

# EPIDEMIOLOGY AND CAUSES

## of CKD-associated Pruritus (CKD-aP) in Dialysis Patients



### BACKGROUND

CKD-aP is defined as itch secondary to kidney disease not explained by alternate causes



### PREVALENCE

Pruritus is widespread and has been reported up to **80% of dialysis patients**, with **almost 40% experiencing moderate to severe itch**



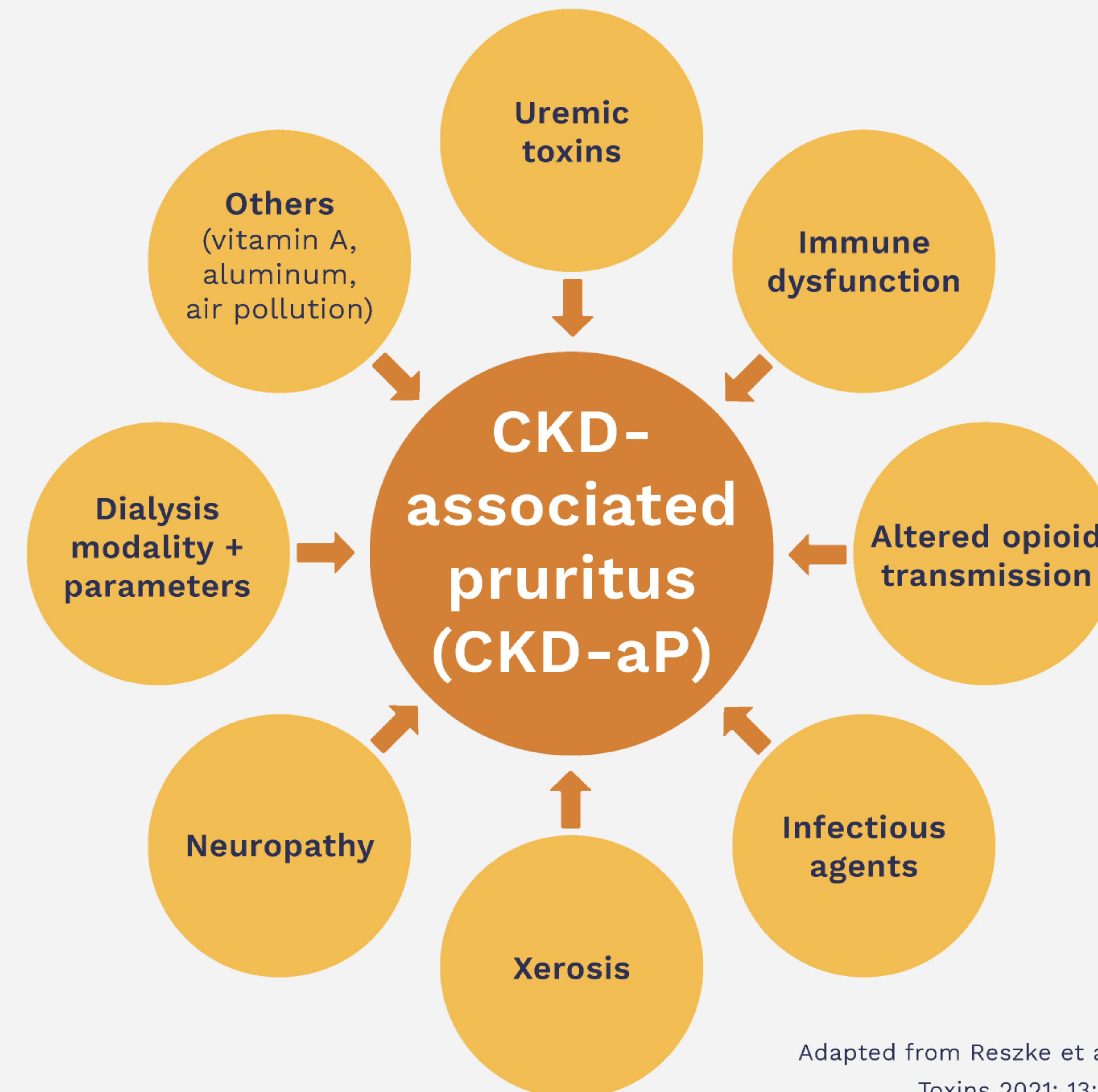
### BURDEN

Pruritus can be debilitating and is associated with lower quality of life, increased risks for infection, hospitalization and even mortality

