Uraemic Pruritus

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HUB DAY – JULY 23, 2020

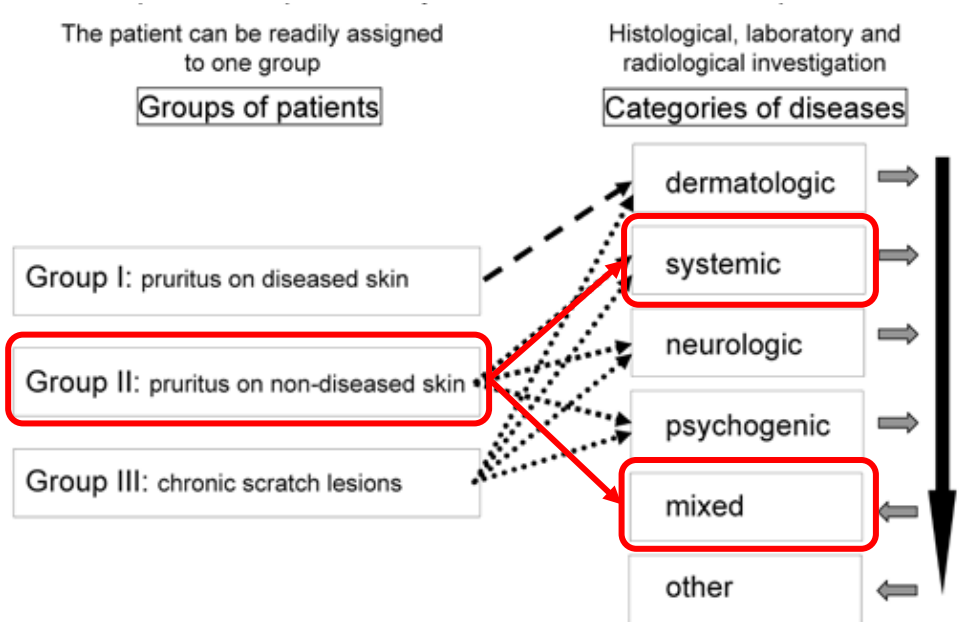
Overview

- Definition
- Clinical epidemiology
- Itch pathway
- Treatment options
- Kappa opioid receptor agonists
  - Nalfurafine
  - Difelikefalin
    - Phase 2 study
    - Phase 3 study

Definition

- Pruritus / Itch
  - An unpleasant cutaneous sensation which provoke the desire to scratch – Samuel Hafenreffer 1660
  - Acute (<6 weeks) vs. chronic (>= 6 weeks)
  - Classification: International Forum for the Study of Itch (IFSI)

Uraemic Pruritus



Stander *et al.*, 2007. Acta Dermato-Venereologica

Itch & Scratch

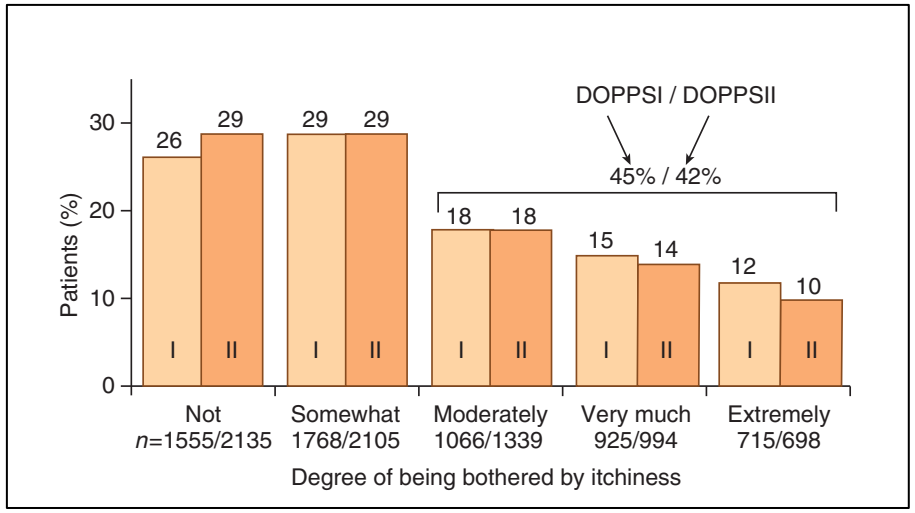
- "Scratching is one of the sweetest gratifications of nature, and as ready at hand as any … But repentance follows too annoyingly close at its heels"

- *M's story*
  - One morning, after she was awakened by her bedside alarm, she sat up and, she recalled, "this fluid came down my face, this greenish liquid." … Only in the Emergency Department at Massachusetts General Hospital, after the doctors started swarming, and one told her she needed surgery now, did M. learn what had happened. She had scratched through her skull during the night—and all the way into her brain."

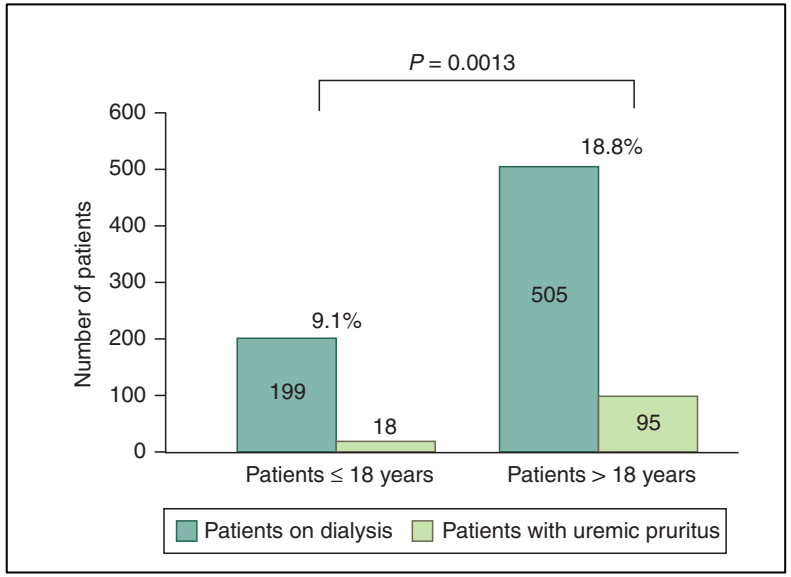
Gawande, 2008. The New Yorker.

