CKD-Associated Pruritus

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DISCLOSURES

- Cara Therapeutics Nephrology Advisory Board

OBJECTIVES

- Describe CKD-associated pruritus (CKD-aP)
- Review current available treatments and data supporting them
- Present new treatments for CKD-aP in the pipeline
- Summarize an approach to therapy

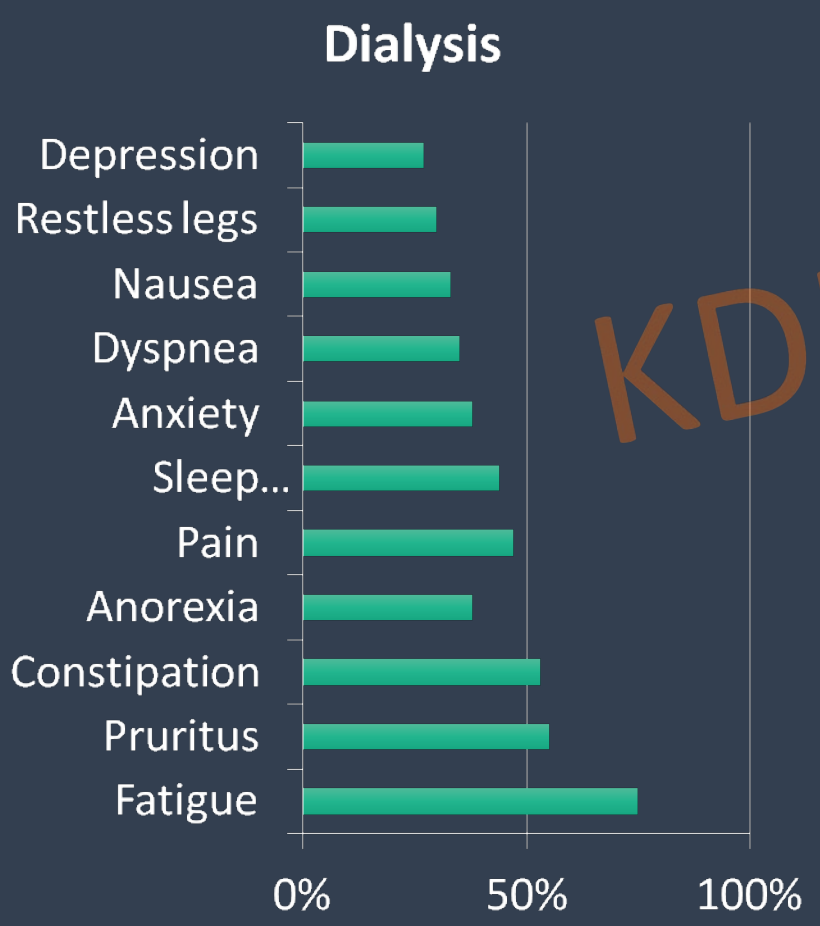
Case: Mr. Martinez

- Mr. Martinez is a 49-year-old man with ESRD on in-center HD for 9 years. He finds you in nephrology clinic one day and tells you he's in crisis because he can't stop itching. He's driving his wife crazy because he can't sleep and is constantly scratching himself. The itching is so bad that he is unable to sit through an entire 4-hour dialysis session.

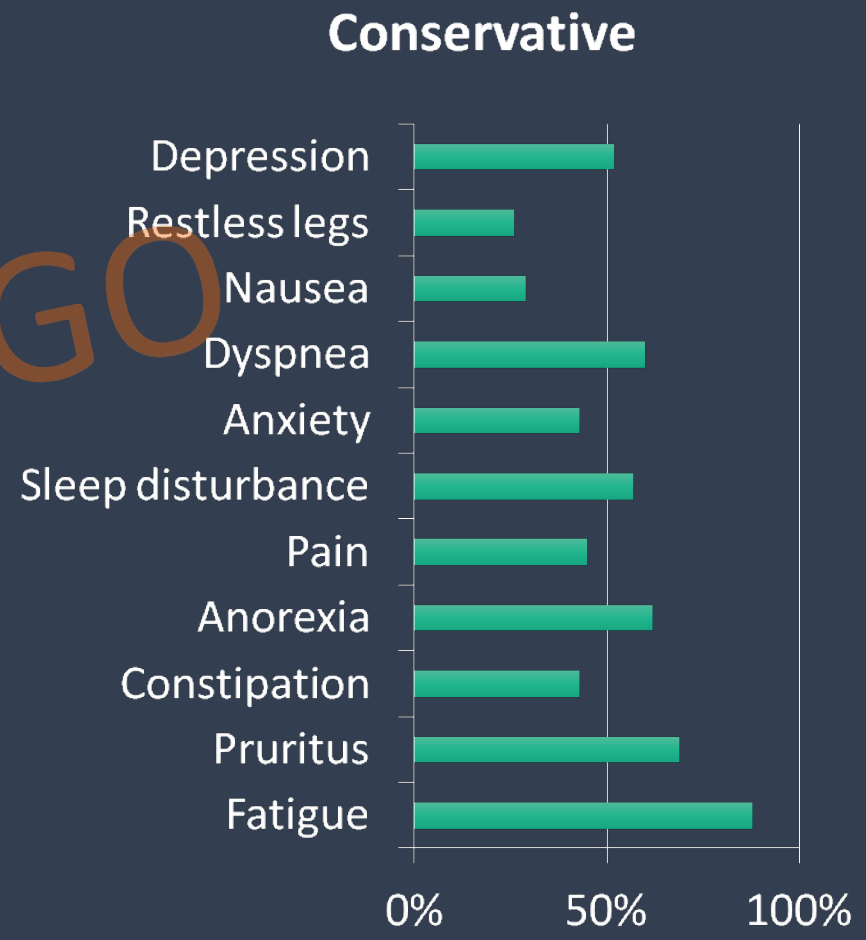
- He looks at you with a serious face and tells you that things are so bad that he is considering "giving up."

- What is your approach to this patient?

Symptom Prevalence:
ESRD on dialysis and conservative management



Fliss, *Adv Chronic Kid Dis* 2007.



Brennan, *Progress Pall Care* 2015.

CKD-aP

- Also known as uremic pruritus
- Common (30-70% of patients)
- Associated with decreased quality of life and worsening symptoms of depression
- Independently associated with increased mortality
- Amplifies other symptoms that impair quality of life
  - e.g., poor sleep
- Research into treatment strategies for pruritus is a high priority for patients

Weisborg, *CJASN* 2007; Weisshar, *NDT* 2009; Manns, *CJASN* 2014; Mettang, *KI* 2014.

International Comparisons of Prevalence, Awareness and Treatment of Pruritus in People on Hemodialysis

METHODS

Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Between 2012 and 2015

17 Countries

6256 Hemodialysis Patients

268 Medical Directors

OUTCOMES

18% of patients were very much or extremely bothered by itchy skin.