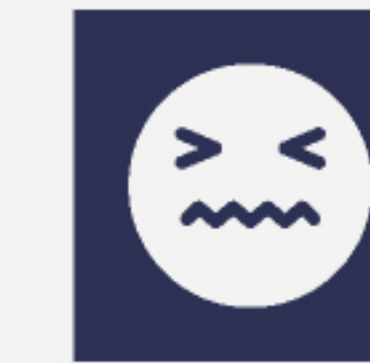
Patients with severe pruritus are more likely to miss their dialysis sessions or withdraw from dialysis than those with mild or no symptoms



### CONTRIBUTING FACTORS



Adapted from Reszke et al.  
Toxins 2021; 13: 3



### CONSEQUENCE & IMPACT



Sleep disturbance

Fatigue



Reduction in ability to work, quality of personal relationships, and self-esteem



Depression

Pain



Poor dialysis and medication adherence



Risk of infection



Hospitalization (cardiovascular-, infection- and skin-related complications)



# DIAGNOSIS AND ASSESSMENT

## of CKD-associated Pruritus (CKD-aP) in Dialysis Patients



### INTRODUCTION

#### Clinical Presentation

Manifestations of CKD-aP are heterogeneous with respect to intensity and duration; there is no pattern of distribution as some patients reported generalized itch while others reported localized areas

#### Underrecognition

Prevalence of pruritus is often underestimated by care providers. **Reasons are several fold:** Patients may have never discussed their itch with clinicians; inadequate attention to or appreciation of pruritus and its impact by clinicians; symptom assessment not routinely performed

#### Undertreatment

In one survey (DOPPS), **20% of patients severely affected by pruritus were not treated for itch**



### ASSESSMENT

Obtain detailed patient history: Inquire about pruritus symptoms; review pre-existing skin diseases and rule out non-CKD causes (e.g., drug-induced pruritus; concomitant dermatological or rheumatological diseases)



Perform laboratory screening: Evaluate for metabolic risk factors and derangements (e.g., C-reactive protein, calcium-phosphate, ferritin), dialysis parameters (Kt/V) and exclude other possible etiologies of chronic pruritus



Consider using patient reported tools validated for CKD-aP: There are two types of tools, unidimensional vs. multidimensional

**Unidimensional:** Subjective scales used to measure itch severity

**Multidimensional:** Scales used to ascertain impact of pruritus on quality of life. These may be helpful for patients who have difficulty in translating their severity on a line or number



### VALIDATED INSTRUMENTS

#### Unidimensional

- Numeric Rating Scale (NRS): Patients identifies itch severity on a numerical scale from 1-10
- Visual Analogue Scale (VAS): Patient draws line to note level of itch
- Verbal Rating Scale (VRS): Patients are assessed based on 5 itching severities
- Q-20 KDQOL-36: A survey of 43 kidney disease-specific questions which includes question 20 that measures itching in the past 4 weeks

#### Multidimensional

- Self-assessed disease severity
- 5-D itch scale: Validated to analyze course of itch
- Skindex-10: Validated to evaluate itch intensity
- Itch Medical Outcomes Study: Assesses sleep disturbance