Uraemic Pruritus

- Clinical epidemiology
  - >40% of dialysis patients (DOPPS)
    - I: 1996 - 1999
    - II: 2002 - 2003

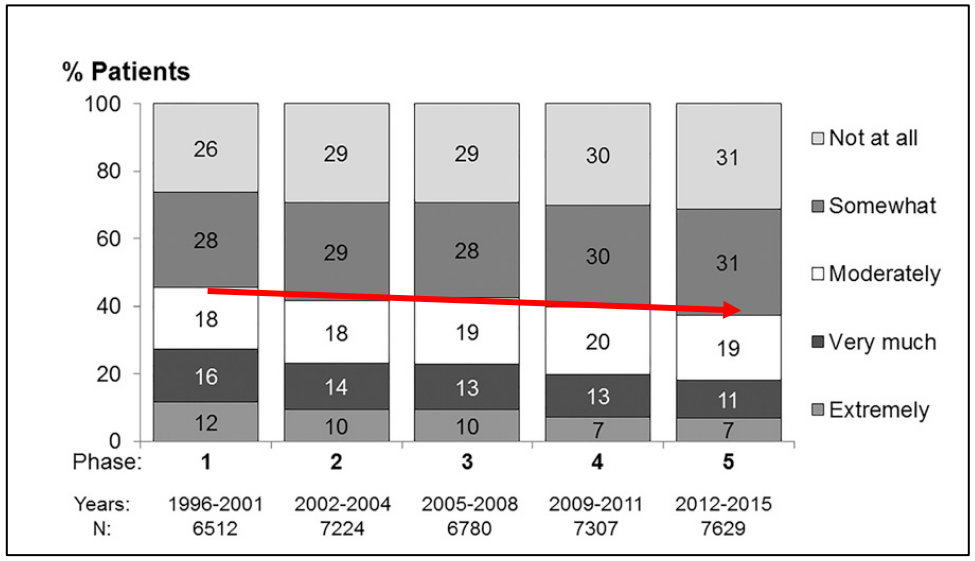


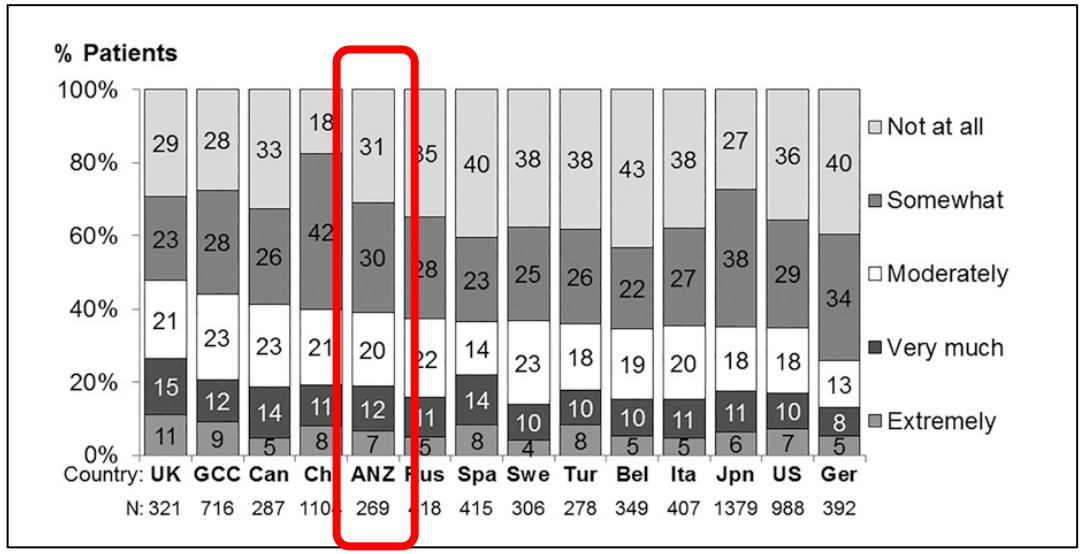
- Most common in adults than children
  - 18.8% vs. 9.1%



Uraemic Pruritus

- DOPPS – haemodialysis patients
  - Mild improvement in last 2 decades
- International trend
  - 39% moderate to severe in ANZ
    - Range 26% Germany – 48% UK





Rayner *et al*., 2017. CJASN

Timing of Uraemic Pruritus

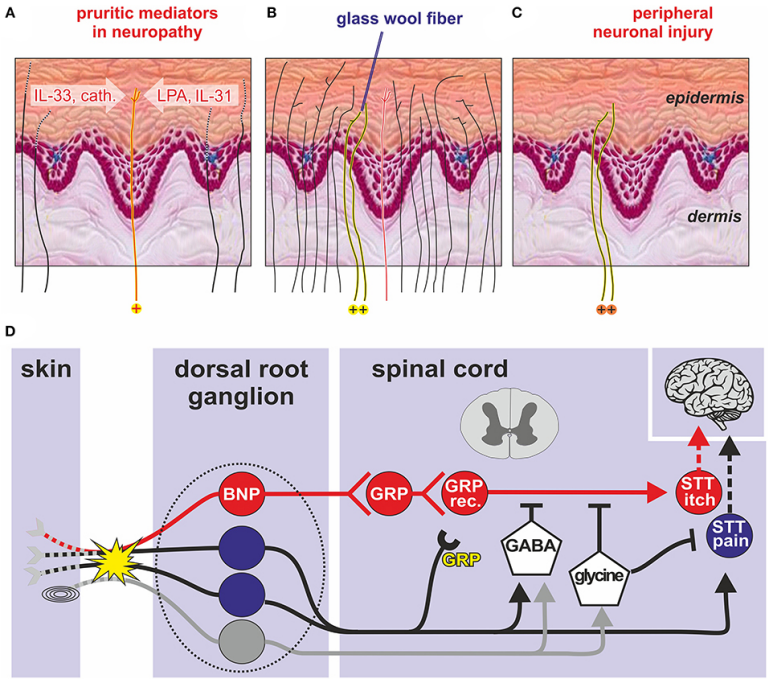
Time of the Day			Timing in relation to dialysis	
Morning	5%		Soon before dialysis	2%
Afternoon	3%		During dialysis	15%
Evening	15%		Soon after dialysis	9%
At night	30%		Non-dialysis days	14%
All the time	48%		All the time	61%

Rayner *et al*., 2017. CJASN

Itch Pathway

- Itch fibres
  - ~5% of C fibres transmits the sensation of itch
  - Of those itch fibres, 10% are histamine dependent and 90% are histamine independent
  - Itch is also transmitted by myelinated A-delta afferents
    - Sensory fibres

	Type	Diameter (µm)	Conduction velocity (m/s)	Function
Myelinated	Aα	13-22	70-120	Proprioception
	Aβ	8-13	40-70	Tactile (discrimina-tive touch)
	Aδ	1-4	5-40	Pain Temperature
Unmyelinated	C	0.2-1.5	0.2-2	Itch Pain Temperature Tactile (emotional touch)



Brennan, 2016. Progress in Palliative Care; Schmelz, 2019. Frontiers in Medicine; Hashimoto & Yosipovitch, 2019. Experimental Dermatology.