69% of medical directors underestimated the prevalence of pruritus in their facility.

Among patients nearly always or always bothered by itching, 18% used no treatment for pruritus.

CONCLUSION

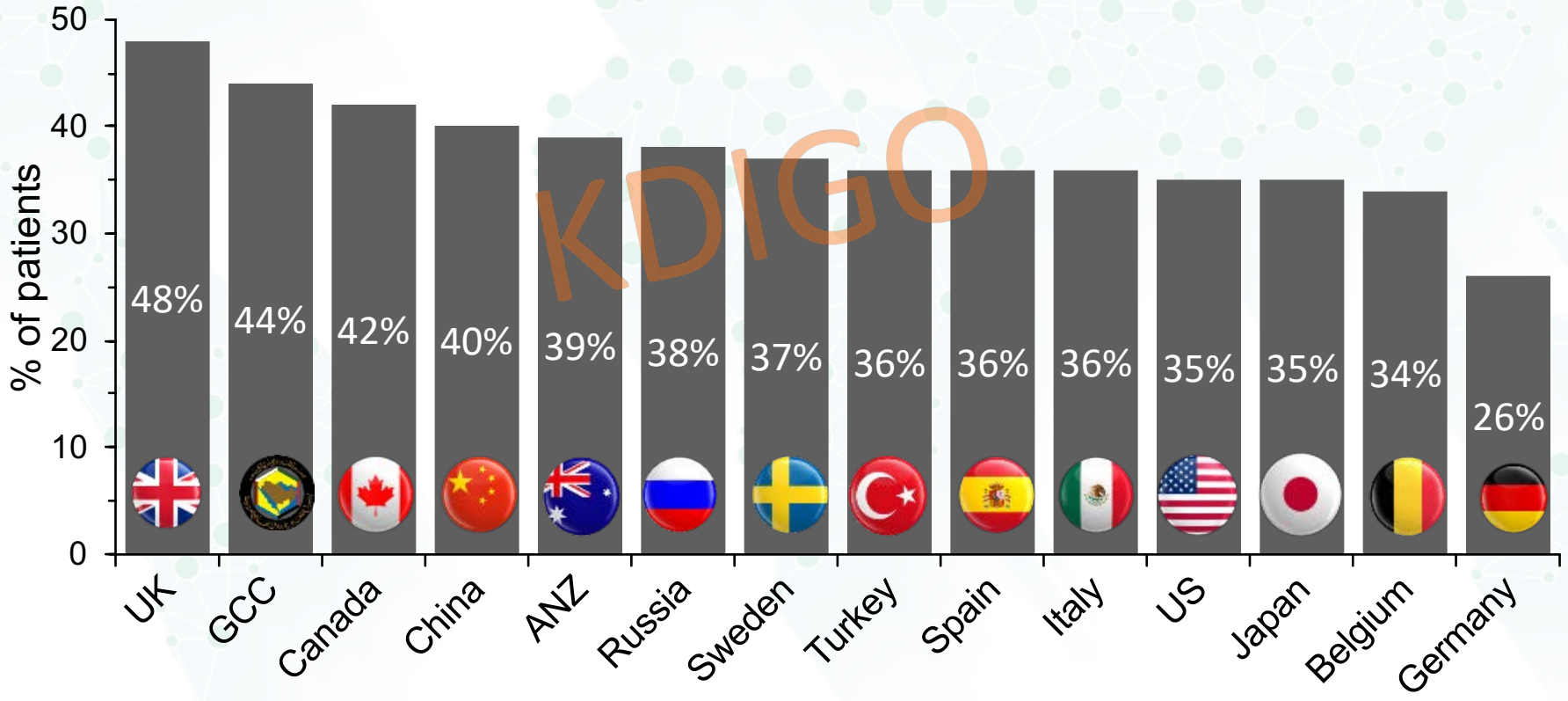
Many patients' lives could be improved by increased awareness and treatment of CKD-associated pruritus.

Hugh Rayner, Maria Larkina, Mia Wang, Matthew Graham-Brown, Sabine van der Veer, Tevfik Ecder, Takeshi Hasegawa, Werner Kleophas, Brian Bieber, Francesca Tentori, Bruce Robinson, and Ronald Pisoni. International Comparisons of Prevalence, Awareness and Treatment of Pruritus in People on Hemodialysis. CJASN doi:10.2215/CJN.03280317.

