LE COMPLICANZE CRONICHE DEL TRATTAMENTO SOSTITUTIVO RENALE

Il prurito nei pazienti in dialisi

Dott Paolo Fabbrini
Direttore SC Nefrologia e Dialisi
ASST NORD MILANO

CHRONIC PRURITUS IS A DEBILITATING CONDITION WITH A VARIETY OF UNDERLYING CAUSES

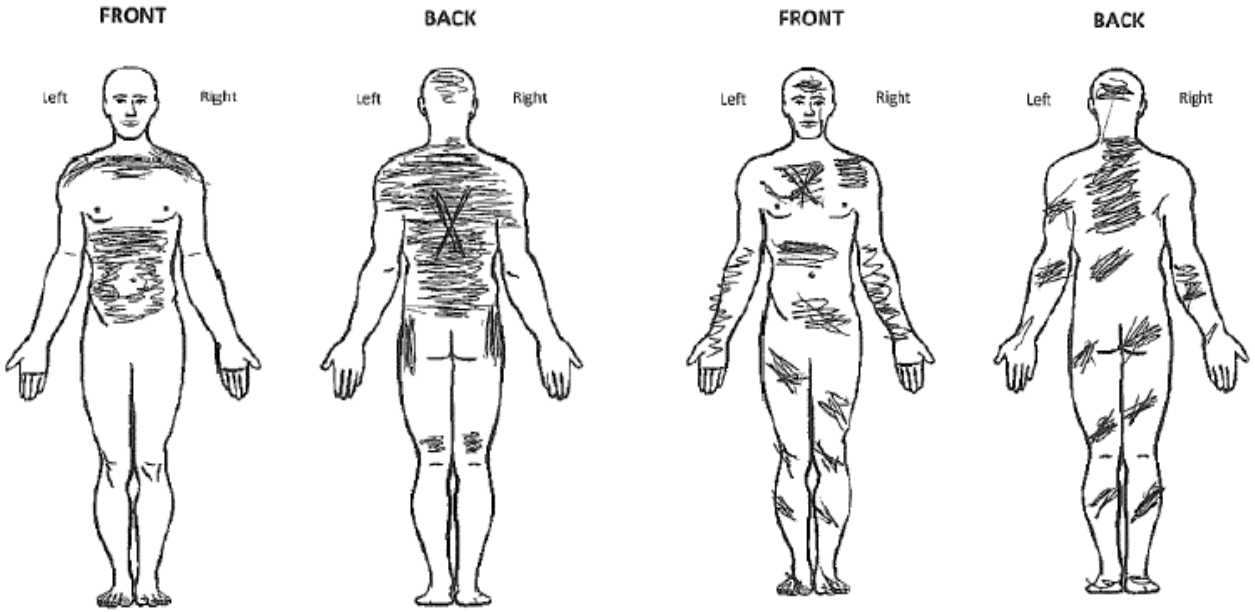
- Chronic pruritus can be defined as an unpleasant sensation of the skin leading to the desire to scratch...with symptoms present for more than 6 weeks

Causes	Presentation	Examples
Dermatologic	Primary skin lesions	Atopic dermatitis, psoriasis, prurigo nodularis, xerosis, scabies, insect bites, unknown origin
Systemic	No primary skin lesions	**Chronic kidney disease (CKD)** Primary biliary cholangitis (PBC), HIV infection, hyperthyroidism
Neuropathic		Postherpetic itch, brachioradial pruritus (spinal-nerve impingement), notalgia paraesthetica
Psychogenic		Obsessive-compulsive disorder, substance abuse, delusions of parasitosis

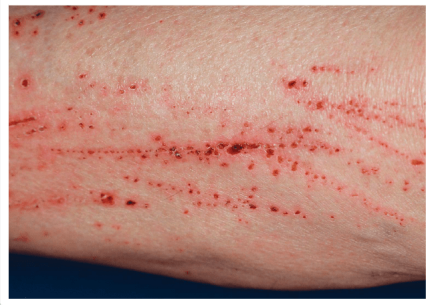
- Ständer S, et al. Acta Derm Venereol 2007;87:291–4; Weisshaar E, et al. Acta Dermatol Venereol 2019;99:469–506; Yosipovitch G, Bernhard J. N Engl J Med 2013;368:1625–34.

CKD-ASSOCIATED PRURITUS IS A CONDITION WITH INTENSE SYMPTOMS THAT MARKEDLY IMPAIR THE QOL OF PATIENTS WITH CKD UNDERGOING HD

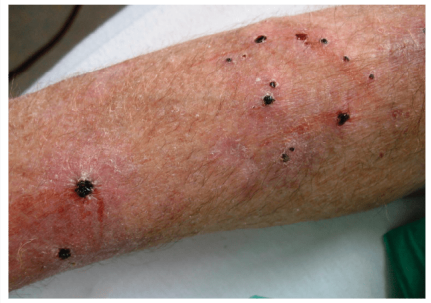
CKD-associated Pruritus is often bilaterally symmetrical, and can be localised or generalised[1,2]



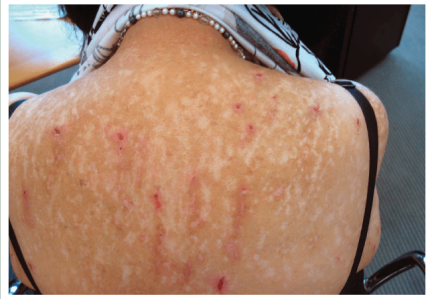
CKD-associated Pruritus is associated with visible skin lesions[3]



Scratch marks with excoriations at the lower leg



Prurigo nodularis located on the forearm



Deep scars and prurigo nodules at shoulders and back

1. Mathur VS, et al. Clin J Am Soc Nephrol 2010;5:1410-19;
2. Shirazian S, et al. Int J Nephrol Renovasc Dis 2017;10:11-26; 3. Mettang T, Kremer AE. Kidney Int 2015;87:685-91.

Nephrol Dial Transplant (2006) 21: 3495–3505
doi:10.1093/ndt/gfl461
Advance Access publication 12 September 2006

Original Article

NDT
Nephrology Dialysis Transplantation

Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Ronald L. Pisoni[1], Björn Wikström[2], Stacey J. Elder[1], Tadao Akizawa[3], Yashushi Asano[4], Marcia L. Keen[5], Rajiv Saran[6], David C. Mendelssohn[7], Eric W. Young[1,8] and Friedrich K. Port[1]

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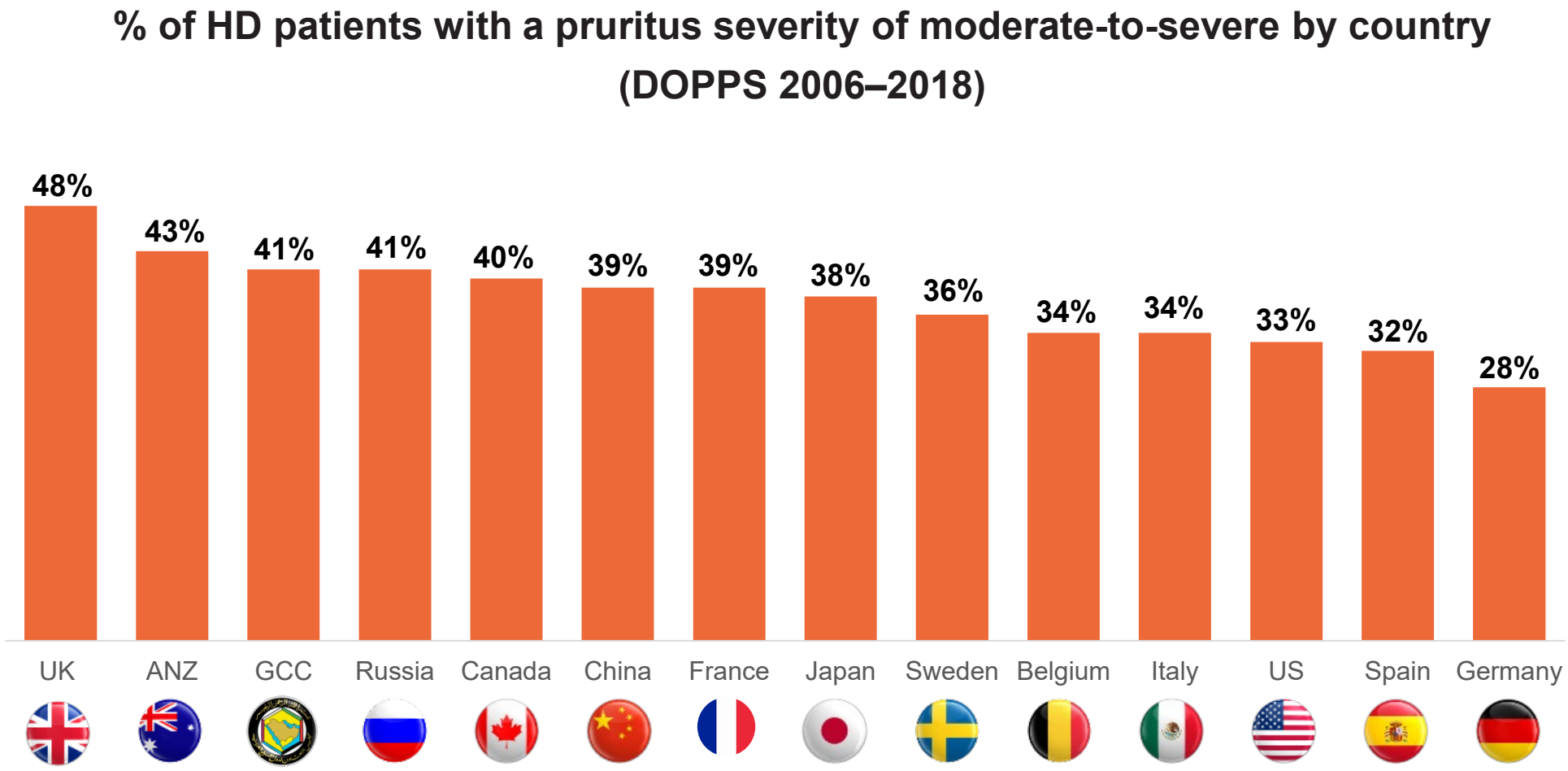
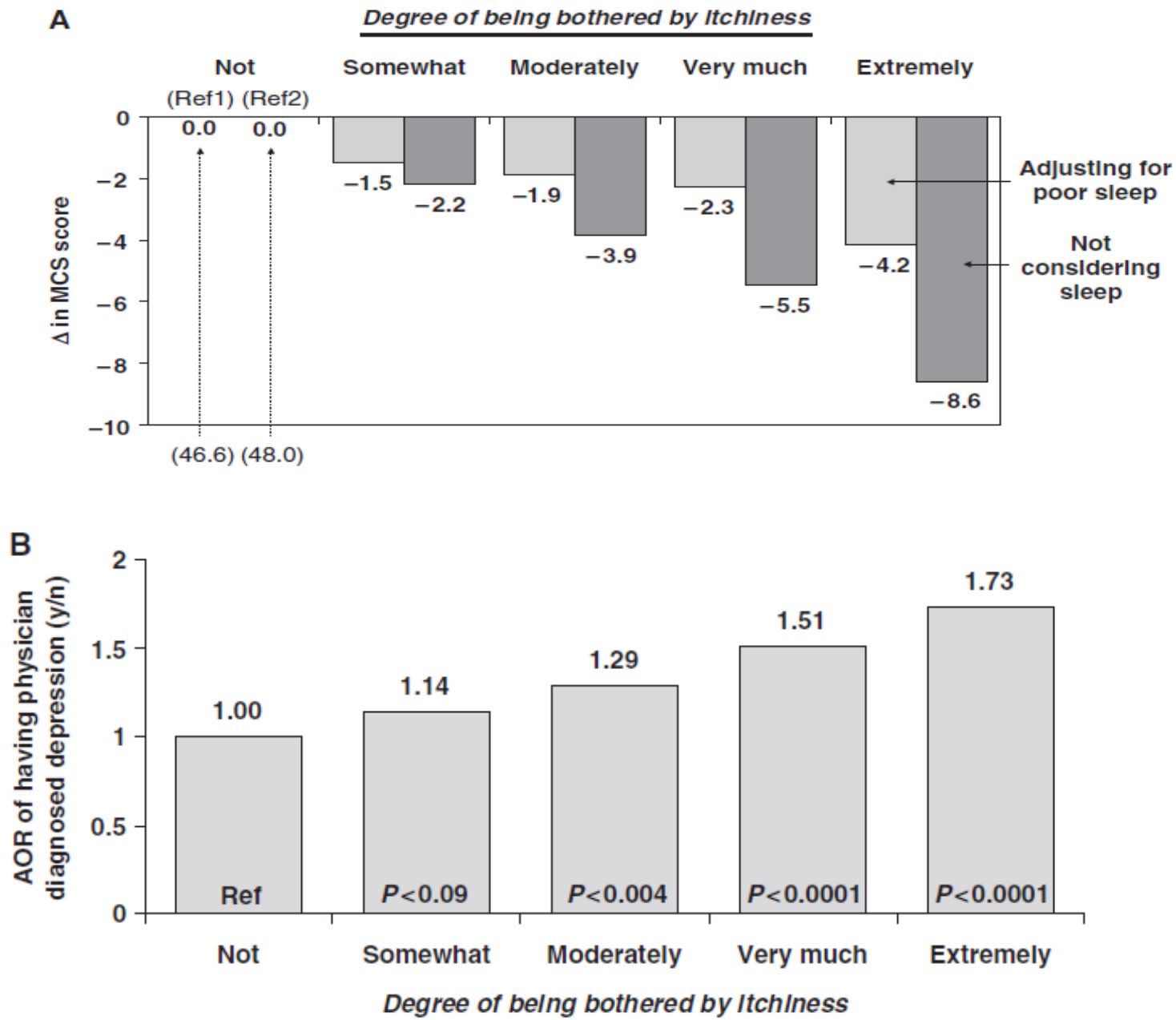
Fig. 1. Degree of pruritus among prevalent HD patients across 6-12 countries participating in DOPPS I (1996-1999) and DOPPS II (2002–2003). The extent to which HD patients were bothered by itchy skin during a 4-week period is shown based upon self-reported data collected from a prevalent cross-section of HD patients at 288 dialysis units participating in DOPPS I (1996–1999) from France, Germany, Japan, Spain, the UK and the US, and 320 dialysis units participating in DOPPS II (2002–2003) from the above six countries plus Australia, Belgium, Canada, Italy, New Zealand and Sweden.

