aP in adults on in-centre haemodialysis by the National Institute for Health and Care Excellence (NICE) (2023) in May 2023 and the Scottish Medicines Consortium (SMC) (2024) in January 2024.

## SUMMARY

CKD-aP is a common, disabling and treatable condition, under-recognised by clinicians involved in management of patients on haemodialysis.

Proactive identification of patients who are experiencing pruritus is required to allow targeted treatment that has been shown to improve quality of life. Psychological support should be offered to patients whose quality of life is being harmed by itching.

Emollients are important to relieve the dry skin associated with itching, but evidence for topical medication is lacking. There is no reliable evidence that phosphate lowering or antihistamines are effective. Gabapentinoids have been proven effective in reducing CKD-aP in some RCTs, but they are unlicensed and need careful dosing to minimise side effects.

KOR agonists seem effective in reducing symptoms in haemodialysis recipients with moderate-to-severe CKD-aP. Difelikefalin is indicated for treatment of moderate-to-severe CKD-aP in adults on in-centre haemodialysis. It is also recommended by NICE and SMC. **JKC**

**Note:** Difelikefalin is the only licensed treatment for moderate-to-severe CKD-aP in adult patients on in-centre haemodialysis. Other pharmacological treatments mentioned in this guide are off-label. Please refer to the relevant summary of product characteristics before making prescribing decisions.

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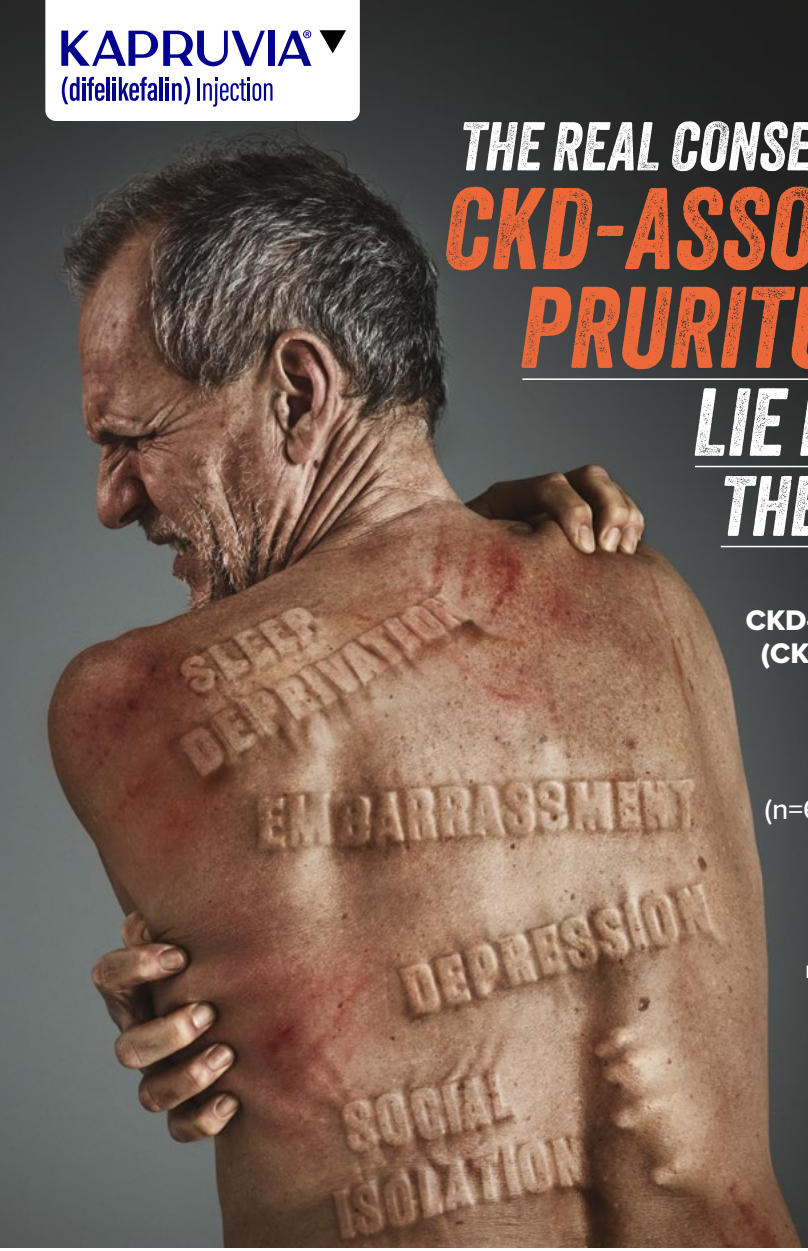


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*In DOPPS, moderate-to-severe CKD-aP is defined as patients moderately, very much, and extremely bothered by itching, severity of itch was established from the KDQoL-36 questionnaire.[1]

**CKD-aP**, chronic kidney disease associated pruritus; **DOPPS**, Dialysis Outcomes and Practice Patterns Study; **KDQoL-36**, Kidney Disease Quality of Life 36-item short form survey; **UK**, United Kingdom.

**References: 1.** Sukul N, et al. *Kidney Medicine*. 2020;3(1):42–53. **2.** KAPRUVIA® Summary of Product Characteristics.

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