CJASN®
Clinical Journal of American Society of Nephrology

Prevalence of Moderate-to-Severe CKD-aP in Hemodialysis Patients

Dialysis Outcomes and Practice Patterns Study (DOPPS), 2012-2015

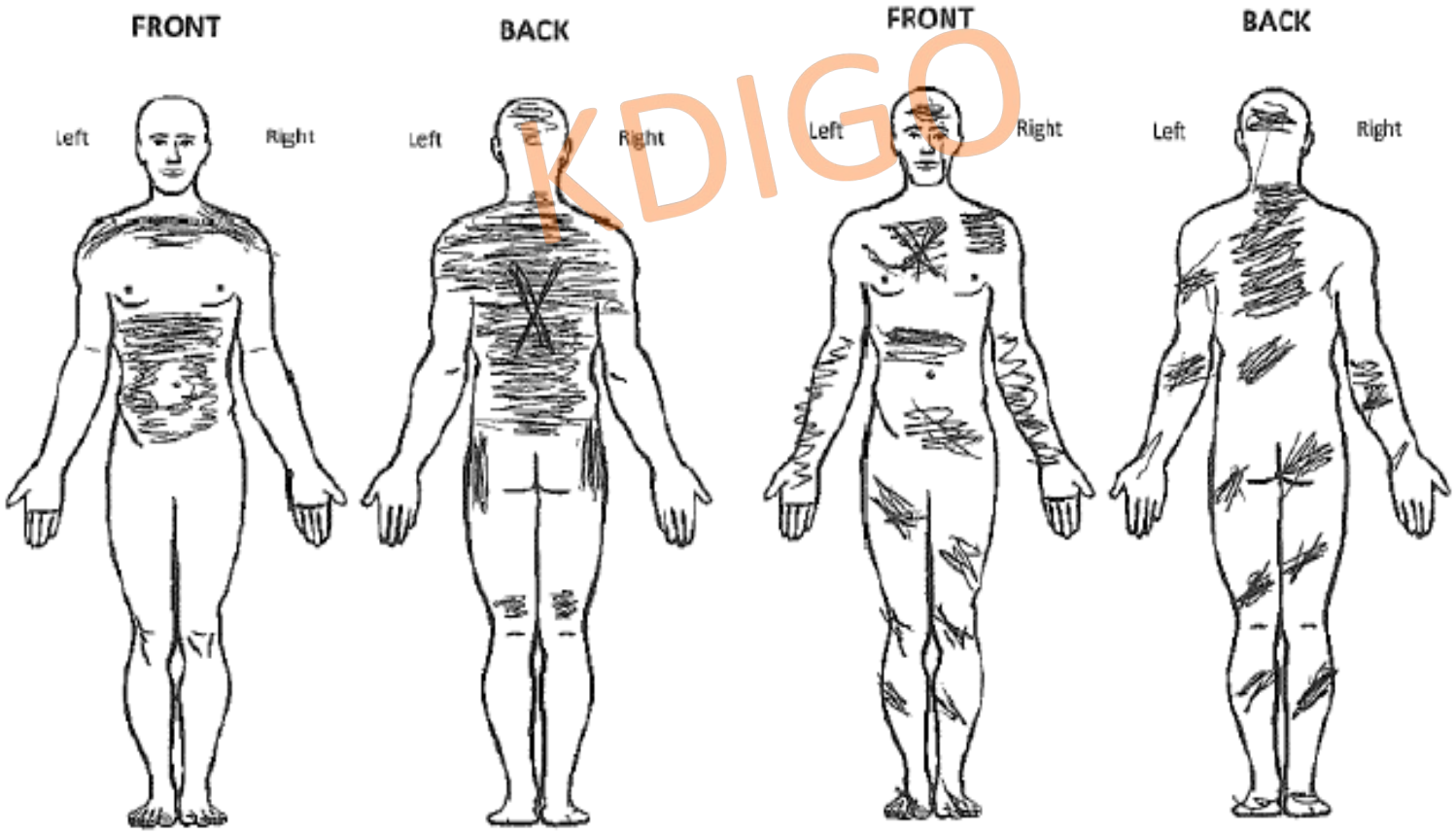


GCC=Gulf Cooperation Council; ANZ=Australia and New Zealand

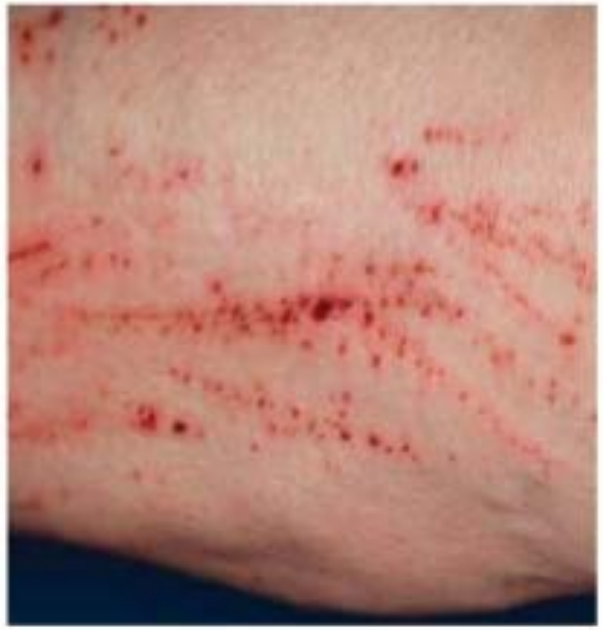
Rayner, *CJASN* 2017.

Anatomical Distribution of CKD-aP

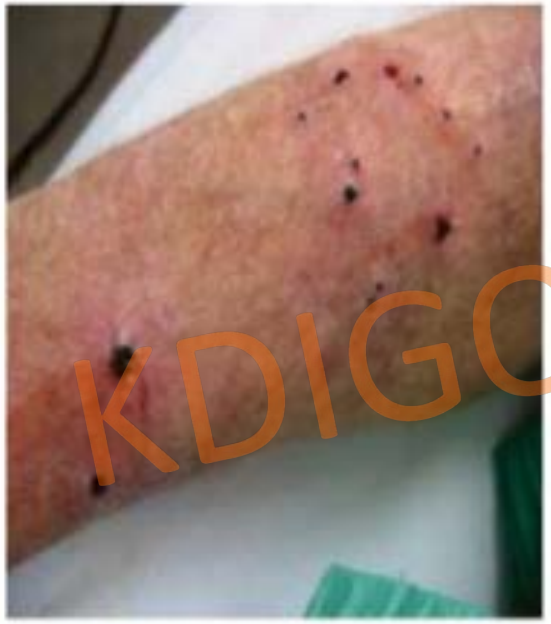
- Severe itching typically bilateral, symmetrical, persistent, and generalized
- Back, abdomen, arms, and legs



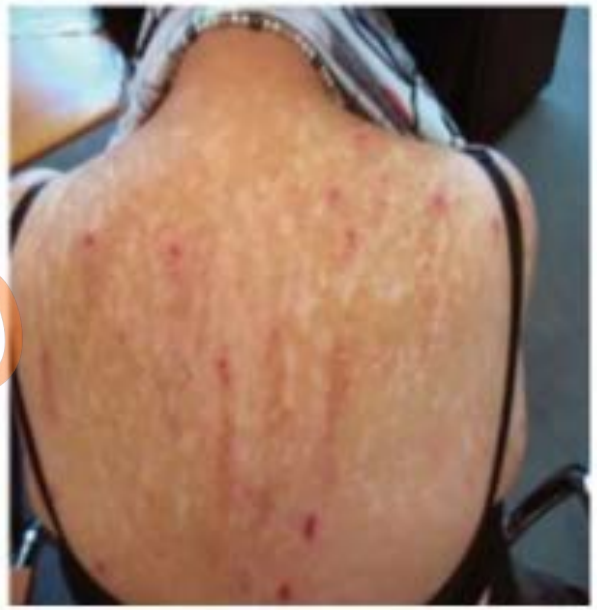
CKD-aP



Scratch marks with excoriations



Hyperkeratotic partly excoriated nodules (prurigo nodularis)



Deep scars and prurigo nodules

Thomas Mettang. Kidney International (2015) 87, 685–691.

Non-Uremic Causes of Itch

Primary Dermatologic Conditions

- Drug-induced hypersensitivity and other allergies
- Contact dermatitis
- Psoriasis
- Dermatophytosis (tinea cruris, tinea pedis, tinea corporis)
- Bullous pemphigoid
- Infestations
  - Bed bugs
  - Scabies
  - Lice

Systemic Conditions

- Cholestasis
- Viral hepatitis
- Primary biliary cirrhosis
- Hematologic malignancy
- Hodgkin's lymphoma
- Cutaneous T-cell lymphoma
- Polycythemia vera
- Post-herpetic neuralgia
- HIV

CKD-aP: Pathogenesis

Hyperparathyroidism (elevated PTH, Phos, Ca)

Histaminergic reaction

Structural Skin Alterations

Systematic Inflammation

Alterations in nociceptive sensory pathways

Opioid Receptor Dysfunction

CKD-aP: Pathogenesis

Hi[illegible]rathyroi[illegible]m
([illegible]vate[illegible]H, Ph[illegible]Ca)