ACROSS COUNTRIES, PRURITUS SYMPTOMS WERE REPORTED AS MODERATE-TO-SEVERE IN ~40% OF PATIENTS UNDERGOING HD

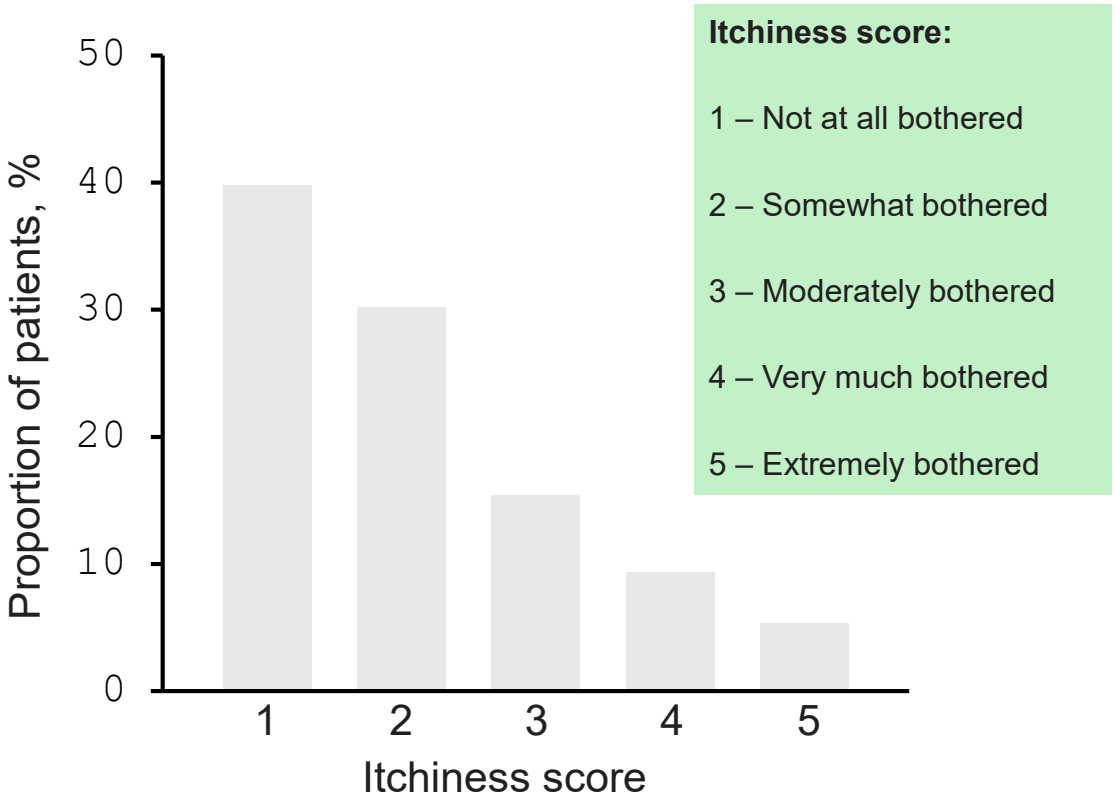


- ANZ, Australia and New Zealand; GCC, Gulf Cooperation Council; HD, haemodialysis..
  Sukul N, et al. Kidney Med 2020;3:42-53.e1.

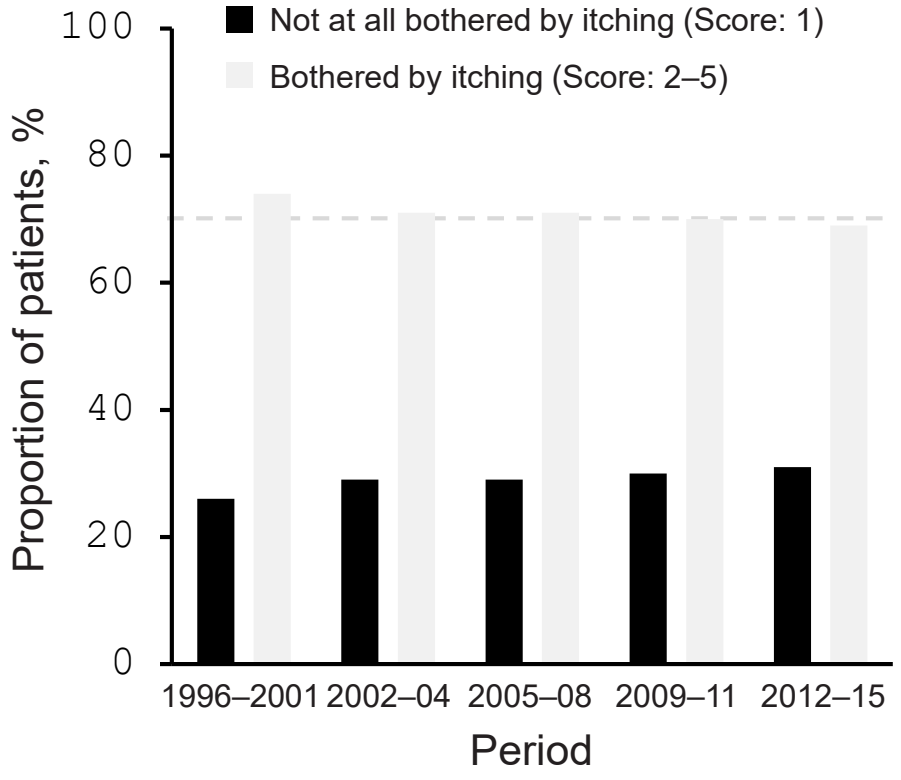

A
Degree of being bothered by itchiness
Not
Somewhat
Moderately
Very much
Extremely
(Ref1) (Ref2)
0.0
0.0
−1.5
−2.2
−1.9
−3.9
−2.3
−5.5
−4.2
−8.6
Adjusting for poor sleep
Not considering sleep
Δ in MCS score
0
−2
−4
−6
−8
−10
(46.6) (48.0)
B
AOR of having physician diagnosed depression (y/n)
2
1.5
1
0.5
0
1.00
1.14
1.29
1.51
1.73
Ref
P<0.09
P<0.004
P<0.0001
P<0.0001
Not
Somewhat
Moderately
Very much
Extremely
Degree of being bothered by itchiness

THE ESTIMATED PREVALENCE OF CKD-ASSOCIATED PRURITUS GLOBALLY IS ~70% AMONG PATIENTS UNDERGOING HD

Presence and severity of itching among patients on HD (N=68,426)[1]



Incidence of CKD-associated Pruritus over time (DOPPS data)[2]

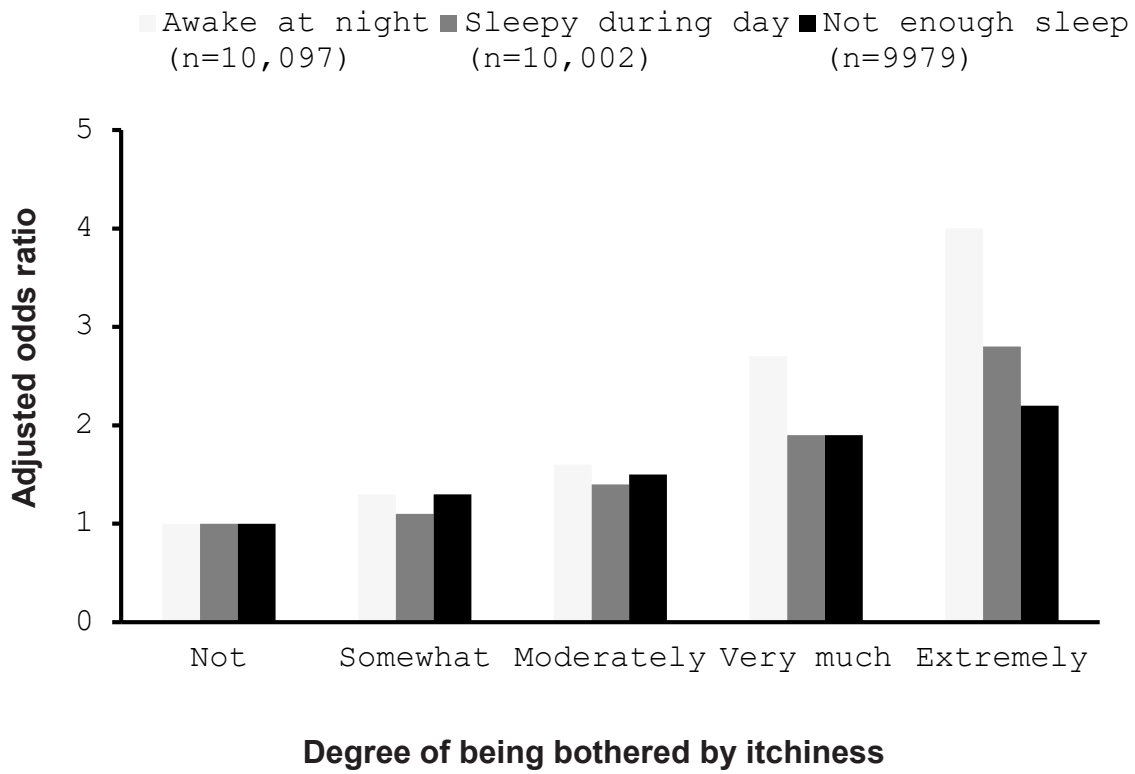


- DOPPS, Dialysis Outcomes and Practice Patterns Study; HD, haemodialysis.

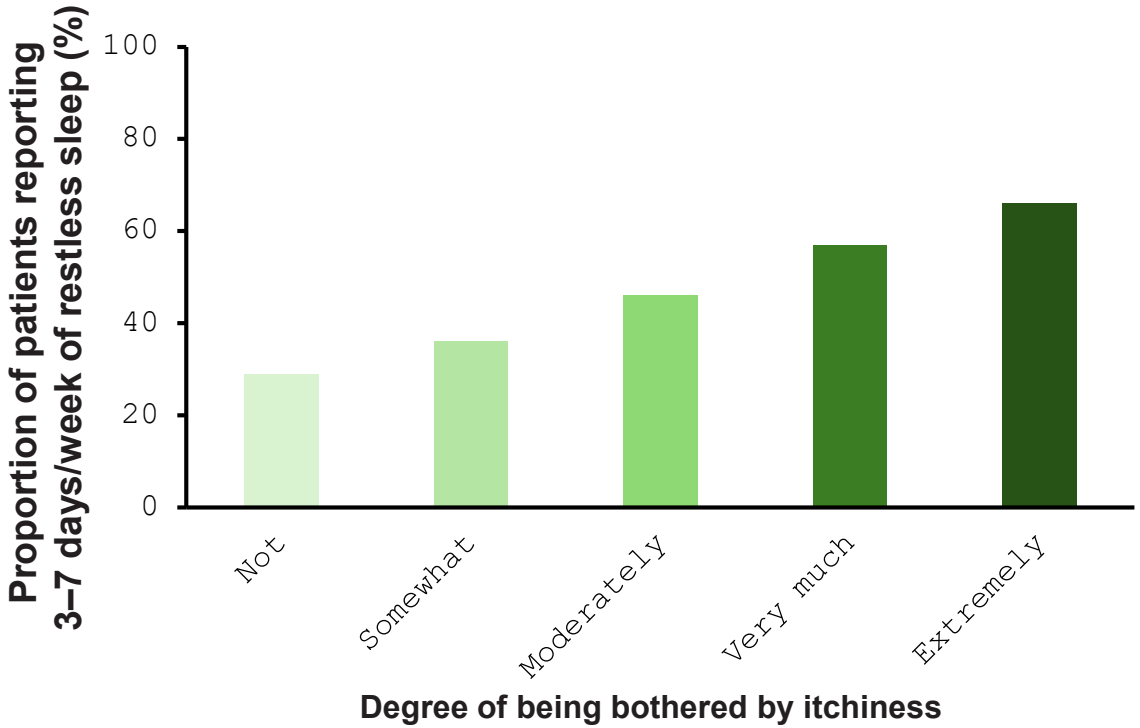
1. Ramakrishnan K, et al. Int J Nephrol Renovasc Dis 2014;7:1–12; 2. Rayner HC, et al. Clin J Am Soc Nephrol 2017;12:2000–7.