# PATHOPHYSIOLOGY

## of CKD-associated Pruritus (CKD-aP) in Dialysis Patients



### PATHOBIOLOGY

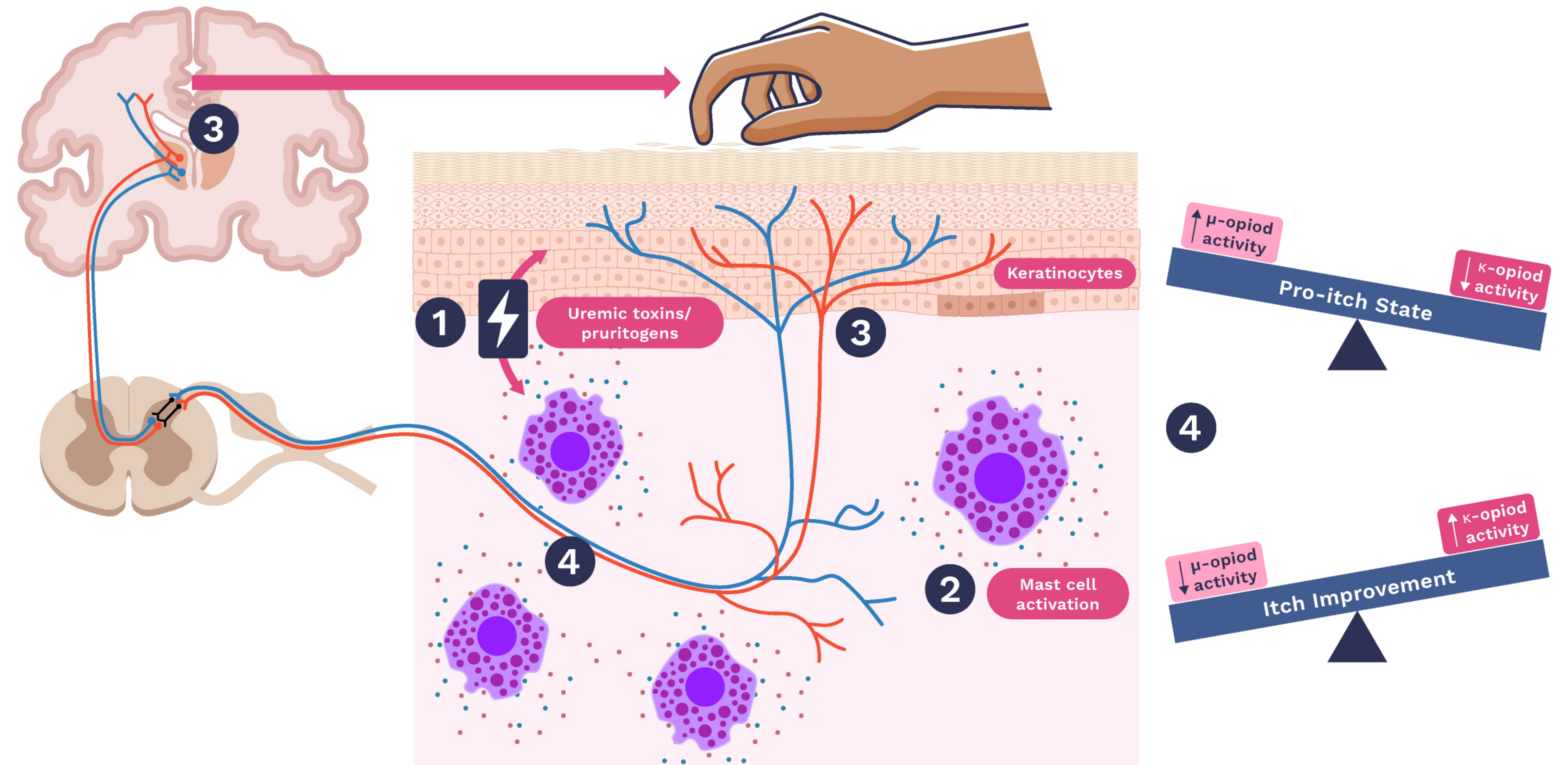
Etiology of CKD-aP is not fully understood but it is likely that **pathogenesis is multifactorial**

Various pathways have been implicated in the generation of pruritus, including:

- 1 Deposition of uremic toxins in the skin and subcutaneous tissues (such as vitamin A, aluminum, calcium, phosphorus and magnesium)
- 2 Immune system dysregulation and inflammation
- 3 Peripheral neuropathy secondary to dysautonomia as well as central neuropathy in brain
- 4 Dysregulation of endogenous opioid system:  $\mu$ -opioid receptor (MOR) which stimulates itching to  $\kappa$ -opioid receptor (KOR) which suppresses itching