Hi[illegible]inergic[illegible]ion

Structural Skin Alterations

Systematic Inflammation

Alterations in nociceptive sensory pathways

Opioid Receptor Dysfunction

CKD-aP: PATHOGENESIS

Hyperparathyroidism

(elevated PTH, Phos, Ca)

MBD parameters are *not* associated with pruritus in the highest quality observational data available

Optimal "goals" for treating phosphorous or PTH in patients with pruritus are unknown

Histaminergic reaction

Antihistamines are not effective

Antihistamines are sedating

Antihistamines have anticholinergic side effects

CKD-aP: PATHOGENESIS

Hyperparathyroidis

(elevated PTH, P a)

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or PT nts with pruritus are
unkno

Histaminergic reaction

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Antihistamines have
anticholinergic side effects

CKD-aP: Pathogenesis

Xerosis (dry skin)

- Xerosis prevalent in patients with CKD
- Emollients are successful in some patients, but not all
- Role of structural skin changes in pruritus unclear

Systemic Inflammation

- Increased inflammatory markers and decreased albumin associated with worse pruritic symptoms
- Transplant patients have decreased prevalence of pruritus as graft failure occurs compared to non-transplant CKD patients

ADJUSTED ODDS OF BEING AFFECTED BY MODERATE-TO-EXTREMELY ITCHY SKIN

Patient characteristics	Adjusted Odds Ratio [95% CI]
Age (per 10 years)	1.06 [1.02-1.10]
Hepatitis B/C	1.26 [1.06-1.50]
Albumin >4	0.87 [0.80-0.95]
Albumin <3.5	1.14 [1.04-1.25]
CRP 10 – 15	1.39 [1.06-1.83]
CRP 15 or higher	1.31 [1.05-1.64]
Phosphorus 5.5 - <6.7	1.01 [0.91-1.13]
Phosphorus ≥ 6.7	1.07 [0.95-1.21]

**no association was observed with serum phosphorus, calcium, calcium-phosphorus product, PTH, or Kt/V.

Rayner, *CJASN* 2017.

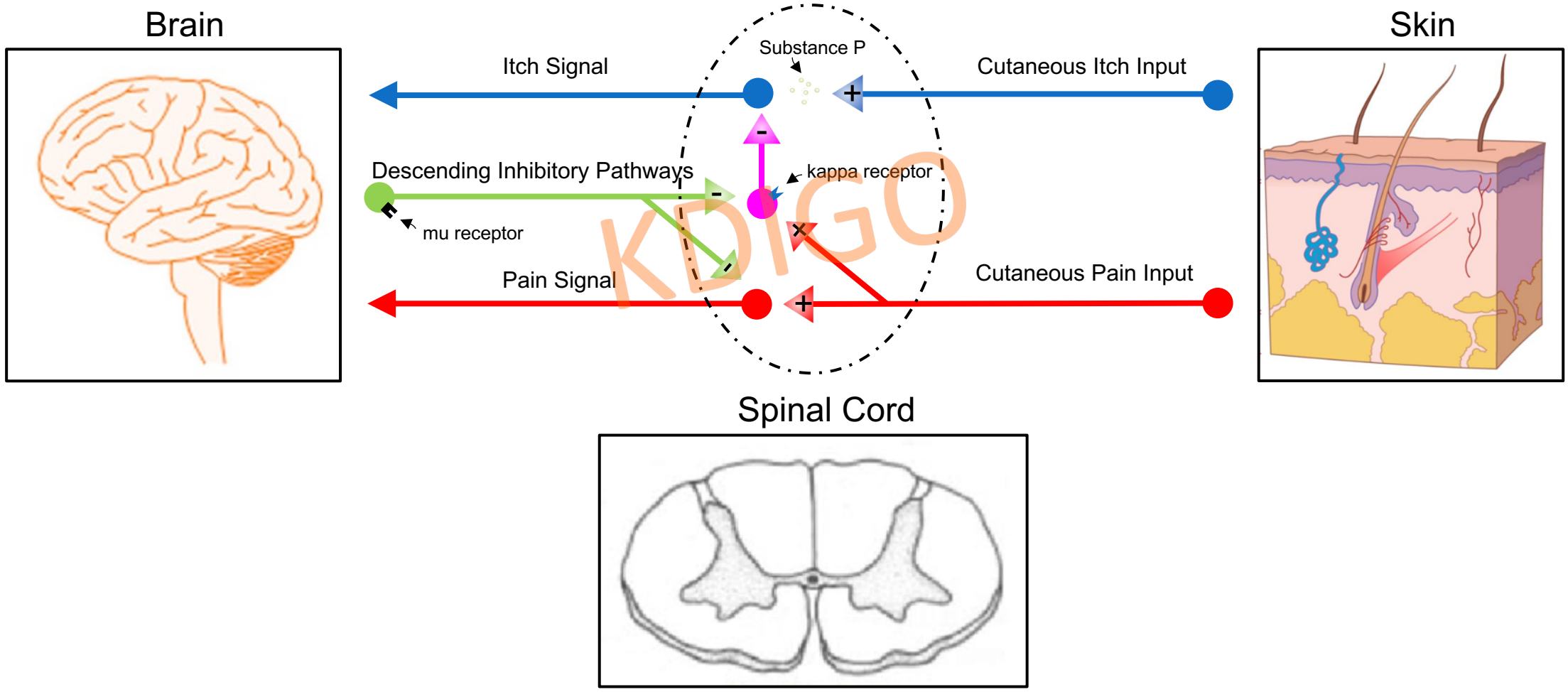
CKD-aP: Pathogenesis

Nociceptive sensory pathway alterations

- Symmetric pattern; “burning, tingling” description of pruritus
- Success with gabapentinoids

Opioid receptor dysfunction

- mu receptor agonists cause pruritus
- Success with opioid modulators in treating uremic pruritus


Brain
Skin
Substance P
Itch Signal
Cutaneous Itch Input
Descending Inhibitory Pathways
kappa receptor
mu receptor
Pain Signal
Cutaneous Pain Input
Spinal Cord
KDIGO

TREATMENT

AJKD

Original Investigation

Treatment of Uremic Pruritus: A Systematic Review

Elizabeth Simonsen, BSc,[1] Paul Komenda, MD, MHA,[1,2,3,4] Blake Lerner, BSc,[1] Nicole Askin, MLIS,[5] Clara Bohm, MD,[1,2,3] James Shaw, MD,[1,2] Navdeep Tangri, MD, PhD,[1,2,3,4] and Claudio Rigatto, MD, MSc[1,2,3,4]

AJKD 2017

TREATMENT REGIMENS EVALUATED

Systemic	Topical	Other
Gabapentin	Mast cell stabilizers	Acupuncture
Pregabalin	Emollients	Phototherapy
Mast cell stabilizers	Tacrolimus	Dialysis Modification
Montelukast	Capsaicin	
Nalfurafine	Sarna	
Naltrexone		
Primrose Oil		
Thalidomide		
Cholestyramine		
Ondansetron		