THE MAJORITY OF PATIENTS WITH CKD-ASSOCIATED PRURITUS SUFFER FROM DISTURBED OR RESTLESS SLEEP

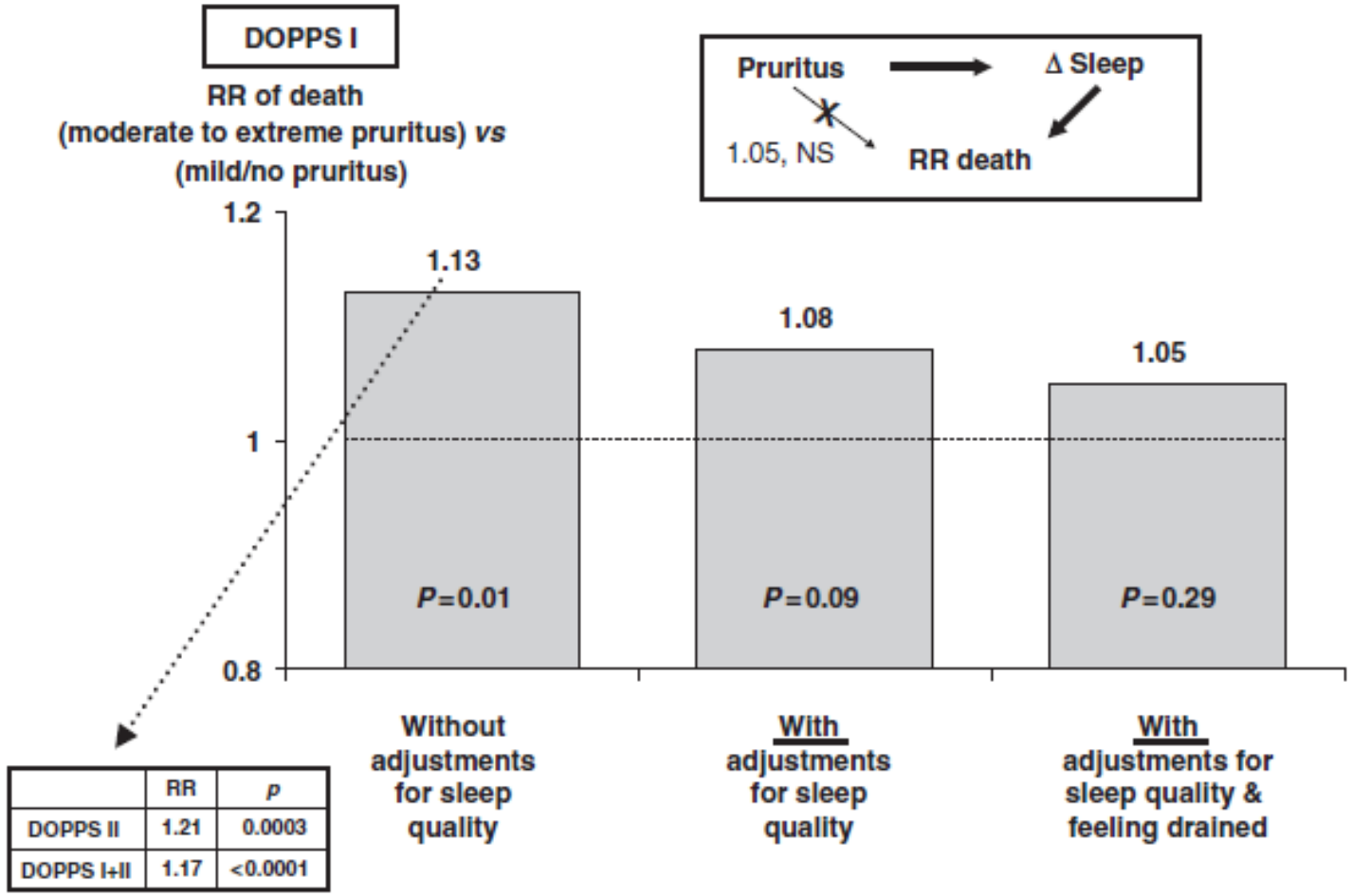
Likelihood of sleep disturbances according to CKD-associated Pruritus severity (DOPPS 1996–1999)[1]



Incidence of restless sleep according to CKD-associated Pruritus severity (DOPPS 2012–2015; N=6256)[2]



*For each model, all comparisons with the reference group ('Not') were significant at P≤0.0002, except for the bar '#' having a P=0.09.
1. Pisoni RL, et al. Nephrol Dial Transplant 2006;21:3495–505; 2. Rayner HC, et al. Clin J Am Soc Nephrol 2017;12:2000–7.


DOPPS I
RR of death
(moderate to extreme pruritus) vs
(mild/no pruritus)
Pruritus
Δ Sleep
1.05, NS
RR death
1.2
1
0.8
1.13
1.08
1.05
P=0.01
P=0.09
P=0.29
Without adjustments for sleep quality
With adjustments for sleep quality
With adjustments for sleep quality & feeling drained
RR
p
DOPPS II
1.21
0.0003
DOPPS I+II
1.17
<0.0001

ALLEVIATING THE BURDEN OF CKD-ASSOCIATED PRURITUS REQUIRES PROACTIVE IDENTIFICATION OF PATIENTS WHO SUFFER FROM IT

Proactive assessment: 3 pillars

1	Identification of **pruritus**	• **Do you itch?** (every 3 months) • Exclusion of potential alternative causes
2	Assessment of **pruritus intensity**	• Use of a **single question:** ➢ ***Worst-Itch Numerical Rating Scale (WI-NRS)***
3	Understanding impact on patient **quality of life**	• Assess impact on sleep, work & social life, mood ➢ ***Self-assessed disease severity (SADS)***

- Sukul N, et al. Kidney Med 2020;42-53; Davison SN, et al. Kidney Int 2015;88:447-59; Phan NC, et al. Acta Derm Venereol 2012;92:502-7; Agarwal R, et al. Clin Kidney J 2022. doi: https://doi.org/10.1093/ckj/sfac187.

PRURITO IN DIALISI, VISTO DALLA PROSPETTIVA DEI PAZIENTI

- **1905** questionari

Prevalenza

100% risponde	53% Sì prurito* media 5,1	20% Talvolta
	47% No prurito	33% Ogni giorno

Rayner DOPPS 2017

No	38%
Talvolta	26%
Sì	36%

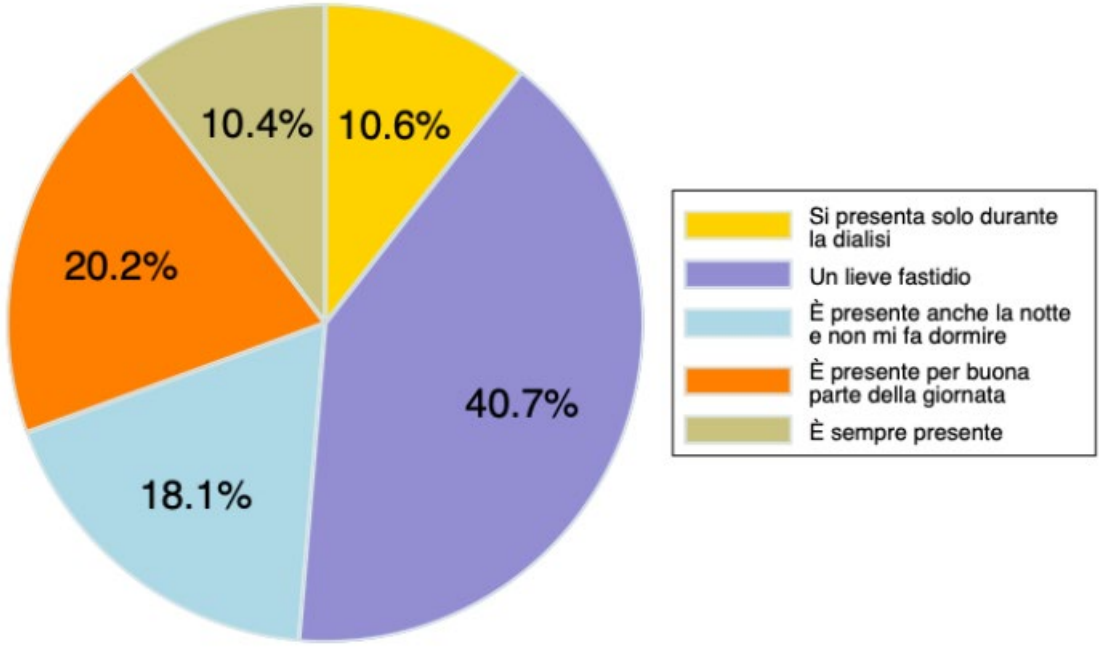


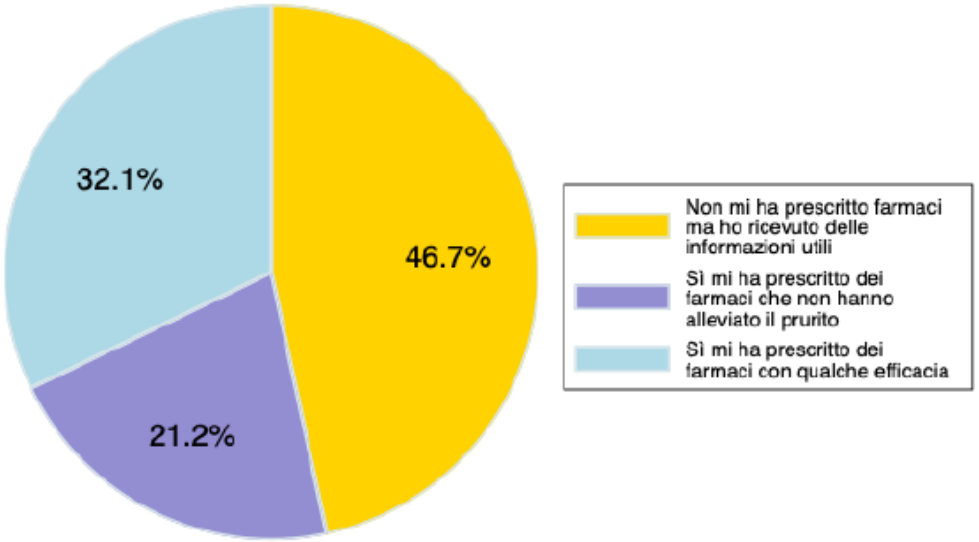
Figura 3: Tempi e modi di comparsa del prurito.