Histamine Independent Pathway

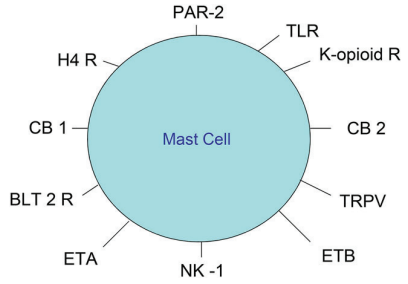
- Multiple itch mediators / Pruritogens
  - Tryptase → protease-activated receptor-2 (PAR-2) activation
  - Thomboxane A2
  - Tumour necrosis factor-alpha (TNF-alpha)
  - Leukotriene B4 (LB4)
  - Substance P (SP) → both histamine dependent and independent pathways
  - Interleukine 31 (IL-31)
  - Endothelin-1 (ET-1)
  - Nerve growth factor (NGF)

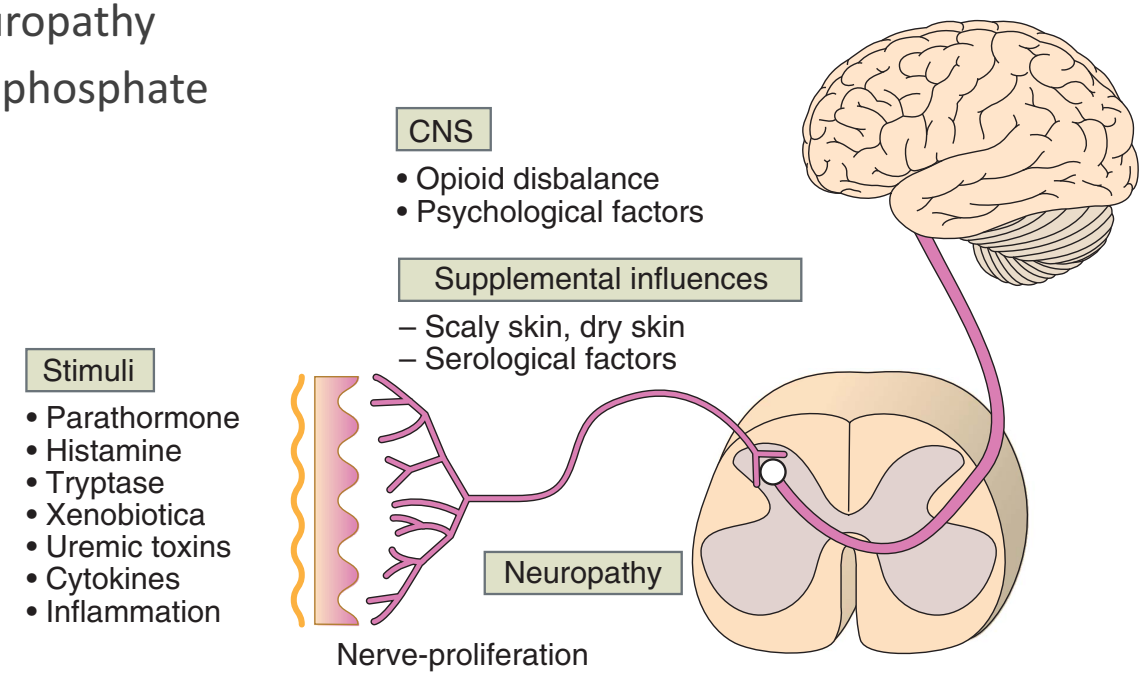
- Itch also has a psychological component
  - The more we think about it, the itchier we get.
  - Itch-scratch cycle is a reflex