Study	Country	Design	Population	N	Pruritus Measurement Tool[a]	Treatment	Comparator
Gabapentin/Pregabalin							
Foroutan[60] (2017)	IR	Parallel arm	HD	90	0-10 VAS	Pregabalin	Doxepin
Amirkhanlou[21] (2016)	IR	Parallel arm	HD	52	5-point VRS	Gabapentin	Ketotifen
Nofal[41] (2016)	EG	Parallel arm	HD	54	10-cm VAS and 5-D pruritus scale	Gabapentin	Placebo
Yue[56] (2015)	CN	Parallel arm	HD	188	10-cm VAS + questionnaire	Pregabalin	Ondansetron or placebo
Solak[47] (2012)	TR	Crossover	HD	29[b]	10-cm VAS	Gabapentin	Pregabalin
Tol[50] (2010)	TR	Crossover	HD	14	10-cm VAS	Gabapentin	Placebo
Wu[59] (2010)	CN	Parallel arm	HD	41	0-10 VAS	Gabapentin	Standard treatment
Naini[38] (2007)	IR	Parallel arm	HD	34	10-cm VAS	Gabapentin	Placebo
Gunal[33] (2004)	TR	Crossover	HD	25	10-cm VAS	Gabapentin	Placebo

Simonsen, *AJKD* 2017.

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[30] (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[31] (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%)
Tof[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)

Simonsen, *AJKD* 2017.

Systematic Review: Conclusions

- With the exception of gabapentin, the current evidence for the available treatments of uremic pruritus is weak

- “Despite many published studies, the combination of flawed methodology, high risk of bias, small sample size, and study heterogeneity prevent generation of robust treatment guidelines”

- “High-quality studies are urgently needed to bridge this major gap between research output and identified patient priorities”

http://www.kidney-international.org meeting report

Executive summary of the KDIGO Controversies Conference on Supportive Care in Chronic Kidney Disease: developing a roadmap to improving quality care

Sara N. Davison[1], Adeera Levin[2], Alvin H. Moss[3], Vivekanand Jha[4,5], Edwina A. Brown[6], Frank Brennan[7], Fliss E.M. Murtagh[8], Saraladevi Naicker[9], Michael J. Germain[10], Donal J. O'Donoghue[11], Rachael L. Morton[12,13] and Gregorio T. Obrador[14]

"Current evidence **is sufficient** to support the development of clinical guidelines to aid in the stepwise approach to **uremic pruritus**, sleep disturbances, restless legs, pain, and depression in CKD"

GABAPENTINOIDS: ARE WE OVERPRESCRIBING?

Gabapentin and Pregabalin for Pain — Is Increased Prescribing a Cause for Concern?

Christopher W. Goodman, M.D., and Allan S. Brett, M.D.

Treatment of chronic noncancer pain during the opioid epidemic has become challeng- line options for pain related to osteoarthritis and low back pain. However, acetaminophen is often pentinoids for the treatment of postherpetic neuralgia (gabapentin and pregabalin), fibromyalgia

Drugs (2017) 77:403–426
DOI 10.1007/s40265-017-0700-x

SYSTEMATIC REVIEW

Abuse and Misuse of Pregabalin and Gabapentin

Kirk E. Evoy[1,2] · Megan D. Morrison[1] · Stephen R. Saklad[1]

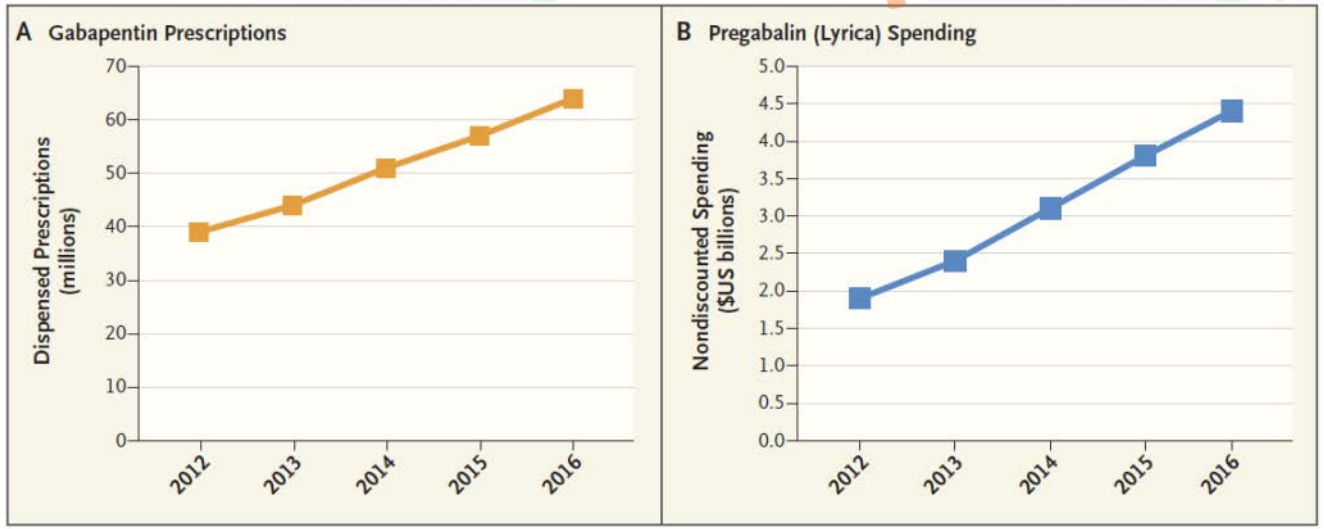
CBS NEWS NEWS SHOWS VIDEO CBSN MORE

CBS/AP / *April 2, 2018, 12:58 PM*

Doctors sound the alarm on "opioid alternative" gabapentin

NEW CONCERNS WITH GABAPENTINOIDS

- In setting of opioid crisis, doctors are looking for alternatives
- In 2016, gabapentin was the 10th most prescribed medication in the US
- 64 million prescriptions dispensed (up from 39 million in 2012)
- In 2016, pregabalin ranked 8th in drug spending in the US



Dispensed Prescriptions for Gabapentin and Nondiscounted Spending for Pregabalin, 2012–2016.

Data are from IMS Health.

Goodman, *NEJM* 2017.