- Santoro et al. GIN 2022 Anno 39 Vol 4 n° 2

* Vari gradi di prurito (punteggio 1-10)

Quanto il prurito la limita e la infastidisce?			
	Poco	60%	
	Mi rende nervoso non dormo	27,5%	40%
	Rapporti con la famiglia e professionali	2,1%	
	Rapporti con tutti	10,4%	

Il 30% dei pazienti è stato indirizzato o si è recato spontaneamente dal dermatologo



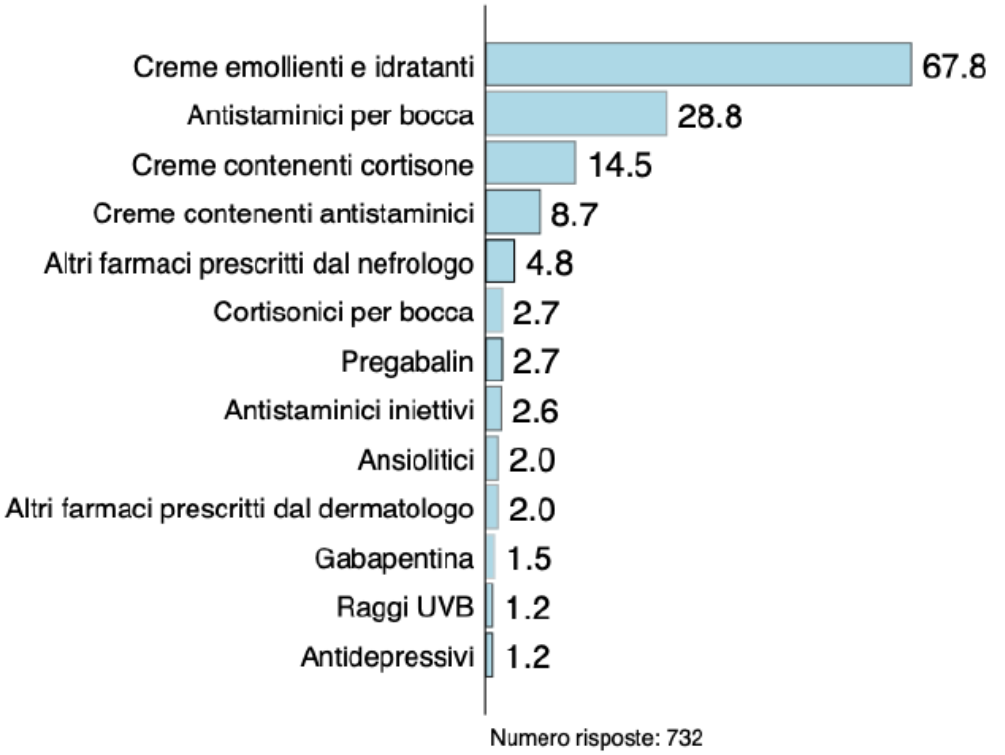


Figura 8: Frequenza percentuale dei rimedi suggeriti e che hanno avuto una certa efficacia.

- Santoro et al. GIN 2022 Anno 39 Vol 4 n° 2

C’È STATA LA RISOLUZIONE DEL SINTOMO PRURITO?

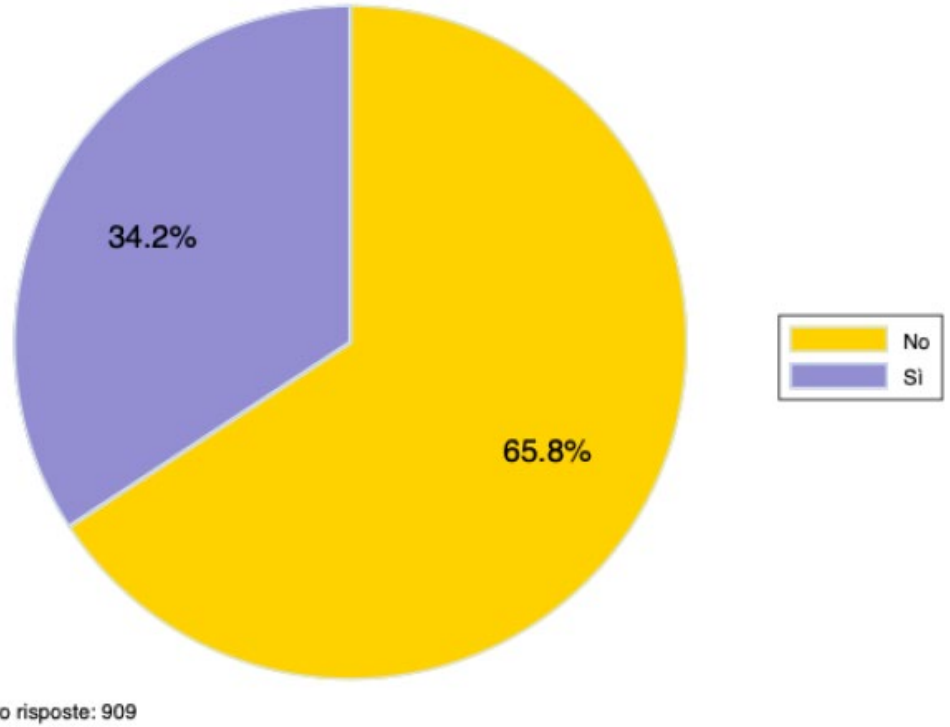


Figura 9: Come paziente continua a richiedere spiegazioni e rimedi al personale del centro dialisi?

- Santoro et al. GIN 2022 Anno 39 Vol 4 n° 2

• SURVEY SIN

- **116** nefrologi, di cui la metà segue più di **100** pazienti in dialisi

Prevalenza

70% risponde	94%	≤30%
	5%	>30%
	1%	Non saprei

87% non usa nessuna scala di valutazione del prurito

QoL

Quanto ritieni impattante il prurito sulla QoL dei tuoi pazienti?	Poco	3,4%
	Abbastanza	23,3%
	Molto	60,4%
	Estremamente	12,9%

Ma…

Valuti la presenza di disturbi del sonno causati dal prurito?	Mai	1,7%
	Solo quando riferiti	45,7%
	Occasionalmente	17,2%
	Regolarmente	35,4%

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

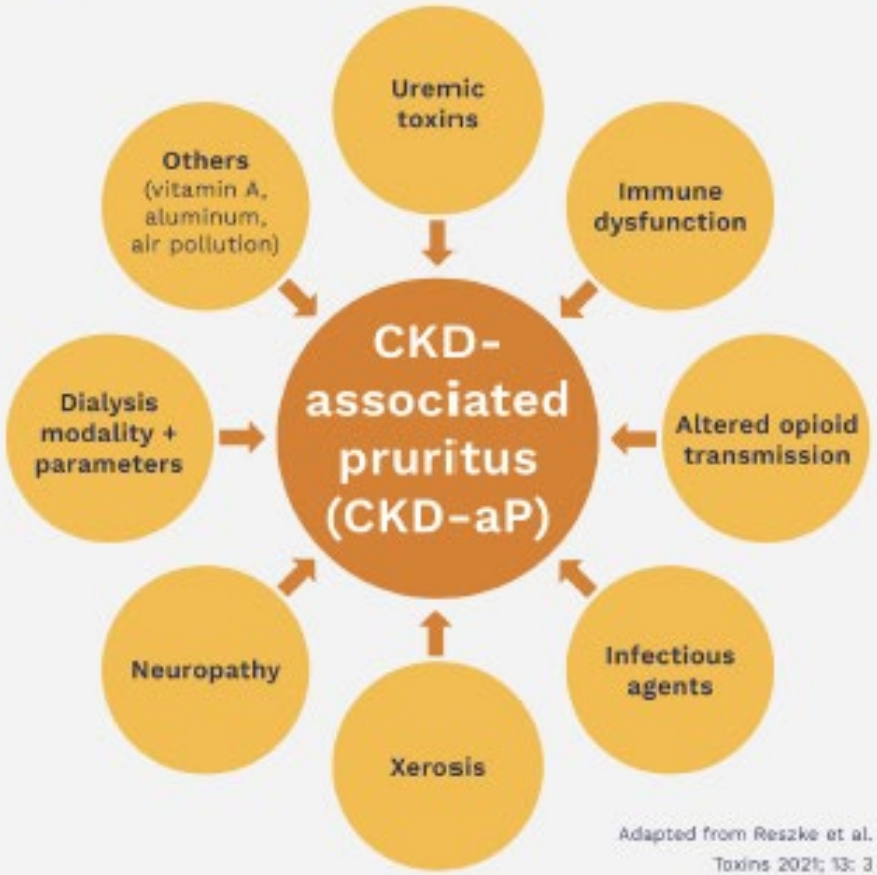
Pruritus is widespread and has been reported up to **80% of dialysis patients,** with **almost 40% experiencing moderate to severe itch**

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

Useful References: https://bit.ly/3PQ3vHn

Supported by Vifor Fresenius Medical Care Renal Pharma

The pathogenesis of CKD-associated Pruritus is multifactorial

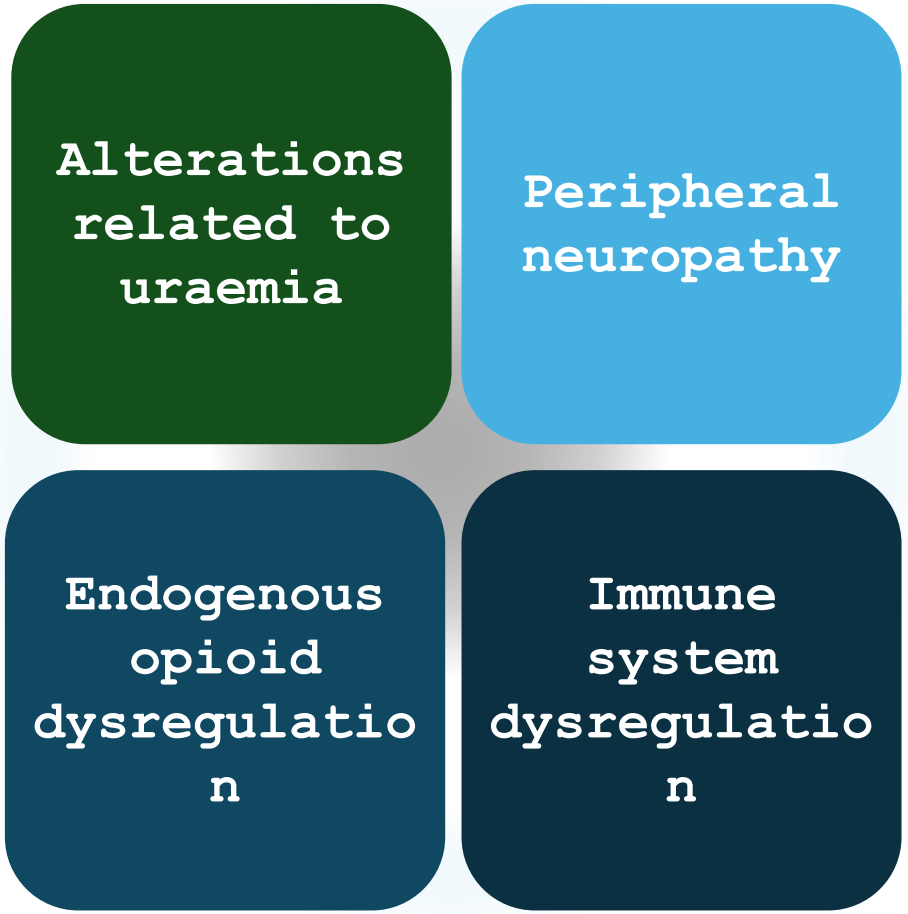
Implicated toxins[1–5]

Vitamin A, aluminium, calcium, phosphorus, magnesium

Imbalanced MOR and KOR activity[1–5, 7]

↑ endorphins (MOR agonist)

↓ dynorphins (KOR agonist)



Altered nerve conduction[1,3,5,6]