### MECHANISM



Adapted from Sutaria N et al. J Am Acad Dermatol 2022; 86: 19, 22



# TREATMENT (1)

## of CKD-associated Pruritus (CKD-aP) in Dialysis Patients



### MANAGEMENT

#### Management Approaches

Numerous treatment strategies have been proposed but demonstration of their efficacy in CKD-aP is limited. It has been suggested that alleviating two or more concurrent symptoms (symptom clusters) may reduce severity of others, including dialysis-associated itching

##### Potential avenues for treating CKD-aP:

- Optimize dialysis prescription
- Optimize CKD-MBD parameters
- Consider topical and systemic treatments
- Contemplate alternative treatments



### OPTIMIZATIONS

#### Optimization of dialysis prescription

Increasing dialysis dose (Kt/V) can be considered to improve clearance of uremic toxins, though such a correlation between higher dose and lesser degree of pruritus has not been consistently reported

Similarly use of high flux vs low flux dialyzers and biocompatible vs bioincompatible membranes may reduce pruritus severity

#### Optimization of CKD-MBD

There has been speculation on the association of CKD-aP with high calcium, phosphate, and PTH, but this has not been confirmed

Clinicians are advised to follow KDIGO goals set forth for CKD-MBD parameters



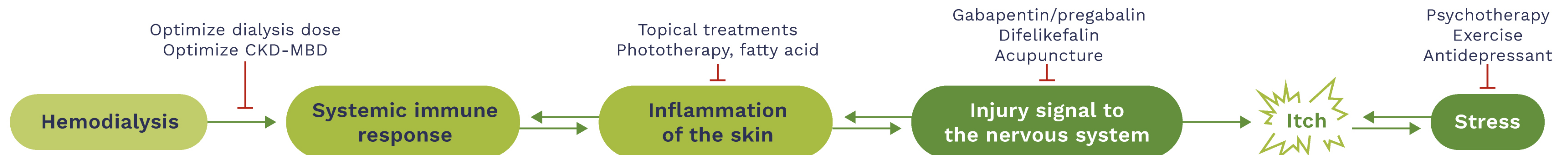
### TREATMENTS

#### Optimize Skin Care

- Topical emollients: since dry skin (xerosis) is common, emollients with high water content could offer relief
- Other topicals: pramoxine, capsaicin, cromolyn sodium, gamma-linolenic acid, sericin, vitamin D, menthol, cannabinoids

#### Systemic Treatment

- Anticonvulsants such as gabapentin and pregabalin, which modulate calcium channels and inhibit itch mediator, and antidepressants such as sertraline, have been used as off-label treatment for CKD-AP. However, there is concern for potential misuse with the former
- Difelikefalin, a  $\kappa$ -opioid receptor agonist, is the only current therapy approved by the US FDA and European Medicines Agency for treating moderate-to-severe pruritus associated with CKD in adults on dialysis therapy



Adapted from Martin CE., et al. Can J Kidney Health Dis 2020; 7:2054358120954024



# TREATMENT (2)

## of CKD-associated Pruritus (CKD-aP) in Dialysis Patients



### SYSTEMIC TREATMENT

Systemic therapy should be considered when response to topical agents has been suboptimal