INCREASED MISUSE AND ABUSE OF GABAPENTINOIDS

- Increasing numbers of patients are taking higher-than-recommended amounts to achieve euphoric highs
- 1.6% prevalence of gabapentinoid abuse in general population
- 3-68% prevalence of gabapentinoid abuse among opioid abusers
- Risk factors for abuse
  - Substance abuse (opioids), psychiatric comorbidities
- Gabapentinoids are increasingly being identified in post-mortem toxicology analyses

Gabapentin and Pregabalin Use and Association with Adverse Outcomes among Hemodialysis Patients

METHODS

National cohort study of US hemodialysis patients n=140,899

USRDS
UNITED STATES RENAL DATA SYSTEM

19% and 4% used gabapentin and pregabalin, respectively, in 2011

OUTCOME: Adjusted Hazard Ratio (95% CI)

Dose*	Altered mental status	Fall	Fracture
Gabapentin			
>0-100 mg	1.10 (0.97-1.24)	1.26 (1.07-1.48)	1.04 (0.82-1.32)
>100-200 mg	1.31 (1.17-1.46)	1.35 (1.15-1.57)	1.20 (0.96-1.49)
>200-300 mg	1.41 (1.30-1.54)	1.30 (1.14-1.48)	1.08 (0.89-1.31)
>300 mg	1.50 (1.39-1.63)	1.55 (1.39-1.72)	1.38 (1.18-1.61)
Pregabalin			
>0-100 mg	1.51 (1.32-1.74)	1.24 (1.00-1.54)	1.20 (0.87-1.66)
>100 mg	1.46 (1.24-1.71)	1.68 (1.36-2.08)	1.38 (1.00-1.92)

*Compared to reference of no use.

CONCLUSION Gabapentin and pregabalin should be used judiciously in patients on hemodialysis, and research to identify the most optimal dosing is warranted.

doi: 10.1681/ASN.2018010096

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

GABAPENTIN/PREGABALIN: RECOMMENDATIONS

- Caution patients about risks of gabapentinoids; perhaps avoid in very frail patients at high risk of falls
- Important to dose gabapentinoids appropriately for renal function
- Caution patients about risks of using gabapentin in ways other than prescribed
  - Many patients taking “prn”
- Be cautious about prescribing to patients at high risk for abuse and/or who are prescribed opiates or benzodiazepines

GABAPENTINOIDS: DOSING IN RENAL FAILURE

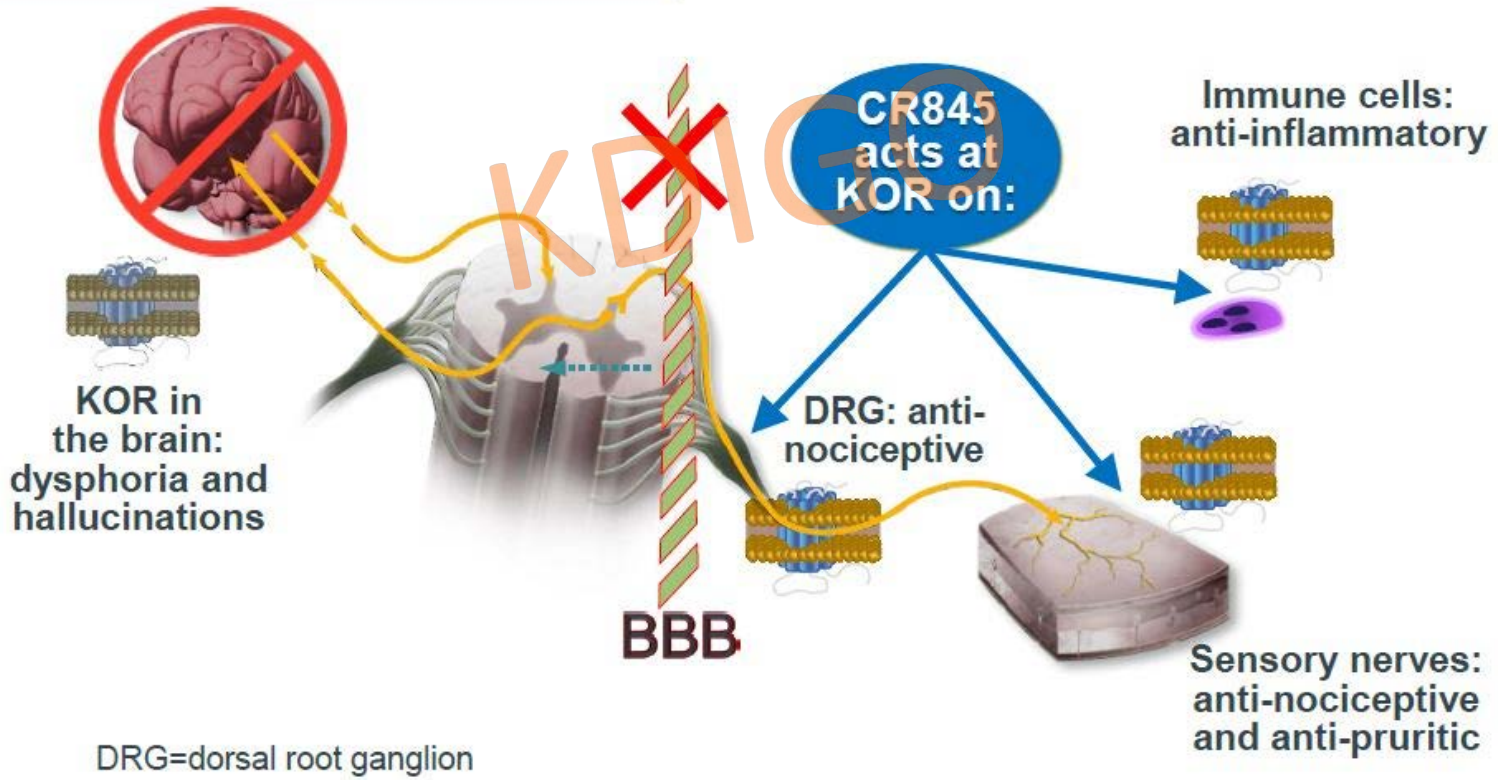
Gabapentin	100-300 mg PO thrice weekly after HD; 100-300 mg PO qHS in PD†; 100 mg PO every other night to 300 mg PO qHS in CKD5-CKM
Pregabalin	25-75 mg PO thrice weekly after HD; 25-75 mg PO qHS in PD†; 25 mg every other night to 75 mg qHS in CKD5-CKM

Emerging Treatment Options for CKD-aP

Treatment	Current Status	Efficacy	Most Common AEs
Nalfurafine Selective κ-opioid receptor agonist[1]	Approved in Japan and Korea for the improvement of pruritus in hemodialysis patients	Significant decreases in VAS scores with oral nalfurafine vs placebo administered for 14 days[2]	Insomnia, constipation, somnolence, dizziness, and nausea
Difelikefalin Selective, peripherally restricted, κ-opioid receptor agonist[3]	Phase III for use in moderate to severe pruritus in patients undergoing hemodialysis	Significant reductions in itch intensity and improvements in QOL with difelikefalin IV vs placebo for 12 weeks	Diarrhea, dizziness, and nausea