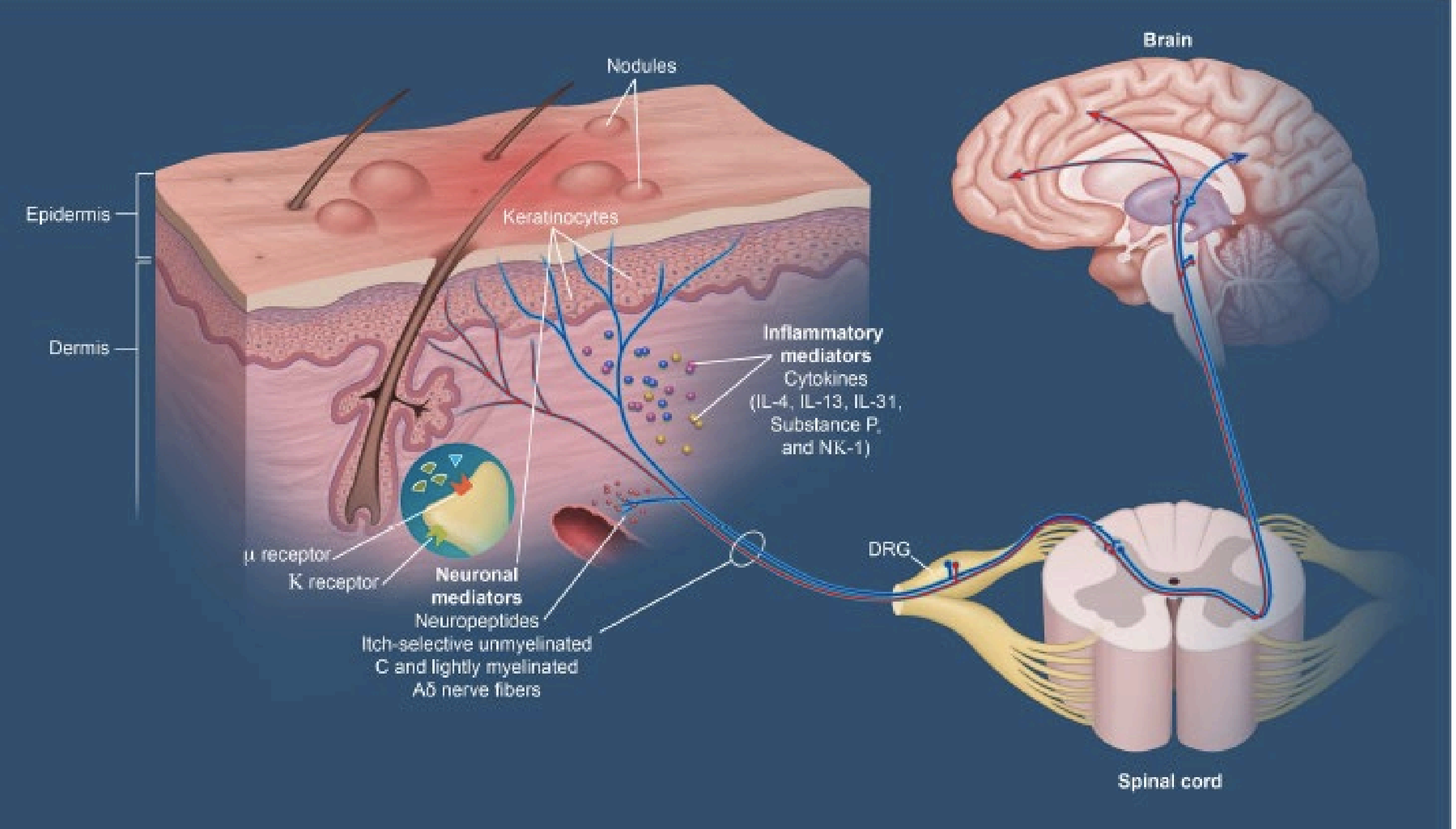
Pattern of cutaneous innervation

Nerve conduction studies

Pro-inflammatory state[1–5, 8]

↑ T-helper 1 cells, C-reactive protein, interleukin (IL)-6, IL-2

1. Shirazian S, et al. Int J Nephrol Renovasc Dis 2017;10:11-26; 2. Mettang T, Kremer AE. Kidney Int 2015;87:685-91; 3. Wang H, et al. Int J Dermatol 2010;49:1-11; 4. Kuypers DR. Nat Clin Pract Nephrol 2009;5:157-70; 5. Patel TS, et al. Am J Kidney Dis 2007;50:11-20; 6. Zakrzewska-Pniewska B, et al. Neurophysiol Clin 2001;31:181-93; 7. Phan NQ, et al. Acta Derm Venereol 2012;92:555-60; 8. Kimmel M, et al. Nephrol Dial Transplant 2006;21:749-55.


Brain
Nodules
Epidermis
Dermis
Keratinocytes
Inflammatory mediators
Cytokines
(IL-4, IL-13, IL-31,
Substance P,
and NK-1)
μ receptor
κ receptor
Neuronal mediators
Neuropeptides
Itch-selective unmyelinated
C and lightly myelinated
Aδ nerve fibers
DRG
Spinal cord

CENTRALLY ACTING OPIOIDS MAY BE USED TO TREAT PAIN AND ITCHING IN CKD PATIENTS, BUT ARE ASSOCIATED WITH A POTENTIAL FOR DRUG DEPENDENCY AND ABUSE

- Centrally acting (ie brain-accessible) opioids, such as fentanyl and tramadol, may be used to treat pain in CKD patients, but are also associated with:[1]
  - Limiting side-effects (eg sedation, dysphoria, increased urine output)
  - Physical/psychological dependence and abuse

Three major opioid receptor classes mediate opioid-based analgesis: **μ (mu)**, **κ (kappa)**, **δ (delta)**[2]

- They are located in the brain, spinal cord, neural tube, skeletal muscle and other organs (eg pancreas, testes)
- μ opioid receptors (MOR) are the most widely targeted for analgesia

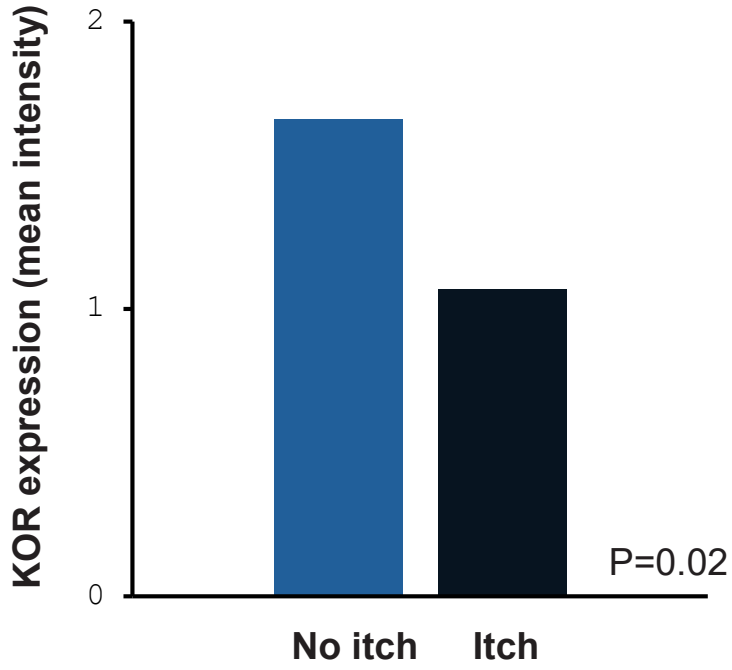
- GPCR, G protein-coupled receptor.

1. Pham PC, et al. Clin Kidney J 2017;10:688–97; 2. Albert-Vartanian A, et al. J Clin Pharm Ther 2016;41:371–82.

In patients with CKD-associated Pruritus, KORs are under-expressed, resulting in an imbalance of receptor activity that favours MOR activation

- In a study of MOR and KOR receptor expression in 21 HD patients with/without CKD-associated Pruritus:[1]
  - KOR expression was significantly decreased in patients with CKD-associated Pruritus vs those without CKD-associated Pruritus
  - MOR expression was similar in both groups
  - KOR expression was negatively correlated with CKD-associated Pruritus severity

KOR expression according to presence of CKD-associated Pruritus[1]



An imbalance between KOR and MOR expression may contribute to CKD-associated Pruritus pathophysiology[2]

HD, haemodialysis; KOR, kappa opioid receptor; MOR, mu opioid receptor.
1. Wieczorek A, et al. J Eur Acad Dermatol Venereol 2020;34:2368-72; 2. Mettang T, Kremer AE. Kidney Int 2015;87:685-91.

Activation of MORs promotes itch sensation, whereas activation of KORs antagonises MOR-mediated itch processing

- Assessment of pharmacological intervention in itch:
- MORs are a key processor of itch sensation
- Itch can be induced in mice through administration of the peptide neurotransmitter Substance-P

Itch sensation can be inhibited by:

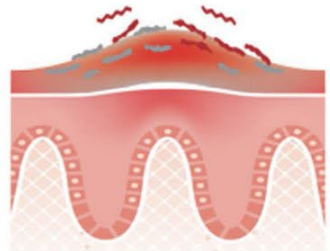
MOR antagonists
(block MOR function)

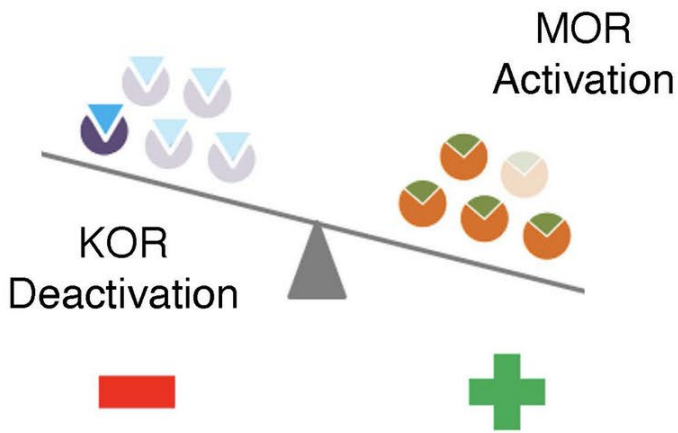
KOR agonists
(antagonise MOR-mediated itch signalling)

- KOR, kappa opioid receptor; MOR, mu opioid receptor.
*P<0.01 vs control (vehicle)-treated group.
Umeuchi H, et al. Eur J Pharmacol 2003;477:29-35.

Pruritic Skin

Too much MOR activation
and/or too little KOR activation

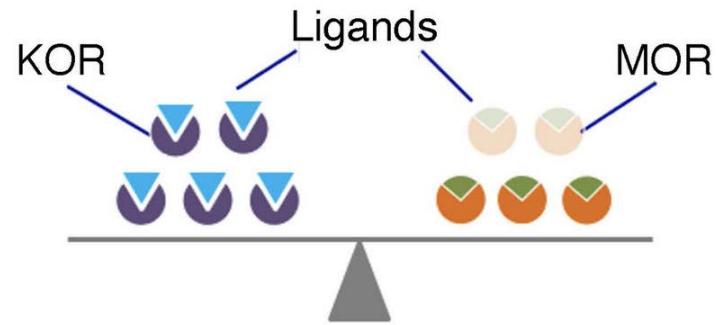




Induction of itch

Expression of MOR/β-endorphin unchanged and KOR/dynorphin A decreased

Normal Skin



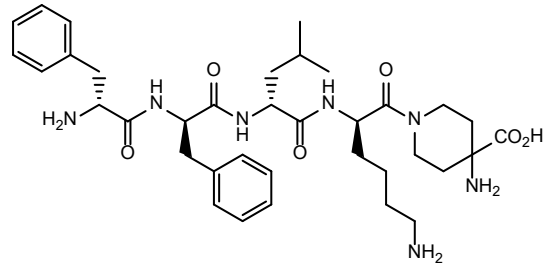
Suppression of Itch

Itch is suppressed when KOR/dynorphin A are strongly expressed

TABLE 1 Opioid receptor-targeting agents in clinical development for chronic pruritus[22,51]

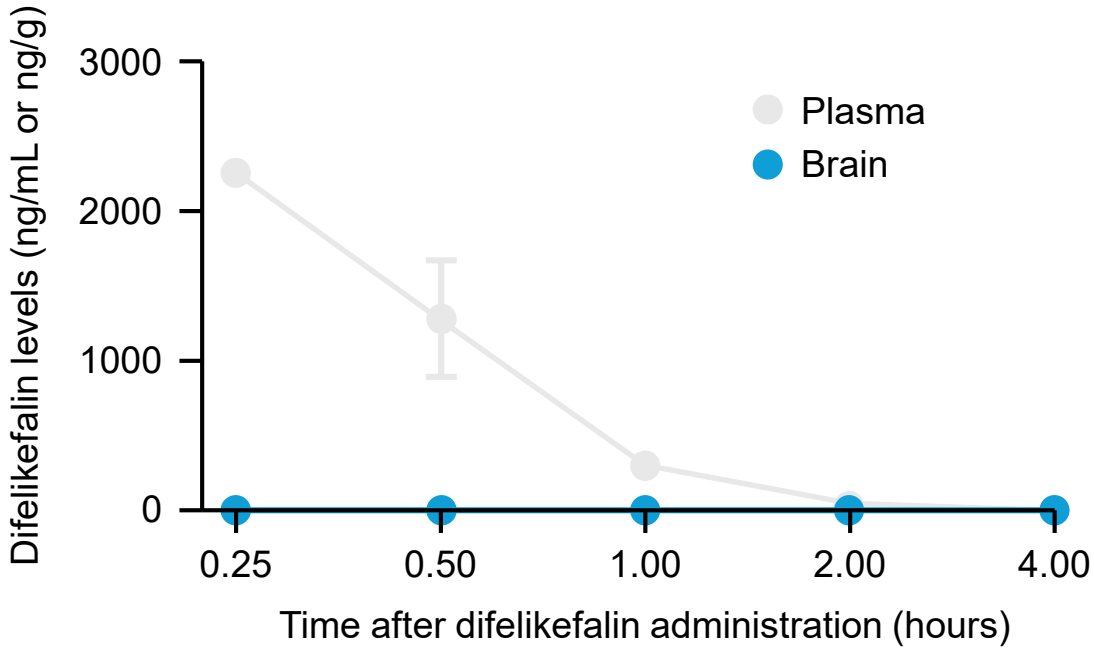
Agent	Mechanism of Action	Itch-Related Indication	ClinicalTrials.gov ID number(s)/citation (if published)	Development Phase
Asimadoline	KOR agonist	Atopic dermatitis	NCT02475447	Phase 2
Difelikefalin (CR845)	KOR agonist	Atopic dermatitis	NCT04018027	Phase 2
		Cholestatic pruritus	NCT03995212	Phase 2
		Chronic kidney disease	NCT03617536	Phase 2
		Chronic kidney disease	NCT02858726[59]	Approve
			NCT03998163	Phase 3
			NCT03636269	Phase 3
			NCT03422653[60]	Phase 3
Nalbuphine ER	KOR agonist/MOR antagonist	Prurigo nodularis	NCT03497975	Phase 2/3
		Chronic kidney disease	NCT02143648[53]	Phase 2/3
Nalfurafine	KOR agonist	Atopic dermatitis	NCT00980629	Phase 2
		Chronic liver disease	NCT00638495	Phase 2
		Chronic kidney disease	NCT01513161	Phase 3
			NCT00793156[61]	Phase 3