Brennan, 2016. Progress in Palliative Care

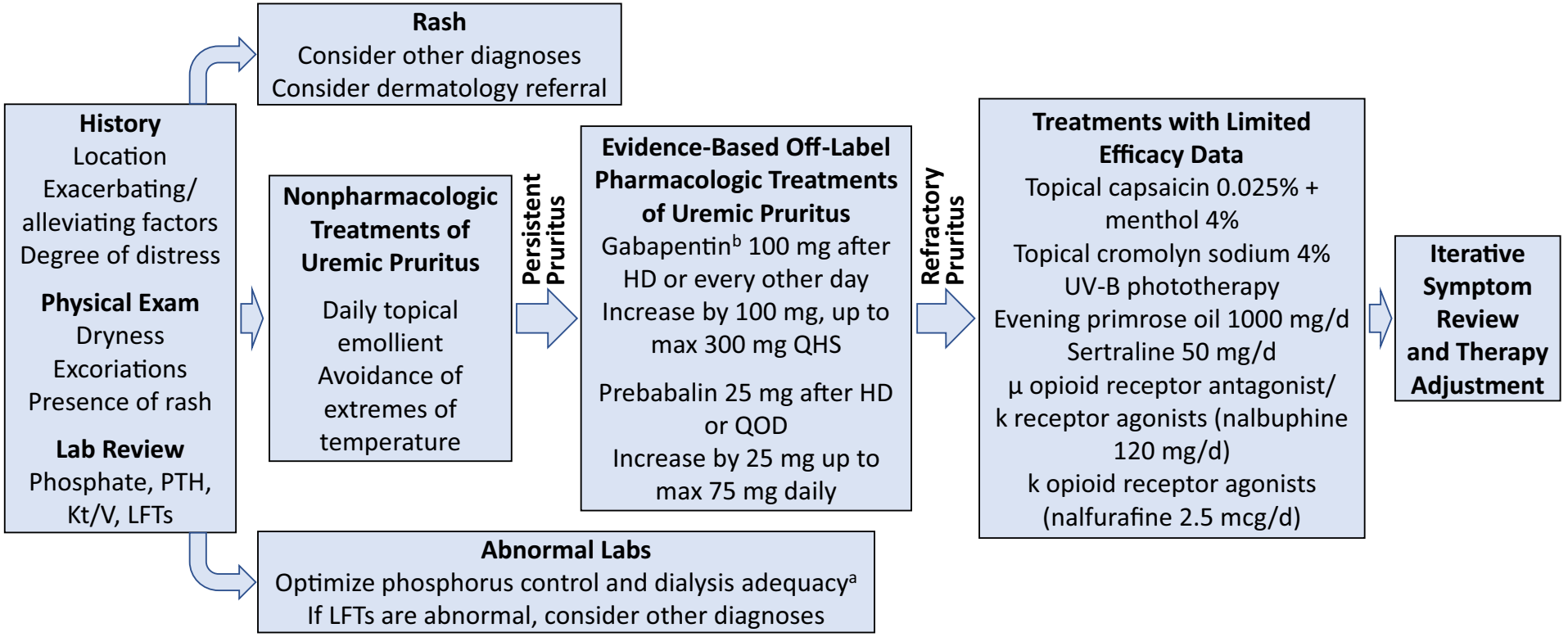
Uraemic Pruritus Pathogenesis

- Potential causes
  - Parathormone
  - Histamine / Tryptase disregulation
  - Uraemic toxins and associated neuropathy
  - Electrolytes: calcium, magnesium, phosphate
  - Microinflammation / cytokines
  - **Opioid-receptor derangements**





Treatment Approach



Gelfand *et al*., 2020. AJKD.

Gabapentin

Study	Treatment Dose and Duration	Comparator Dose and Duration	Pruritus Measurement	Outcome Measurement	Results	Statistically Significant Difference Between Treatments?	Adverse Drug Reactions
			Gabapentin/Pregabalin				
Foroutan[60] (2017)	Pregabalin 50 mg 3×/wk post-HD (titrated up to 50 mg 1×/d) for 4 wk	Doxepin 10 mg 1×/d (titrated up to 10 mg 2×/d) for 4 wk	0- to 10-cm VAS; 5-D pruritus scale, questionnaire	Mean VAS scores at BL & post	Pregabalin: 7.5 ± 1.4 BL, 2.1 ± 2.6 post; doxepin: 7.1 ± 1.3 BL, 4.2 ± 2.6 post	Yes, in favor of pregabalin	Pregabalin: somnolence (16.2%), edema (8.1%), drowsiness (8.1%), imbalance (2.7%), numbness (2.7%); doxepin: somnolence (14.2%), nervousness (2.9%)
Amirkhanlou[21] (2016)	Gabapentin 100 mg 1×/d for 2 wk	Ketotifen 1 mg 2×/d for 2 wk	5-point VRS	% Responders[b]	Gabapentin: 88.4%; ketotifen:76.9%	No	Gabapentin: drowsiness (15.4%), dizziness (3.8%); ketotifen: drowsiness (15.4%), dizziness (3.8%)
Nofal[41] (2016)	Gabapentin 100 mg (titrated up to max of 300 mg) 3×/wk post-HD for 1 mo	Placebo 3×/wk post HD for 1 mo	10-cm VAS, 5-D pruritus scale	% Responders (scores decreased by ≥50%)	Gabapentin: 88.9%; placebo: 22.2%	Yes, in favor of gabapentin	Gabapentin: dizziness (18.5%), somnolence (11.1%) fatigue (3.7%).
Yue[56] (2015)	Pregabalin 75 mg 2×/wk for 12 wk	Ondansetron 8 mg 1×/d for 12 wk; placebo for 12 wk	10-cm VAS, questionnaire	Mean change from BL, VAS vs placebo	Pregabalin: −4.6; ondansetron: −0.5	Yes, in favor of pregabalin	Pregabalin: somnolence (4.5%), dizziness (1.5%), loss of balance (1.5%); ondansetron: nausea & vomiting (3.1%)
Solak[47] (2012)	Gabapentin 300 mg 3×/wk post-HD for 6 wk	Pregabalin 75 mg 1×/d for 6 wk	10-cm VAS	% difference in VAS post	Gabapentin: 77.9%; pregabalin: 79.2%	No	Gabapentin: dizziness (15%), somnolence (12.5%), dry mouth (7.5%), balance disorder (5%), myoclonus (2.5%), diarrhea (7.5%), nausea (5%), constipation (5%), tremor (7.5%); pregabalin: dizziness (17.5%), somnolence (12.5%), dry mouth (2.5%), balance disorder (2.5%), myoclonus (2.5%), insomnia (2.5%), euphoria (2.5%)
Tol[50] (2010)	Gabapentin 300 mg 3×/wk post HD for 8 wk	Placebo for 8 wk	10-cm VAS	Mean VAS scores at BL & post	Gabapentin: 7.6 ± 1.2 BL, 1.3 ± 1.4 post	Yes, in favor of gabapentin	NR
Wu[59] (2010)	Gabapentin 100 mg 1×/d for 1 wk	Standard treatment	0- to 10-cm VAS	% of patients with symptom improvement[c]	Gabapentin: 89%; control: 25%	Yes, in favor of gabapentin	Gabapentin: dizziness (16.6%), drowsiness (11.1%), weakness (11.1%)
Naini[38] (2007)	Gabapentin 400 mg 2×/wk post HD for 4 wk	Placebo 2×/wk post HD for 4 wk	10-cm VAS	Mean decrease from BL VAS	Gabapentin: 6.7 ± 2.6; placebo 1.5 ± 1.8	Yes, in favor gabapentin	Gabapentin: somnolence, dizziness, & nausea (subsided after 5-10 d)
Gunal[33] (2004)	Gabapentin 300 mg 3×/wk post HD for 4 wk	Placebo 3×/wk post HD for 4 wk	10-cm VAS	Mean VAS scores at BL & post	BL: 8.4 ± 0.94; post: 7.6 ± 2.6 for placebo, 1.2 ± 1.8 for gabapentin	Yes, in favor of gabapentin	Gabapentin: somnolence, dizziness, fatigue (subsided after 7 d)

Statistically Significant Difference Between Treatments?