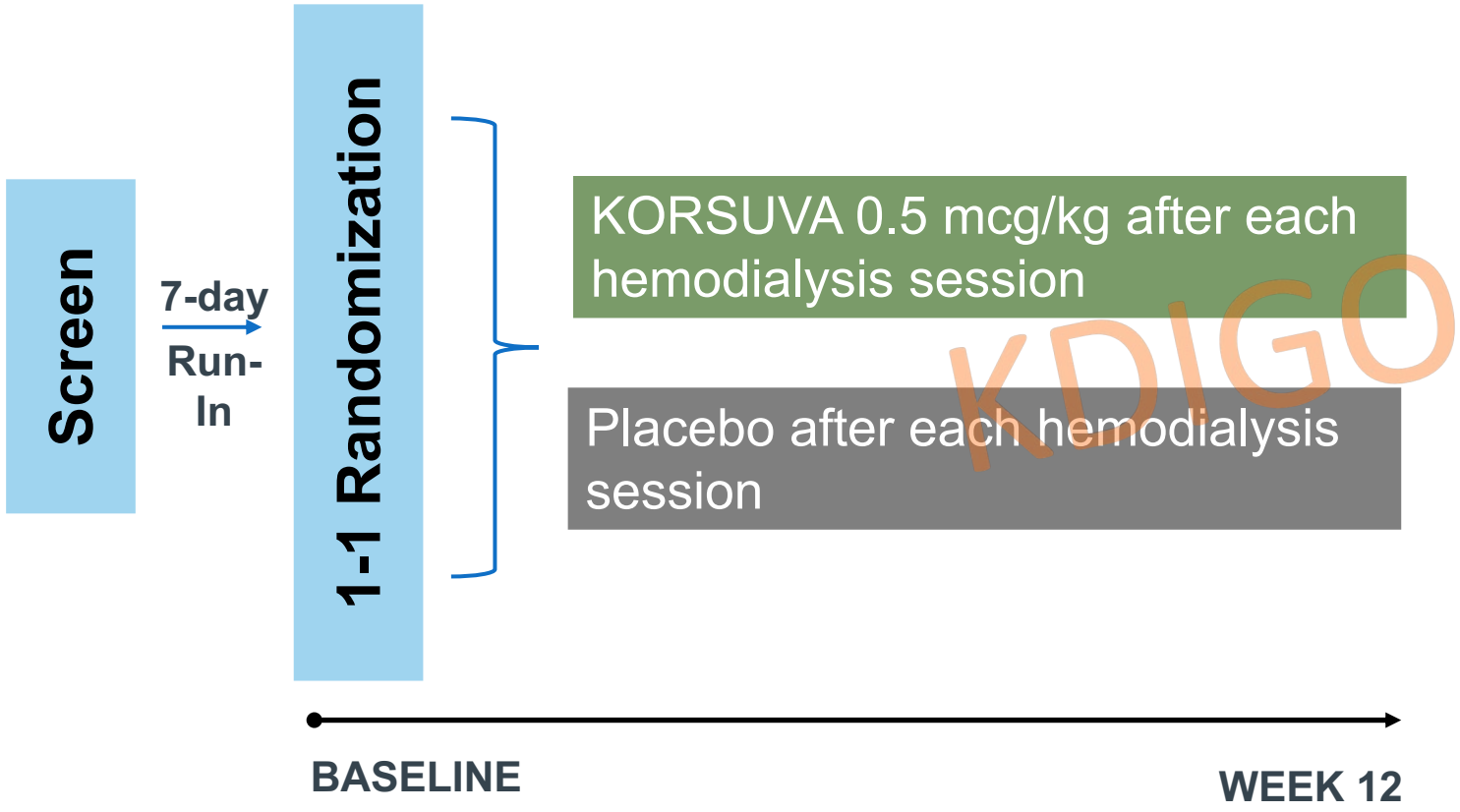
CR845 Effects Mediated by Peripheral κ-Opioid Receptors

Novel Chemical Class – "hydrophilic" tetrapeptide



DRG=dorsal root ganglion

Phase 3 Study Design



52 Week Open-Label Extension Ongoing

Endpoints: Week 12

Primary

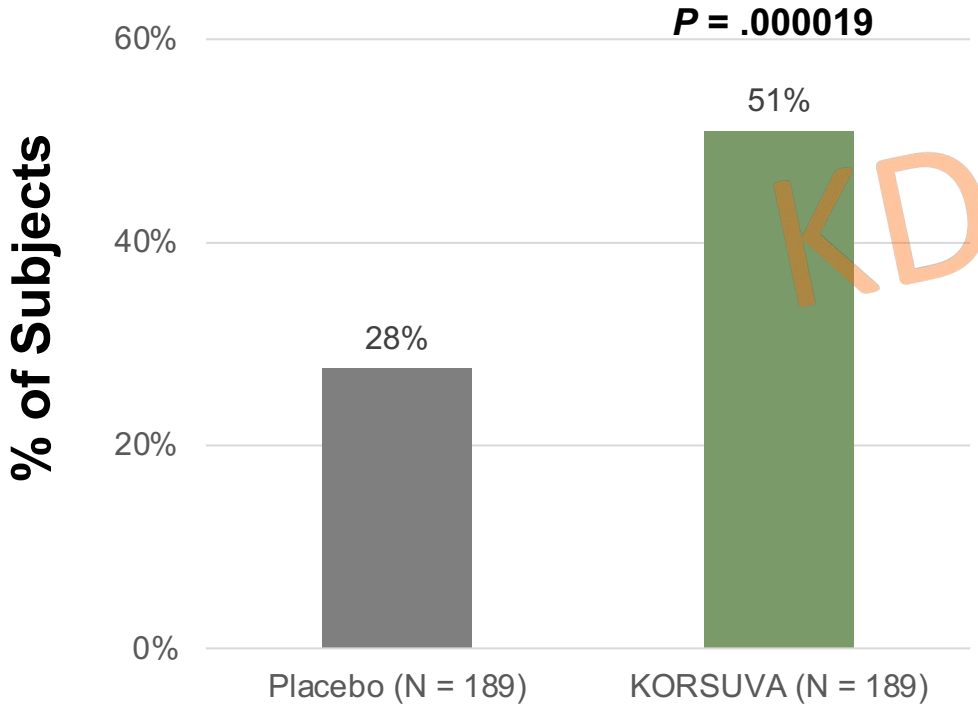
- Proportion of subjects achieving ≥3 point improvement from baseline in weekly mean of daily worst itching intensity NRS (WI-NRS)

Secondary

- Proportion of subjects achieving ≥4 point improvement from baseline in weekly mean of daily WI-NRS
- Change from baseline in itch-related Quality of Life as measured by 5-D Itch and Skindex-10 questionnaires