Difelikefalin is a small hydrophilic, peripherally restricted peptide



- Difelikefalin:
- Small (penta) synthetic peptide (M_W: 680 g/mol)[1]
- Picomolar *in vitro* activity and high selectivity[2]
- Strong *in vivo* activity in multiple animal models, long duration of action[2]
- High solubility in water (>200 mg/mL)[3]
- Hydrophilic with low membrane permeability, limiting penetration into the CNS[4,5]

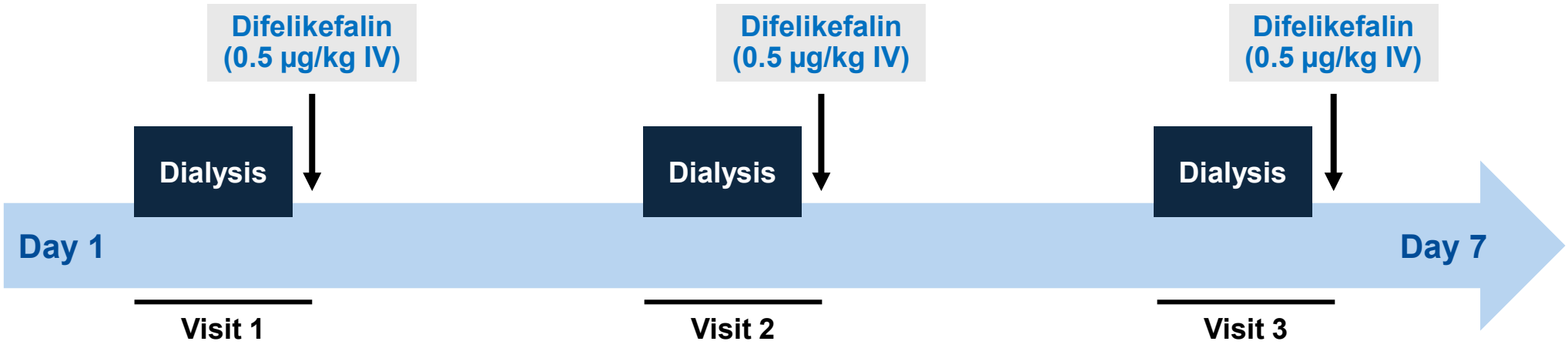
Levels of difelikefalin in blood and brain[4]
(Rat preclinical model; 1 mg/kg IV difelikefalin)



- Difelikefalin is not currently licensed for use in the treatment of CKD-aP.
- 1. Cara Therapeutics Difelikefalin Investigator's Brochure; 2. Gardell LR, et al. IASP 2008; Abstract PW-231 and poster presentation; 3. O'Connor SJ, et al. IASP 2010; Abstract PT-371 and poster presentation; 4. Spencer RH, et al. IASP 2010; Abstract PH-251 and poster presentation; 5. Cara Therapeutics Request for Breakthrough Therapy Designation Document.

Difelikefalin is available as an IV formulation that can be administered at the end of each hD session

- Difelikefalin is administered as an IV bolus into the venous port of the dialysis circuit after each HD session[1,2]
  - Ensures high treatment adherence
  - Minimal additional burden to patients and healthcare resources
  - Plasma concentrations of difelikefalin were reduced by 73–80% at the end of dialysis treatment

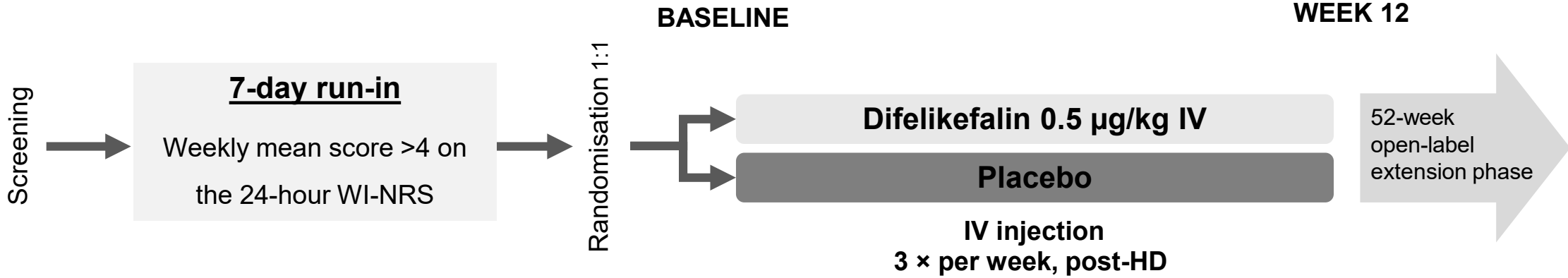


- Difelikefalin is not currently licensed for use in the treatment of CKD-aP.

1. Fishbane S, et al. N Engl J Med 2020;382:222–32;
2. Cara Therapeutics Difelikefalin Investigator's Brochure.

KALM-1 and KALM-2: Overview of Pivotal Phase 3 studies

- Patients ≥18 years of age with ESRD and moderate-to-severe pruritus
  - On HD (≥3x per week) for ≥3 months



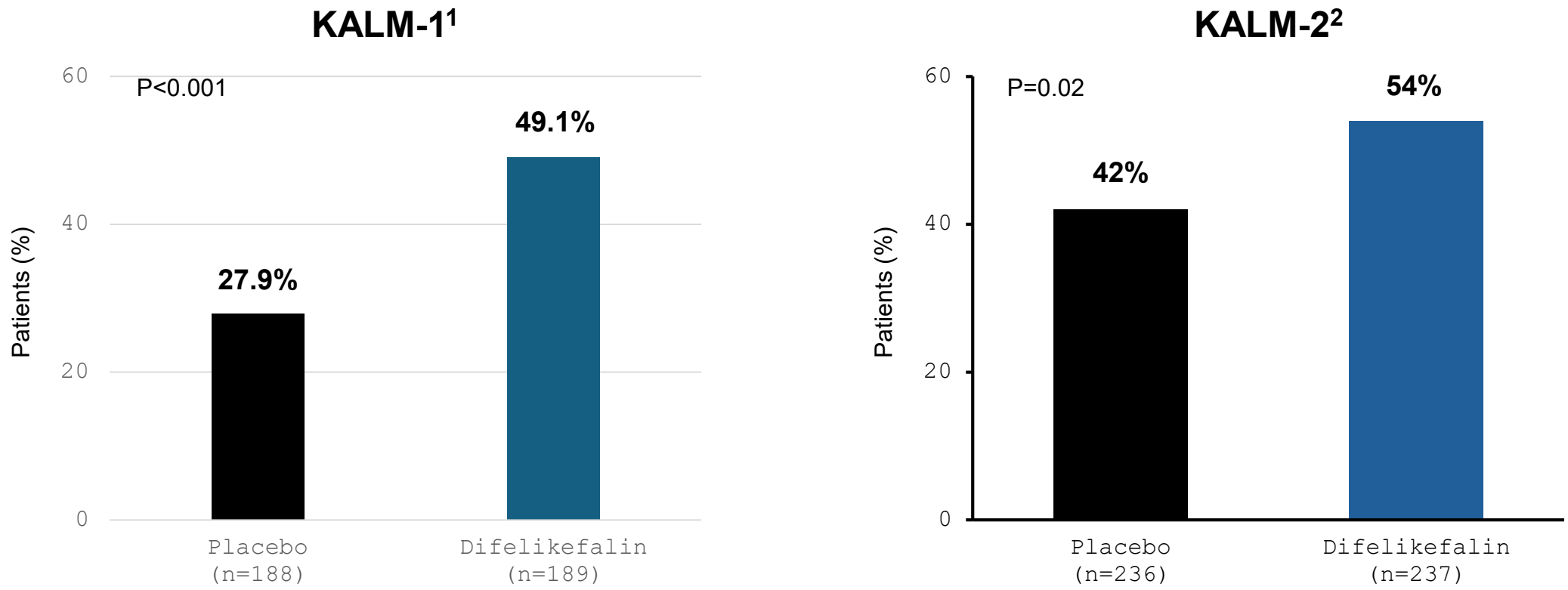
KALM-1[1]
US multicentre study
Difelikefalin (n=189) vs placebo (n=188)*
Completion date: April 2020

KALM-2[2]
Global multicentre study
Difelikefalin (n=237) vs placebo (n=236)
Completion date: March 2020

Difelikefalin is not currently licensed for use in the treatment of CKD-aP.
*1 patient withdrew post-randomisation and before first dose of placebo.
1. Fishbane S, et al. N Engl J Med 2020;382:222-32; 2. Wooldridge T, et al. ASN 2020; Abstract FR-OR24.

A significantly greater proportion of patients achieved a ≥3-point improvement from baseline in the weekly mean of the daily WI-NRS score with IV difelikefalin vs placebo

Proportion of patients achieving ≥3-point improvement in WI-NRS score at Week 12



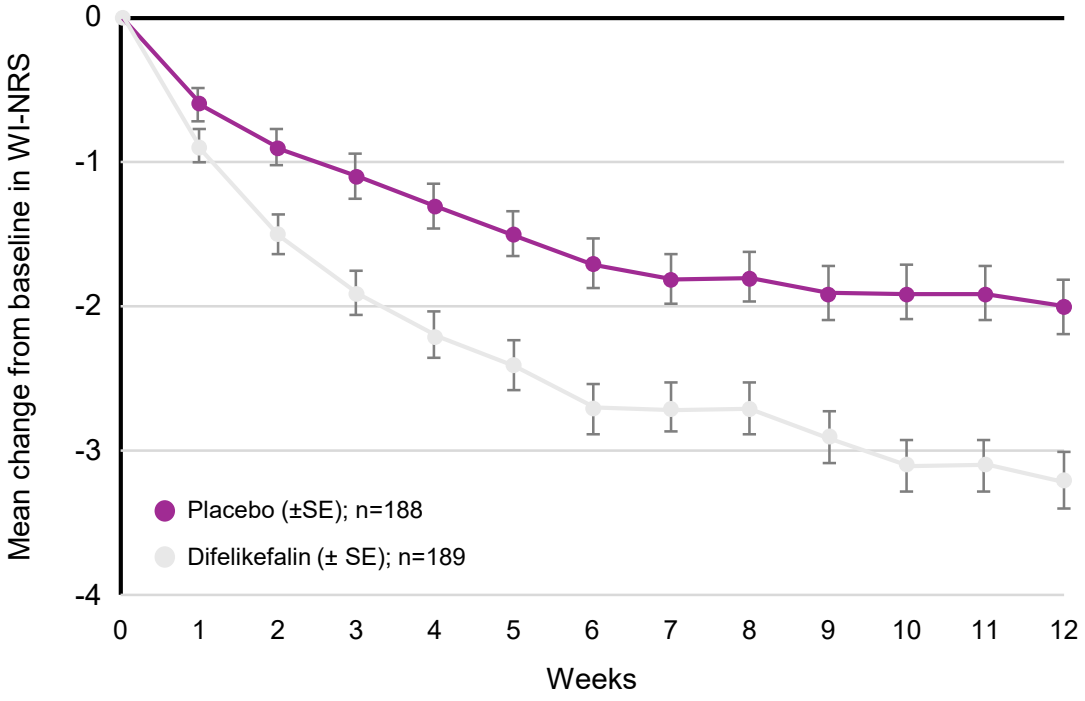
- Difelikefalin is not currently licensed for use in the treatment of CKD-aP.