- Yes, in favor of pregabalin
- No — vs. Ketotifen
- Yes, in favor of gabapentin
- Yes, in favor of pregabalin
- No — vs. pregabalin
- Yes, in favor of gabapentin
- Yes, in favor of gabapentin
- Yes, in favor gabapentin
- Yes, in favor of gabapentin

Simonsen *et al.*, 2017. AJKD.

Global Uraemic Pruritus Treatment

- Medical directors' drug options (DOPPS)

Treatment	First Line	Second Line	Third Line	Acute Use	Never Use
Gabapentin	**5%**	**19%**	**21%**	**4%**	**52%**
Topical antihistamine	23%	9%	7%	24%	36%
Oral antihistamine	46%	24%	5%	19%	7%
IV antihistamine	2%	6%	9%	35%	48%
Topical corticosteroids	9%	11%	12%	39%	29%
Oral corticosteroids	2%	2%	4%	26%	66%
IV corticosteroids	1%	1%	1%	18%	79%
Antidepressants	2%	8%	21%	8%	60%
Anti-anxiolytics	2%	6%	20%	19%	53%
Opioids	1%	5%	9%	6%	79%

Rayner *et al*., 2017. CJASN

Opioid Receptors

- Pathogenesis – hypothesis
  - Increased activity of opioid receptor due to kidney impairment leading to upregulation of endospinal endogenous opioids
- Opioid receptor antagonists
  - Nalfurafine, naltrexone, naloxone, and butorphanol
- Mechanism of opioid receptor mu-antagonists or kappa-agonist
  - Downregulation of endogenous or exogenous opioids
  - Downregulation of serotoinin (5-HT3) receptors and mu opioid receptors in the 'itch centre' of the spinal cord

Opioid Receptors	Effect
Mu1	Euphoria, supraspinal analgesia, confusion, dizziness, nausea, low additional potential
Mu2	Respiratory depression, cardiovascular and gastrointestinal effects, miosis, urinary retnetion
Delta	Spinal analgesia, cardiovasucular depression, decreased brain and myocardial oxygen demand
Kappa	Spinal analgesia, dysphoria, psychomimetic effets, feed-back inhibition of endorphin system

Andrade *et al*., 2020. Cochrane Review.

Nalfurafine Hydrochloride

- Selective kappa-opioid receptor agonist
- 2 RCTs (n=79, n=339)
  - Dose: nalfuratine HCl 5ug vs. placebo (cross-over) / nalfurafine HCl 2.5 or 5ug vs. placebo

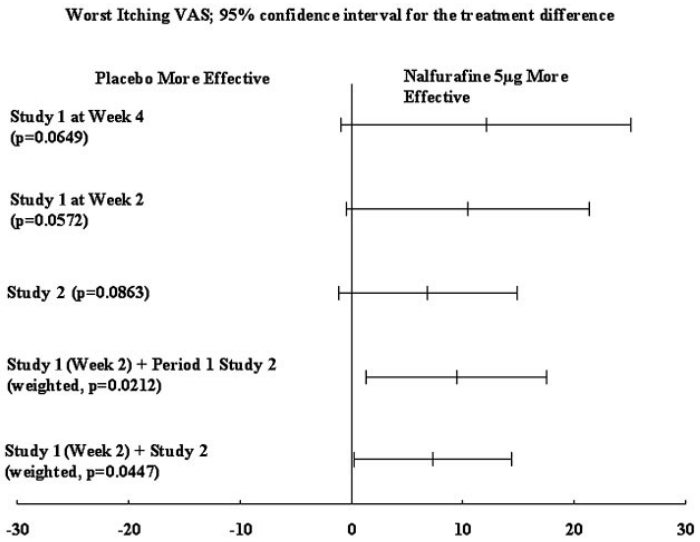


Figure 1. "Worst itching" visual analog scale; 95% confidence interval for the treatment difference.

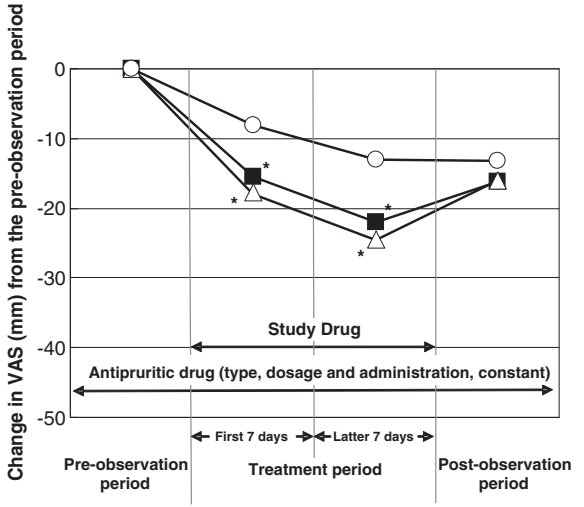


Fig. 2. Changes in VAS values from the pre-observation period. Open circle, placebo group; open triangle, nalfurafine 2.5-μg group; filled square, nalfurafine 5-μg group. All symbols show the mean value of VAS changes. *$P < 0.025$ vs. the placebo group, one-sided ANCOVA.

Wikstrom *et al*. 2005, JASN; Kumagai *et al.* 2010, *NDT*.

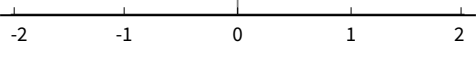
Nalfurafine

Analysis 2.1. Comparison 2 Nalfurafine versus placebo, Outcome 1 A) Pruritus on VAS scale (0-10 cm) in UP participants; parallel-group design; Wikström b: Wikström a (week 2) + period 1 Wikström b.