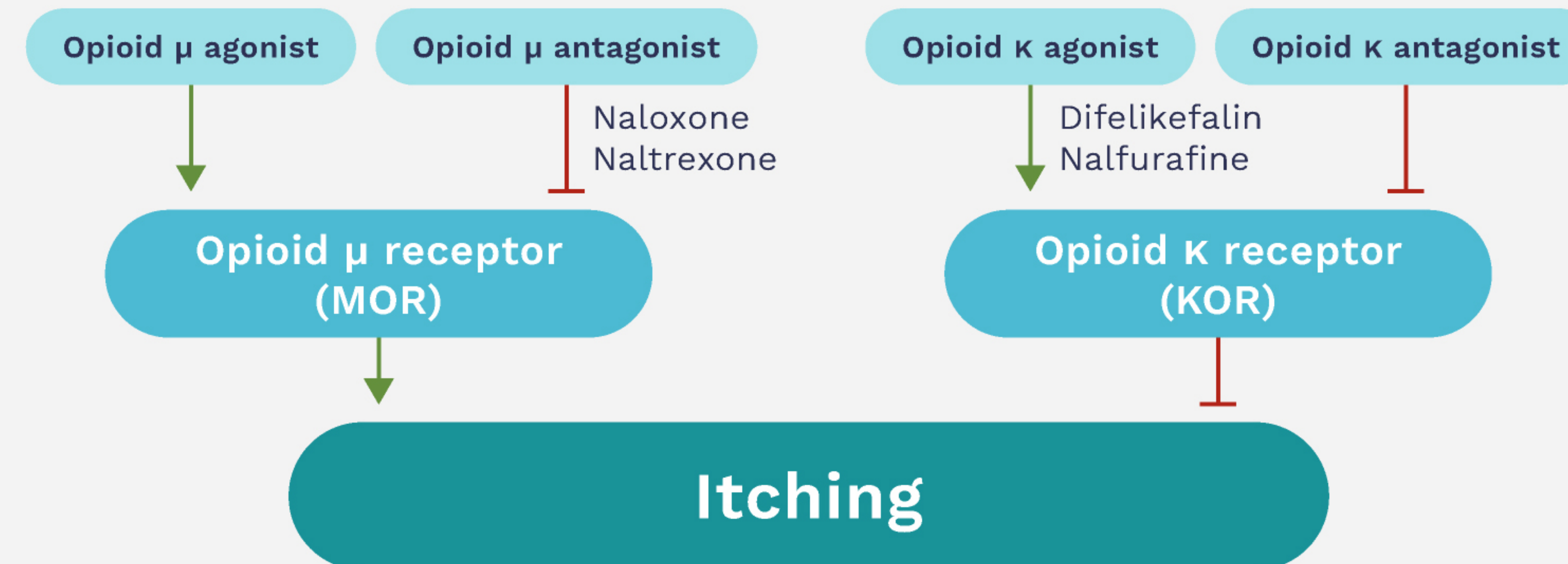
**Agents used to treat peripheral neuropathy such as gabapentin or pregablin have shown to reduce pruritus.** Doses should be monitored closely since common side effects include dizziness and somnolence

There is greater recognition for the role of opioid receptors in the pathogenesis of CKD-aP. It is thought there is an imbalance of activation between the  $\mu$ -opioid receptor (MOR) and  $\kappa$ -opioid receptor (KOR) systems. The MOR system stimulates itching while KOR system suppresses it

**A novel periphery selective KOR agonist, difelikefalin, has demonstrated to be effective at reducing itch intensity and improving quality of life.** Abuse potential is low since KOR agonists do not induce euphoria



### ROLE OF OPIOID SYSTEM



Dual  $\mu$ -antagonist/ $\kappa$ -agonist such as nalbuphine, buprenorphine are not depicted above.  
Adapted from Lipman ZM and Yosipovitch G. Expert Opin Pharmacother. 2021; 22:551

#### KALM-1 trial: 378 hemodialysis patients with moderate-to-severe itching, difelikefalin vs placebo

Improvement with itch intensity (WI-NRS)	51.9% vs 30.9%
Mean change $\pm$ SD in 5D itch scale	-5.0 $\pm$ 0.3 vs -3.7 $\pm$ 0.3
Mean change $\pm$ SD in Skindex-10 scale	-17.2 $\pm$ 1.3 vs -12.0 $\pm$ 1.2

Common adverse events reported were diarrhea, dizziness and vomiting

Similar results from pooled analyses with the multinational KALM-2 trial also suggested difelikefalin was effective in itch reduction and improvement in quality of life that persisted longer term (1 year)



### ALTERNATIVE TREATMENTS

**Sertraline:** Antidepressants have been used for treatment of pruritus and sertraline specifically has shown to lower itch score

**UV-B phototherapy:** Purported to decrease proinflammatory cytokines and has demonstrated effectiveness in patients with refractory CKD-aP

**Acupuncture and acupressure** have been hypothesized to reduce itching via parasympathetic activation; positive outcomes have been reported in several trials

**Omega-3 fatty acid supplementation** has been posited to lower inflammation by treating underlying essential fatty acid deficiency

**Aerobic intradialytic exercise and psychotherapies** can be considered as adjunctive stress reduction therapies to counter any unpleasant symptom stimuli, including pruritus