1. Fishbane S, et al. N Engl J Med 2020;382:222-32; 2. Wooldridge T, et al. ASN 2020; Abstract FR-OR24.

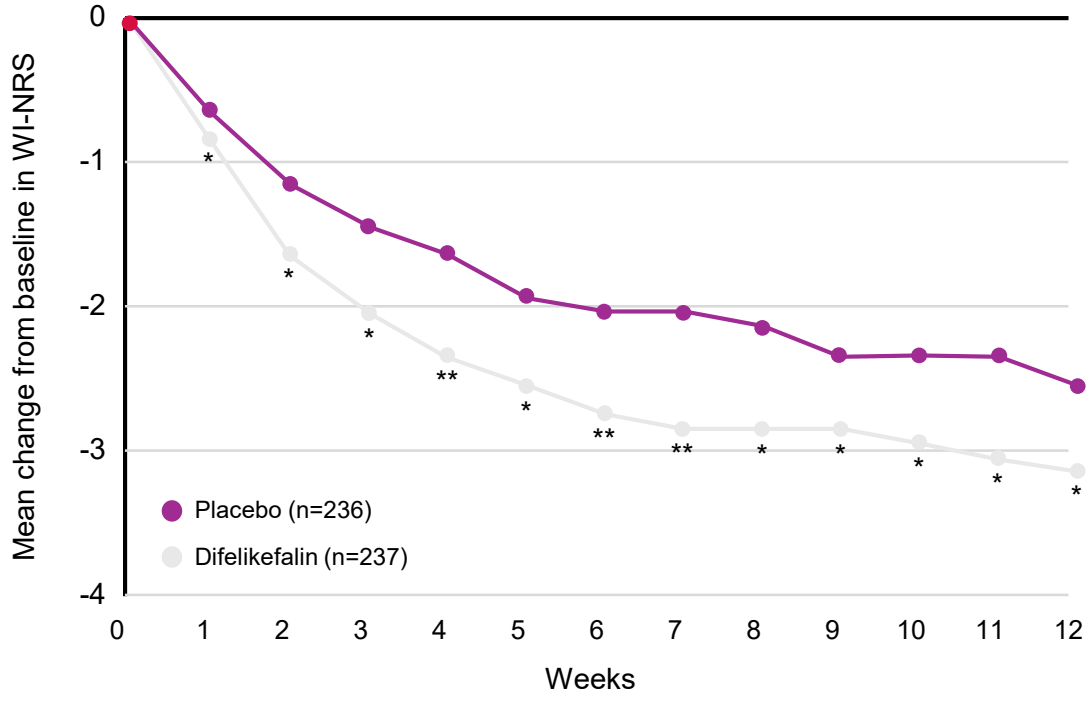
Among patients who received IV difelikefalin, a significantly greater mean reduction in pruritus vs placebo was evident at Week 1 and persisted through Week 12

Mean change in WI-NRS score over 12 weeks (difelikefalin vs placebo)

KALM-1[1]



KALM-2[2]



Significant differences in the proportion of patients who achieved a ≥3-point improvement with IV difelikefalin vs placebo emerged at Week 3 and persisted through Week 12[1]

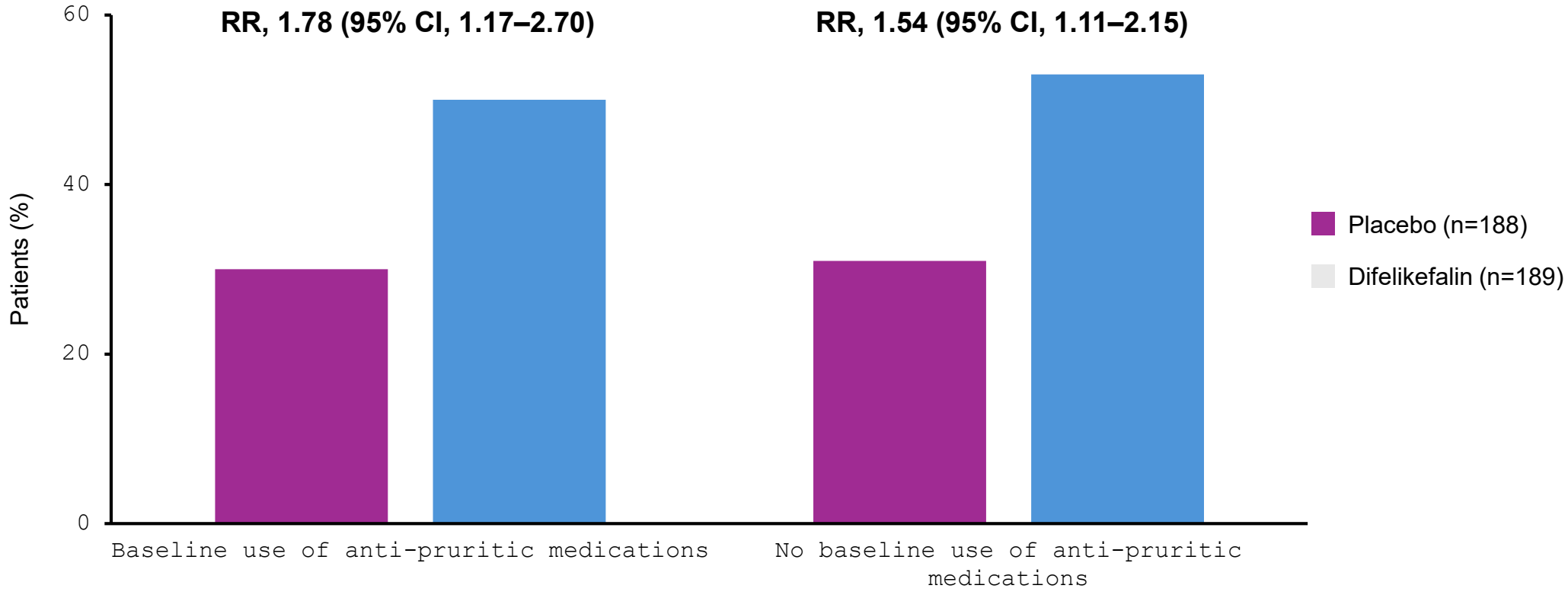
- Difelikefalin is not currently licensed for use in the treatment of CKD-aP.

1. Fishbane S, et al. N Engl J Med 2020;382:222-32; 2. Wooldridge T, et al. ASN 2020; Abstract FR-OR24.

*P<0.05, **P<0.001
SE, standard error.

The efficacy of difelikefalin was consistent among subgroups stratified according to use of anti-pruritic medications

Proportion of patients achieving ≥3-point improvement in WI-NRS score at Week 12 (KALM-1)[1]



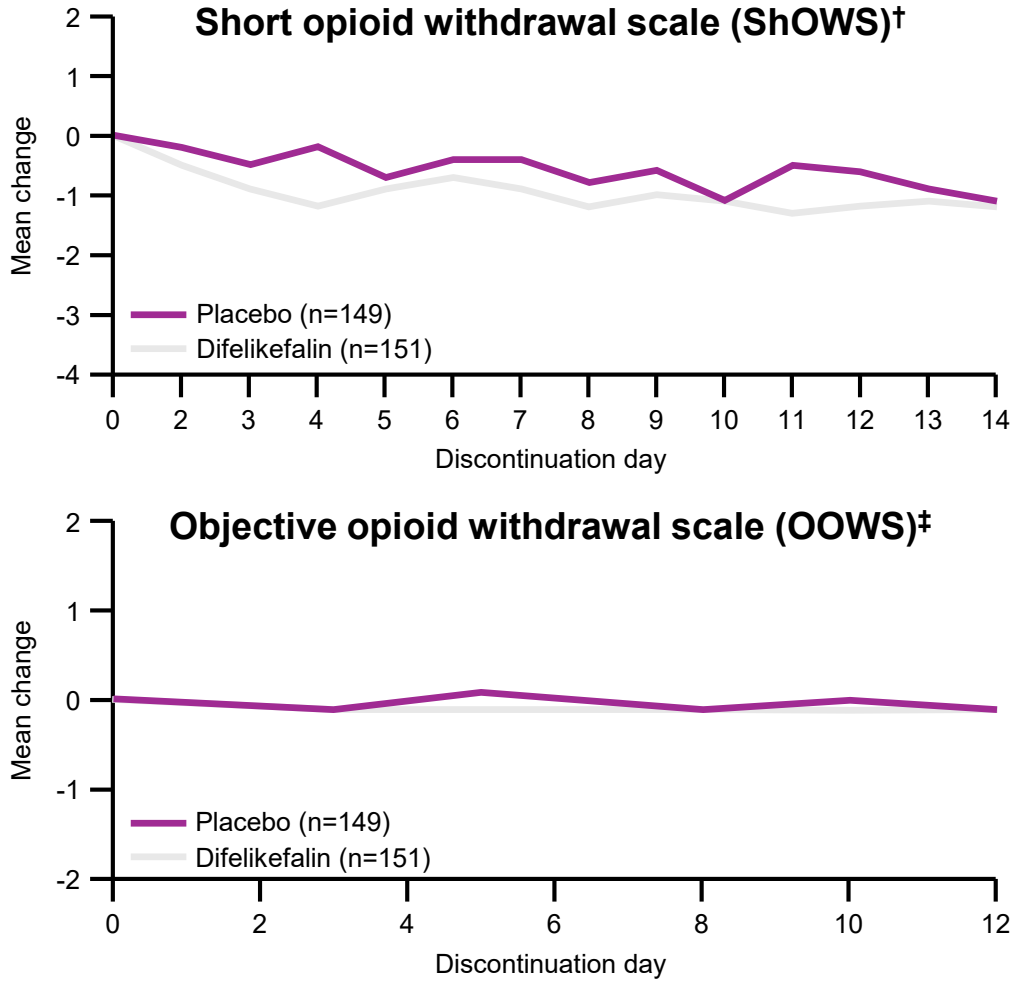
Difelikefalin is not currently licensed for use in the treatment of CKD-aP.
RR, relative risk.
Similar efficacy of difelikefalin according to baseline medications was observed in the randomised Phase 2 CLIN2101 study.[2]
1. Fishbane S, et al. N Engl J Med 2020;382:222-32; 2. Fishbane S, et al. Kidney Int Rep 2020;5:600-10.

Studies of difelikefalin demonstrated no abuse potential and no signs of physical dependence

- No AEs of euphoria, hallucinations or dysphoria were observed in the Phase 3 (KALM-1) and Phase 2 (CLIN2101) studies of difelikefalin in HD patients with moderate-to-severe pruritus[1,2]

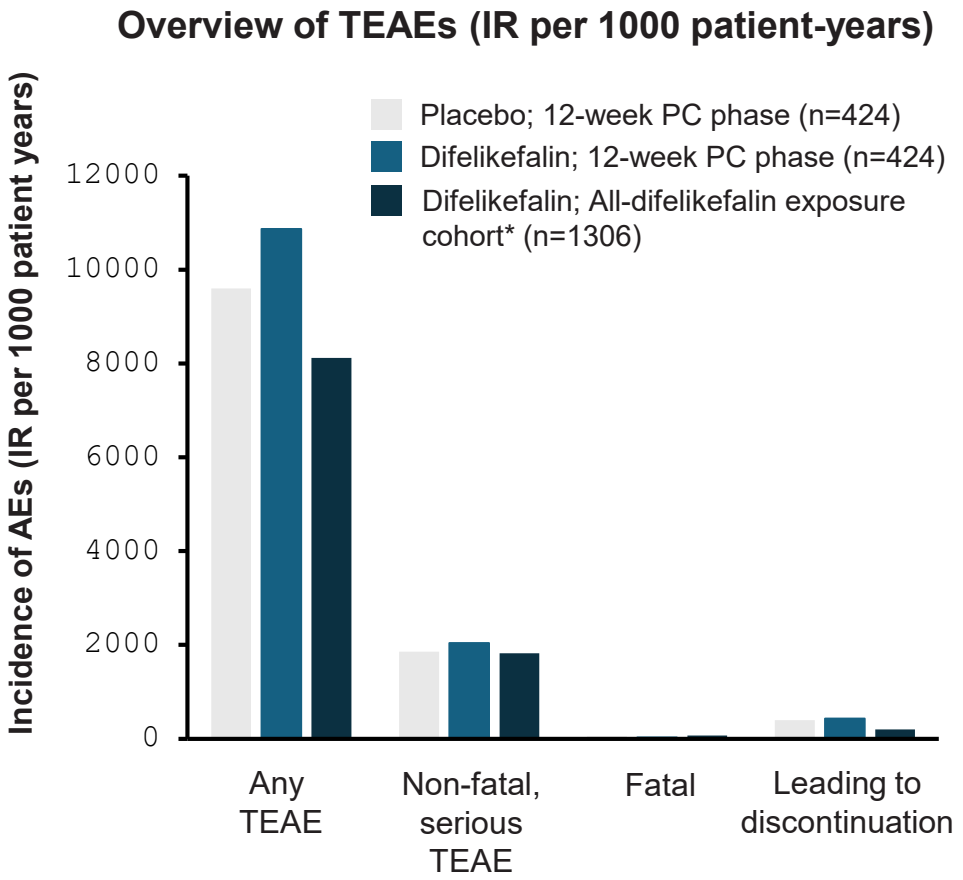
- No signs of potential physical dependence or AEs related to withdrawal were observed in the Phase 3 (KALM-1) study of difelikefalin in HD patients with moderate-to-severe pruritus[1]