Study or subgroup	Nalfurafine N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Kumagai 2010	226	111	-0.9 (0.214)		78.17%	-0.95[-1.37,-0.53]
Wikström 2005b	42	43	-1 (0.405)		21.83%	-0.95[-1.75,-0.16]
Total (95% CI)					**100%**	**-0.95[-1.32,-0.58]**

Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=1(P=0.99); $I^2=0\%$

Test for overall effect: Z=5.02(P<0.0001)



Favours nalfurafine — Favours placebo

Difelikefalin (CR845)

- Peripherally restricted and selective agonist of **kappa opioid receptors**
  - Hydrophilic small-peptide structure → No passive diffusion across membranes/BBB
  - No identified off-target activity
- Pharmacokinetics
  - Mostly renally excreted
  - Long half-life in haemodialysis patients (24hrs)

Phase 2 Trial – 28 Jan, 2020

ARTICLE IN PRESS

KI REPORTS
KIReports.org

CLINICAL RESEARCH

Randomized Controlled Trial of Difelikefalin for Chronic Pruritus in Hemodialysis Patients

Steven Fishbane[1], Vandana Mathur[2], Michael J. Germain[3], Shayan Shirazian[4], Sarbani Bhaduri[5], Catherine Munera[6], Robert H. Spencer[6] and Frédérique Menzaghi[6]; on behalf of the Trial Investigators[7]

Study Design

- Randomised, double-blind, placebo-controlled phase 2 trial between 2016-2017
- Aims
  - To assess the efficacy and safety of multiple doses of difelikefalin over 8 weeks
- Exposure / Control
  - IV Difelikefalin 0.5ug/kg, 1.0ug/kg, 1.5ug/kg
  - Placebo
- Randomisation
  - 1:1:1:1 randomisation stratified by use or non-use of antipruritic medication
- Blinding
  - Patients, investigators, clinical study site staff, sponsor staff

Inclusion & Exclusion Criteria

- Inclusion criteria
  - Adult haemodialysis patients 3x/week for at least 3 months
  - Persistent moderate-to-severe uraeamic pruritus (WI-NRS >4)
  - Weight between 40-135kg
  - At least 2 x Kt/V >=1.2 *OR* at least 2 x URR>=65% *OR* 1 x Kt/V>=1.2 AND 1 x URR >=65%
- Exclusion criteria
  - Use of opioid antagonists (eg. naloxone, naltrexone) or opioid mixe agonist (eg. buprenorphine, nalbuphine)
  - Allergy to opiates
  - Anticipated to receive a kidney transplantation
  - Pregnant women
  - Non-compliance
  - History of alcohol, narcotic, or other durg abuse of dependence 12 months prior to screening
  - AST or ALT > 2.5xULN OR total bilirubin >2xULN
- Continuation of regular anti-pruritus agents

Regular Anti-Pruritus Agents

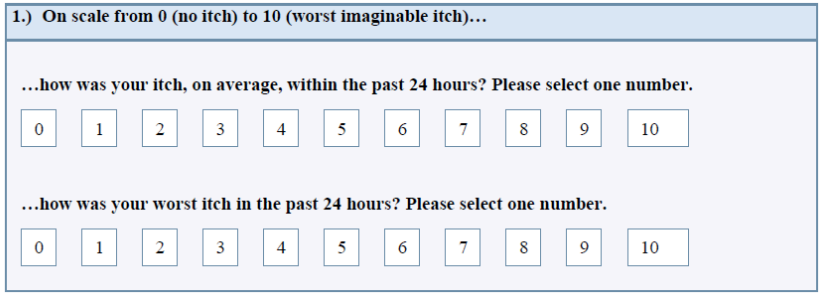
Table 1. Baseline demographics and clinical characteristics

Baseline demographics	Placebo (n = 45)	Difelikefalin 0.5 μg/kg (n = 44)	Difelikefalin 1.0 μg/kg (n = 41)	Difelikefalin 1.5 μg/kg (n = 44)	Total (n = 174)
Use of antipruritic medication,[c] n (%)					
Any prior anti-pruritic medication	18 (40.0)	20 (45.5)	17 (41.5)	18 (40.9)	73 (42.0)
Diphenhydramine hydrochloride	11 (24.4)	11 (25.0)	11 (26.8)	11 (25.0)	44 (25.3)
Hydroxyzine hydrochloride	2 (4.4)	6 (13.6)	2 (4.9)	3 (6.8)	13 (7.5)
Topical hydrocortisone	5 (11.1)	1 (2.3)	2 (4.9)	1 (2.3)	9 (5.2)

- < =2% taking gabapentin

Outcomes

- PROM
  - Primary outcome: Worst Itching Intensity Numerical Rating Scale (WI-NRS)
    - Daily over past 24hrs from the week before randomisation to the end of treatment period
      - Mild: 0-3
      - Moderate: 4-6
      - Severe: 7-10
    - Measurement: Change from baseline at week 8 in the weekly mean of the 24hr daily WI-NRS score
  - Skindex-10 scale
    - Disease
    - Mood/emotional distress
    - Social functioning

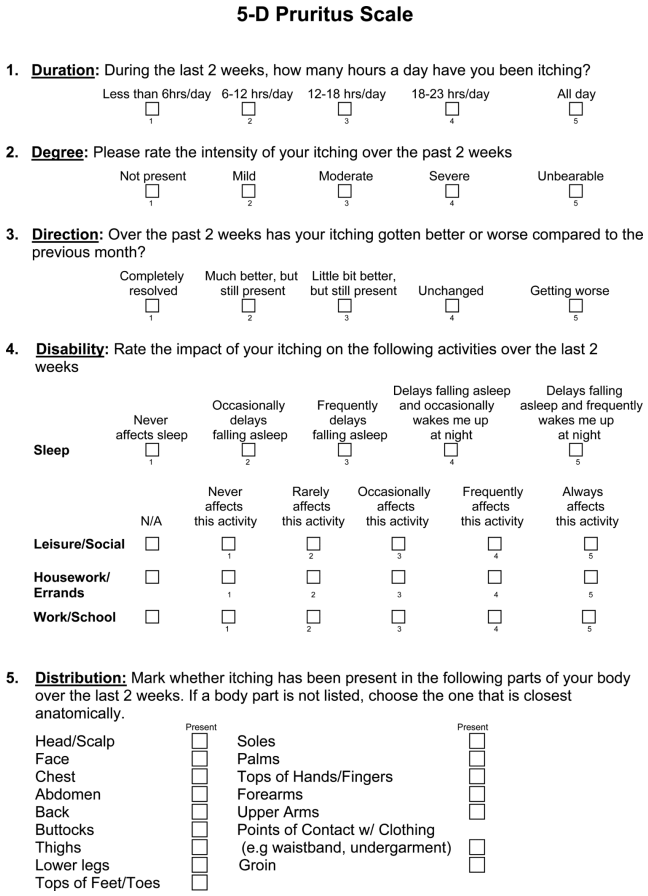


During the past WEEK, how often have you been bothered by:

1. Your itching
2. The persistence/recurrence of your itching
3. The appearance of your skin from scratching
4. Frustration about your itching
5. Being annoyed about your itching
6. Feeling depressed about your itching
7. Feeling embarrassed about your itching
8. The effects of your itching on your interactions with others (for example: interactions with family, friends, close relationships, etc.)
9. The effects of your itching on your desire to be with people
10. The effect of your itching making it hard to work or do what you enjoy

Outcomes

- PROM
  - 5-D itch scale
    - Duration
    - Degree
    - Direction
    - Body distribution of itch
    - Disability due to itch
  - Medical outcomes study sleep disturbance scale
  - Patient Global Impression of Worst Itch Severity
  - Patient Global Impression of Change



5-D Pruritus Scale

1. **Duration**: During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree**: Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction**: Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability**: Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

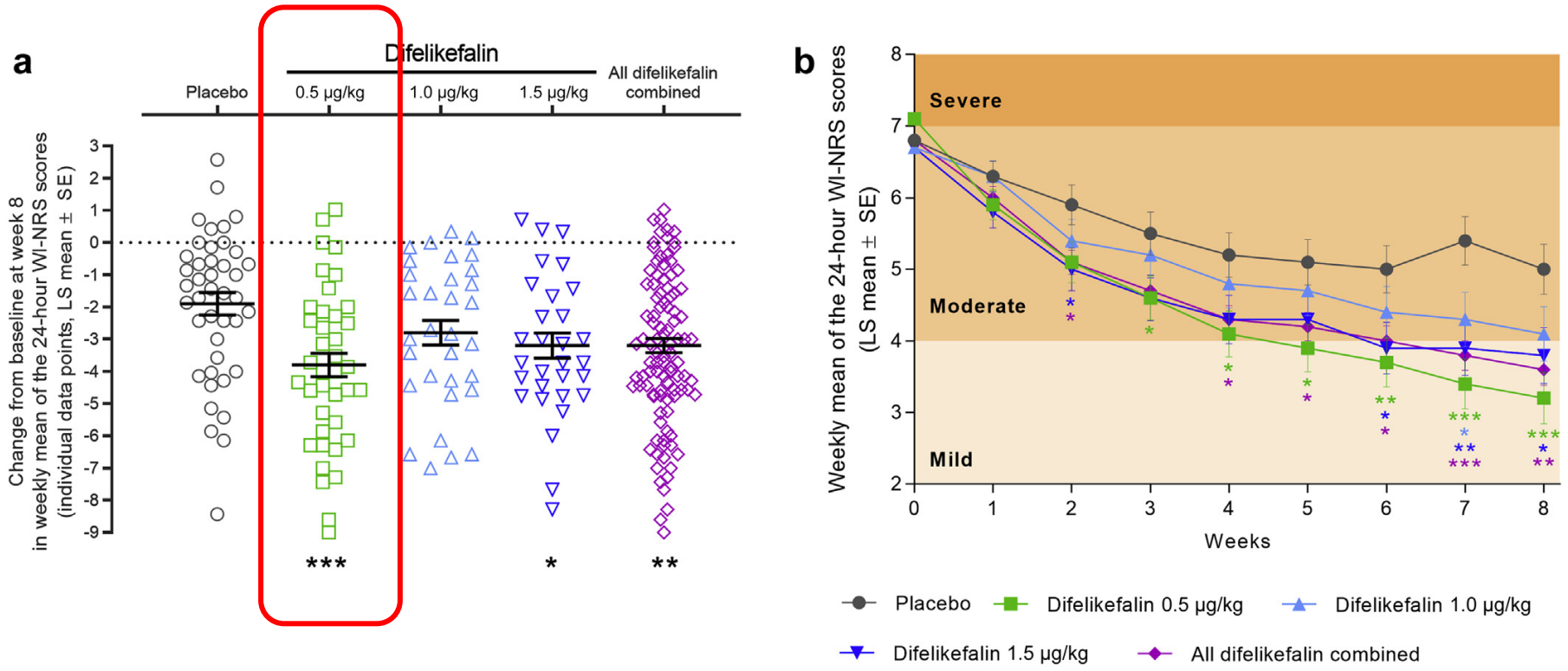
	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

Results – Difelikenfalin Dosing

- n= 174



NEJM – Nov 8, 2019

ORIGINAL ARTICLE

A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus

Steven Fishbane, M.D., Aamir Jamal, M.D., Catherine Munera, Ph.D.,
Warren Wen, Ph.D., and Frédérique Menzaghi, Ph.D.,
for the KALM-1 Trial Investigators*

Study Design

- Double-blinded, placebo-controlled, phase 3 trial in 56 sites in US
- Aim
  - To evaluate the efficacy and safety of difelikefalin in adult patients undergoing hemodialysis with moderate-to-severe pruritus.
- Exposure / Control: **3x per week for 12 weeks**
  - IV Diflikfalin 0.5ug/kg of body weight at conclusion of dialysis
  - Placebo
- Randomisation
  - 1:1 randomisation for placebo vs. IV 0.5ug/kg difelkefalin
- Blinding – *not specified*
- Inclusion criteria
  - *Same as the Phase 2 Trial*

Study Design

- Outcomes
  - Primary outcome
    - Percent of patients with >=3 point improvement on WI-NRS at week 12
  - Secondary outcome
    - Percentage of patients with an improvement of at least 4 points in the WI-NRS score at week 12
    - Change from baseline in itch-related quality of life measures
      - 5D-itch scale total score, Skindex-10 scale
    - Safety
- Statistical analysis
  - ANOVA models
  - Missing information estimated by multiple imputation

Results

- N=378
  - Difelikefalin: 189 (158 [84%] at 12 weeks)
  - Control: 188 (165 [88%] at 12 weeks)
- Baseline charateristics