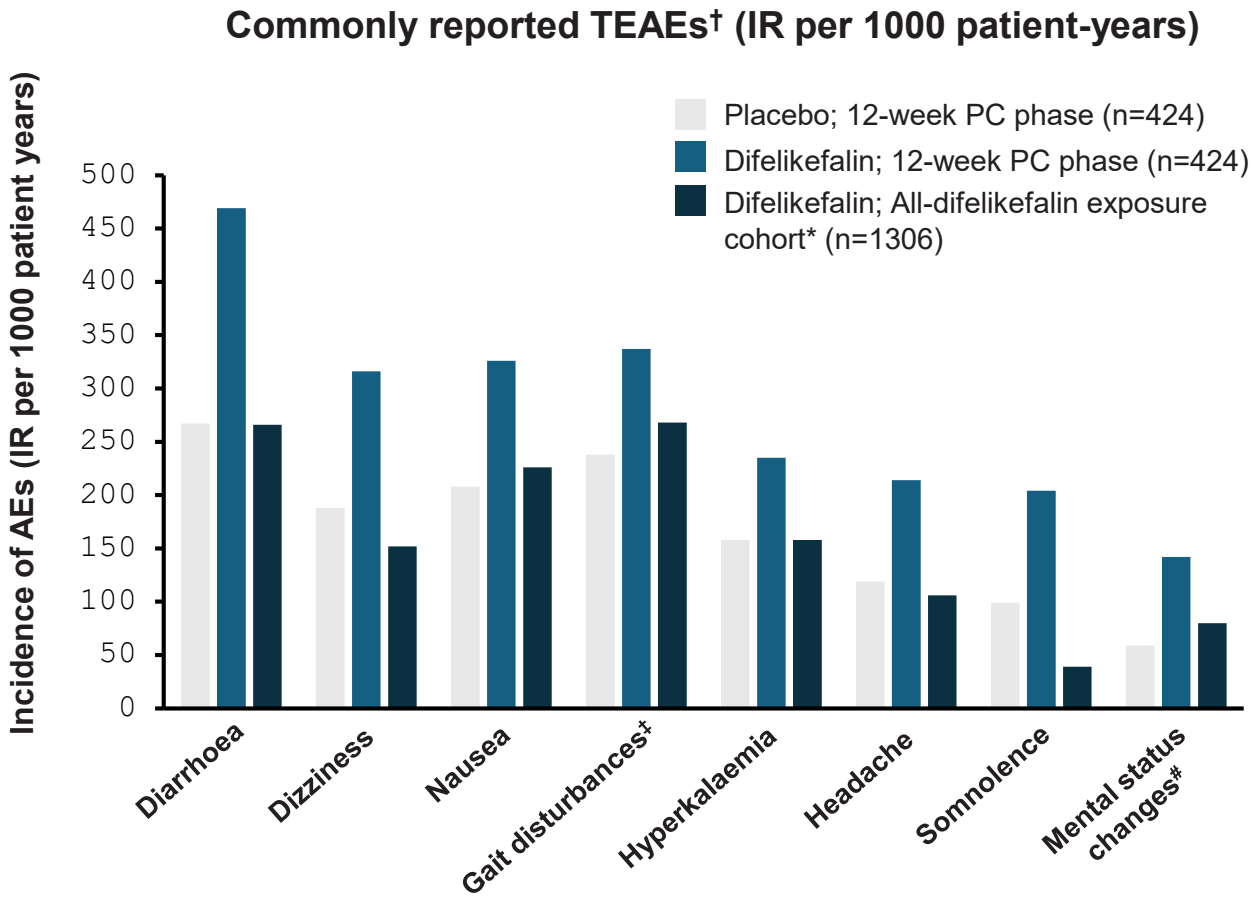
Analyses for potential withdrawal symptoms* (KALM-1)[1]



- Difelikefalin is not currently licensed for use in the treatment of CKD-aP.
*Among patients who completed 12 weeks of treatment, received at least six doses of study drug in the last 2 weeks of the treatment period, and had at least one visit in the discontinuation period.
†ShOWS total score ranges from 0–30; higher scores indicate more severe withdrawal symptoms.
‡OOWS total score ranges from 0–13; higher scores indicate more severe withdrawal symptoms.
1. Fishbane S, et al. N Engl J Med 2020;382:222–32; 2. Fishbane S, et al. Kidney Int Rep 2020;5:600–10

POOLED SAFETY DATA UP TO 64 WEEKS WERE CONSISTENT WITH FINDINGS OF THE PIVOTAL STUDIES





- *The all-difelikefalin-exposure cohort included all participants who received ≥1 dose of IV difelikefalin at 0.5 µg/kg for up to 64 weeks from the placebo-controlled periods of KALM-1 and KALM-2 (if randomised to difelikefalin) and from the open-label extension periods (up to 52 weeks) of these studies, as well as participants from the 2 additional open-label, phase 3 supportive studies (CLIN3101, for up to 52 weeks; and CLIN3105, for up to 12 weeks). †Preferred terms of TEAEs reported in ≥2% of difelikefalin participants with an incidence ≥1 percentage point higher than in placebo participants. ‡Gait disturbances include preferred terms of falls and gait disturbances. #Mental status change includes preferred terms of confusional state and mental status change.
TEAE, treatment-emergent adverse event.
IR, incidence rate; PC, placebo-controlled; OLE, open-label extension.
Fishbane S, et al. Kidney Med 2022;4:100513.

Reduction of Pruritus by Difelikefalin Correlates With Reductions in Markers for Pruritus and Inflammation in Subjects Undergoing Hemodialysis

Shayan Shirazian[1]; Robert H. Spencer[2]; Stephen A. Kilfeather[3]; Elaine Lee[3]; Catherine Munera[2]; Warren Wen[2]; Frédérique Menzaghi[2]

[1]Columbia University College of Physicians and Surgeons, New York, NY, USA; [2]Cara Therapeutics, Inc., Stamford, CT, USA; [3]Aeirtec Limited, Newcastle Upon Tyne, UK

METHODS

BIOMARKERS

- Serum samples were collected predose (day 1) and at the end of the 12-week double-blind period (day 85) of both the KALM-1 and KALM-2 studies (N=848 total)
- Twenty prespecified markers of pruritus and inflammation (eg, chemokines, cytokines, neurotrophic factors) were measured by multiplex enzyme-linked immunoassay (**Table 1**)
  - These markers were selected based on their involvement in pruritus as reported in published literature, critical role in the hierarchy as mediators of immune and inflammatory response, and established ability to control certain aspects of immune and inflammatory activity

Table 1. Twenty Prespecified Markers of Pruritus and Inflammation Evaluated in This Study

Pruritic		Chemotaxis		Immune Activation	
CTACK (CCL27)		IP-10 (CXCL10)	ITAC (CXCL11)	GM-CSF	IL-1β
Endothelin	IL-31	MCP-1 (CCL2)	MDC (CCL22)	IL-2	IL-2Rα
NGF	NT-4	MIP-2α (CXCL2)	TARC (CCL17)	IL-6	IL-8 (CXCL8)
TSLP				IFNγ	TNFα

CTACK, C-C Motif Chemokine Ligand 27; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFNγ, interferon gamma; IL-1β; interleukin 1 beta; IL-2, interleukin 2; IL-2Rα, interleukin 2 receptor alpha; IL-6, interleukin 6; IL-8, interleukin 8; IL-31, interleukin 31; IP-10, interferon gamma-induced protein 10; ITAC, interferon gamma-induced protein 9; MCP-1, C-C Motif Chemokine Ligand 2; MDC, macrophage-derived chemokine; MIP-2α, Chemokine (C-X-C motif) ligand 2; NGF, nerve growth factor; NT-4, neutrophin 4; TARC, C-C Motif Chemokine Ligand 17; TNFα, tumor necrosis factor alpha; TSLP, thymic stromal lymphopoietin.

BIOMARKER CORRELATION WITH DFK VS PLACEBO

- Multivariate analyses demonstrated statistically significant correlations between biomarker levels and DFK-induced improvements in WI-NRS score in subjects with CKD-aP undergoing HD treated with placebo or DFK (**Table 4**)

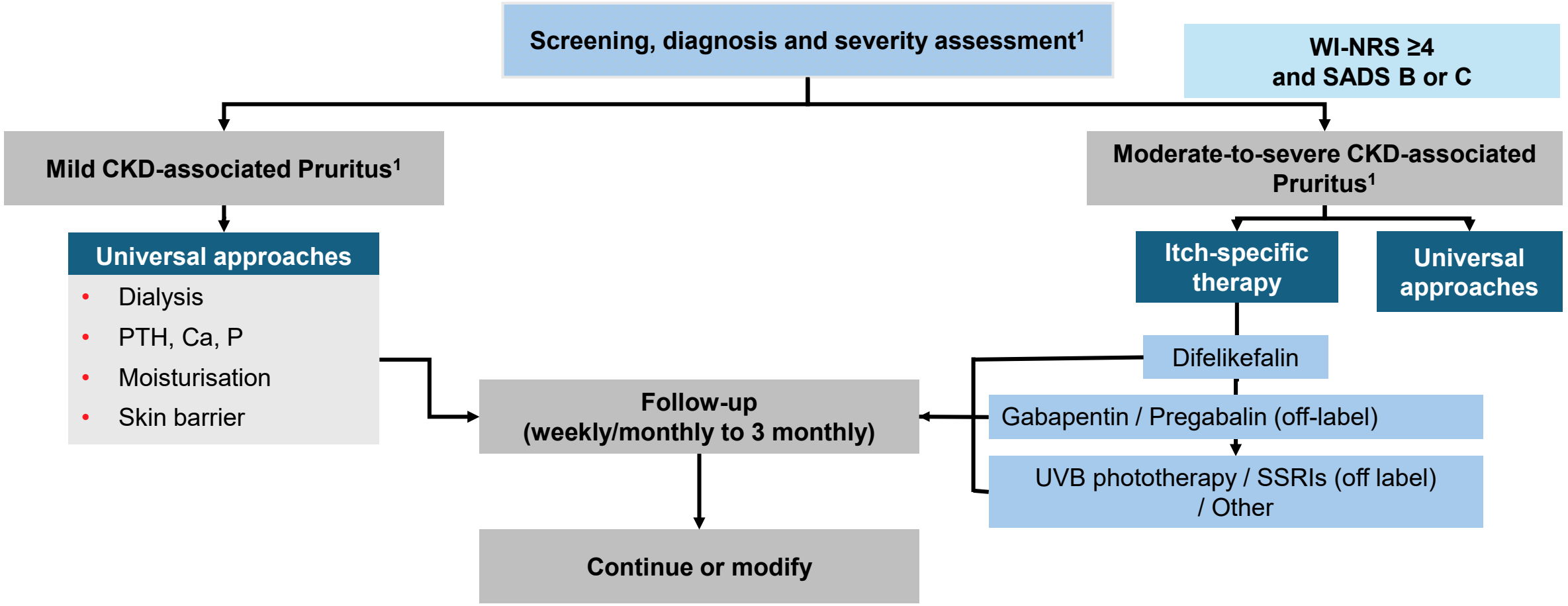
Table 4. Linear Regression Showed Significant Correlations Between Biomarker Levels and DFK-Induced Improvements in WI-NRS Score[a]

	Correlation With WI-NRS Change, *P* Value	
Biomarker	Placebo	DFK
CCL2	0.446	0.0005
CXCL10	0.299	0.0010
TNFα	0.373	0.0012
IFNγ	0.206	0.0069
NGF	0.270	0.0073
IL-2Rα	0.265	0.0100
CCL22	0.325	0.0110
IL-8	0.092	0.0200
IL-31	0.165	0.0250
Average significance of marker correlations	**0.074**	**0.0002**

[a]Responders: change in WI-NRS -40% to -100%; nonresponders: change in WI-NRS +30% to -29%.

S. Shirazian presended at the National Kidney spring Clinical Meeting April 6–10 2022

A MODERNISED THERAPEUTIC APPROACH IN CKD-ASSOCIATED PRURITUS



Therapeutic approach should consider patient goals and promote 'life participation'[2]

1. Agarwal R, et al. Clin Kidney J 2022. doi: https://doi.org/10.1093/ckj/sfac187; 2. Kalantar-Zadeh K, et al. Clin Kidney J 2021;14:476–81.