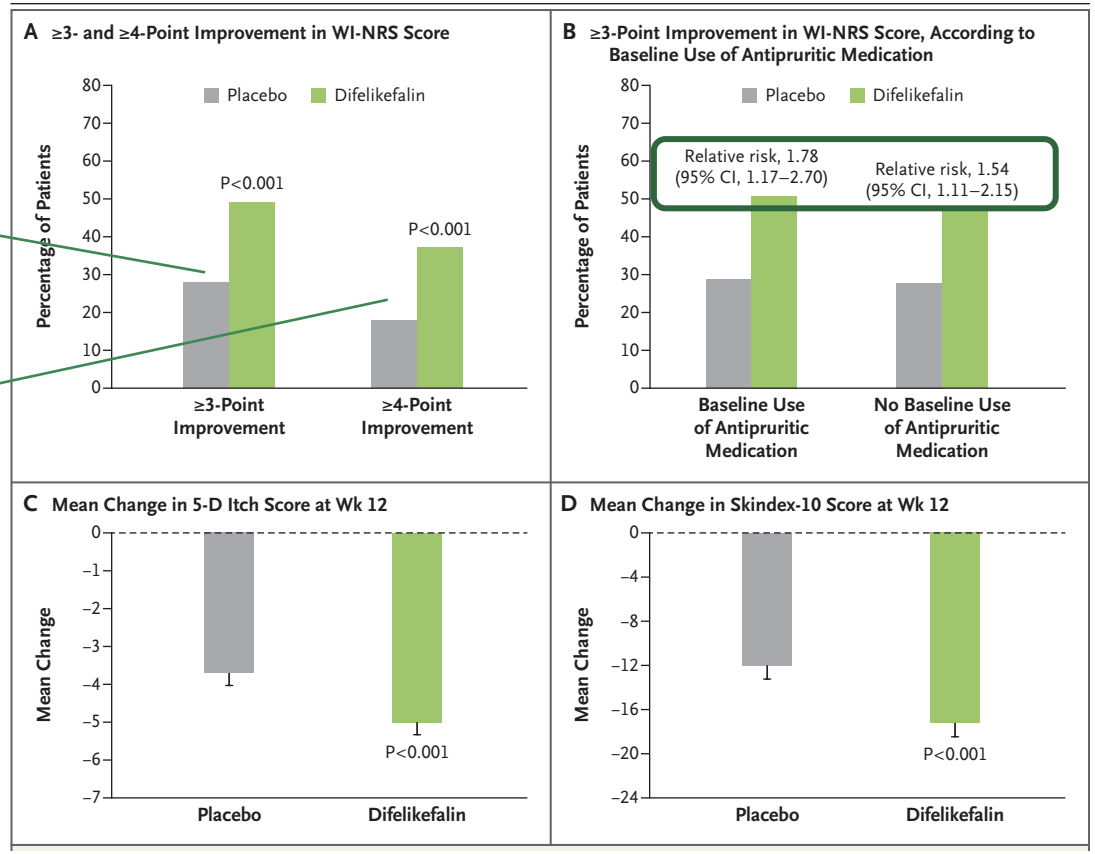
Characteristics	Placebo (n=188)	Difelikefalin (n=189)
Age	56.7 ± 13.9	58.2 ± 11.2
Sex (n, %)	118 (62.8)	112 (59.3)
Race – Caucasian (n, %)	93 (49.5)	91 (48.1)
IBW	85.0 ± 21.1	85.9 ± 20.3
Duration of Pruritus (yr)	3.5 ± 3.4	3.2 ± 3.2
Antipruritis meds (n,%) Diphenhydramine	78 (41.5) 71 (37.8)	72 (38.1) 61 (32.3)

Results

- Efficacy outcomes

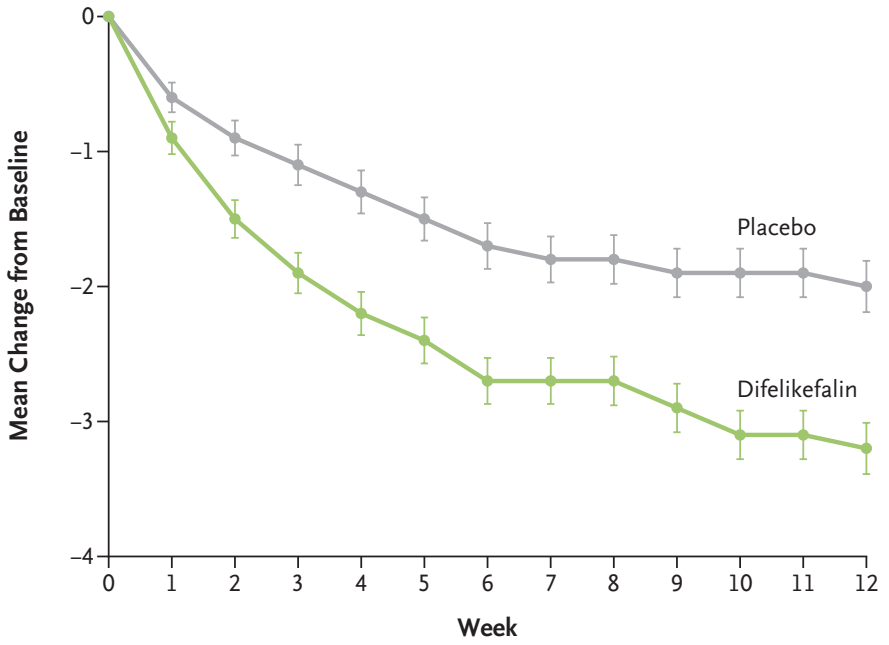
28% vs. 49%
RR: 1.65 (1.24-2.14)

18% vs. 37%
RR: 1.92 (1.37-2.68)



Results

- Mean change in WI-NRS score



Results

- Adverse Events

Event	Placebo	Difelikefalin
12-Wk double-blind intervention period		
No. of patients with data	188†	189
Any adverse event — no. (%)	117 (62.2)	130 (68.8)
Adverse event leading to discontinuation of trial regimen — no. (%)	9 (4.8)	15 (7.9)
Most frequent adverse events — no. (%)‡		
Diarrhea	7 (3.7)	18 (9.5)
Dizziness	2 (1.1)	13 (6.9)
Vomiting	6 (3.2)	10 (5.3)
Nasopharyngitis	10 (5.3)	6 (3.2)
Serious adverse event — no. (%)	41 (21.8)	49 (25.9)
Death — no. (%)	2 (1.1)	2 (1.1)

More GI Adverse Events

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Take Home Messages

- Uraemic pruritus is common in patients on dialysis
- Aetiology of pruritus is complicated and multifactorial, including opioid receptor derangement
- Difelikefalin is a peripherally restricted and selective agonist of kappa opioid receptors
  - IV Difelikefalin 0.5ug/kg three times a week is a potential agent targeting uraemic pruritus
    - Doesn't help patients on a conservative, non-dialysis pathway though.

Watch this space

Questions?

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