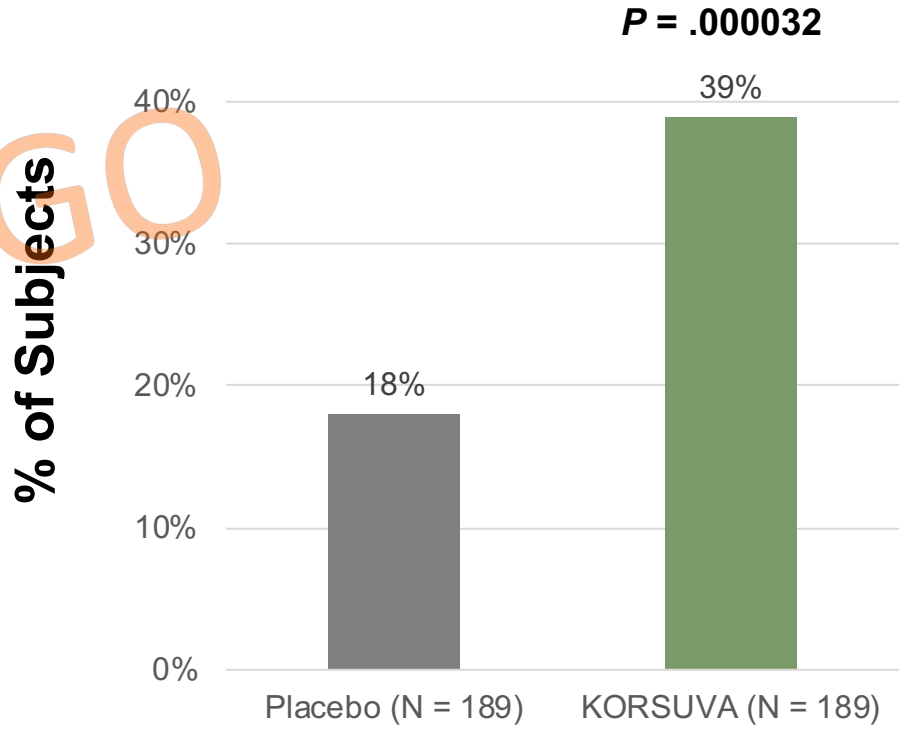
IMPROVEMENT IN WORST ITCH-NRS (WEEK 12)

- **KORSUVA subjects >2.5 times more likely to experience ≥3-point improvement**



Primary Endpoint
Odds Ratio: 2.72

KORSUVA subjects ~3 times more likely to experience ≥4-point improvement



Odds Ratio: 2.9

Estimated percentages & P-values based on a logistic regression model with terms for treatment group, baseline WI-NRS score, and strata.
Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption.

SUMMARY OF SAFETY

Treatment-emergent Adverse Events	Placebo N = 188 n (%)	KORSUVA N = 189 n (%)
Subjects with at least one treatment-emergent adverse event	117 (62)	130 (69)
Subjects with at least one serious treatment-emergent adverse event	41 (22)	49 (26)
Deaths	2 (1)	2 (1)
Non-fatal SAEs	39 (21)	47 (25)
Treatment-emergent adverse events resulting in discontinuation	9 (4.8)	14 (7.4)

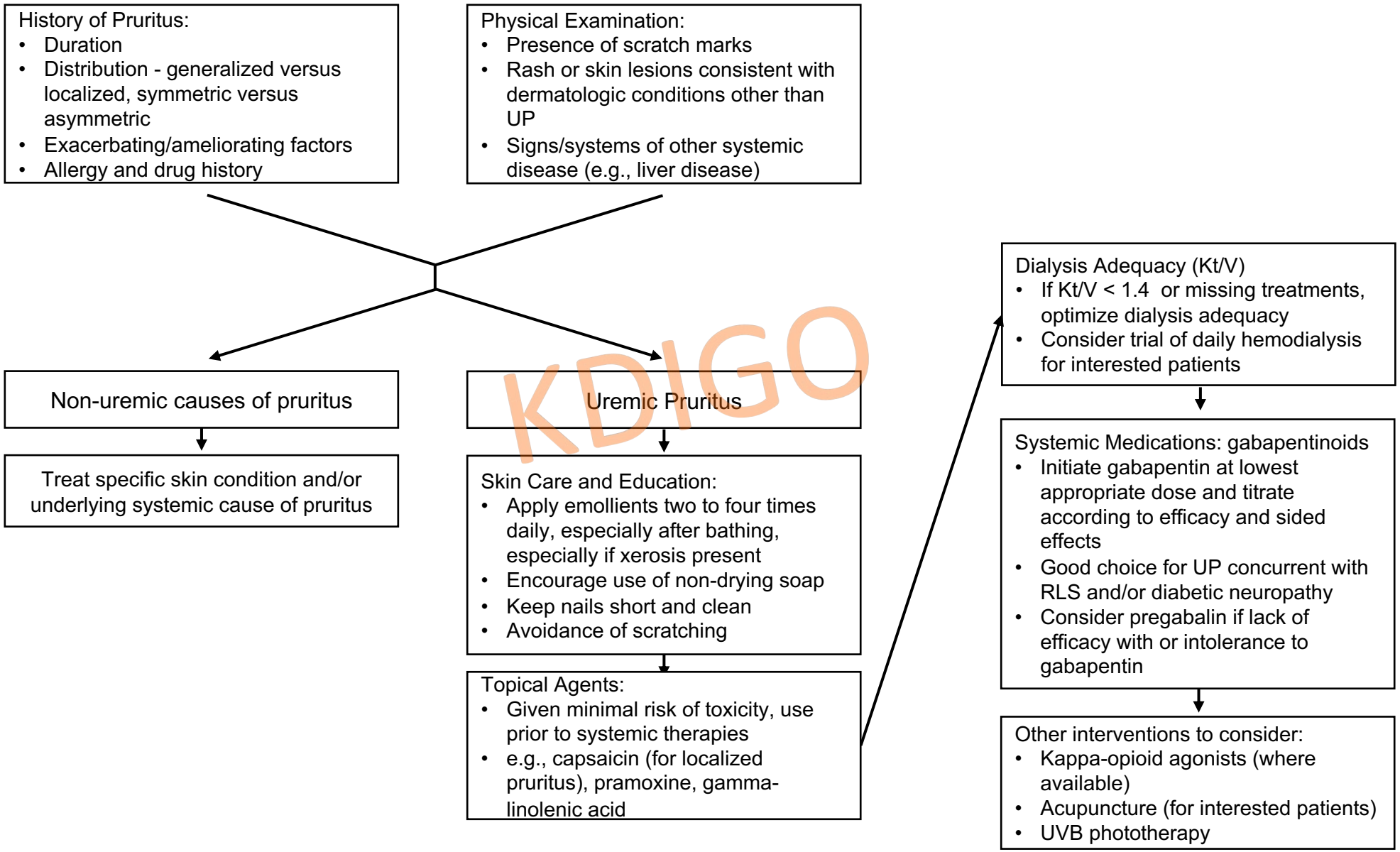
Most common AEs (≥ 5%) included diarrhea, dizziness, vomiting, nasopharyngitis

Case: Mr. Martinez

- Mr. Martinez is a 49-year-old man with ESRD on in-center HD for 9 years. He finds you in nephrology clinic one day and tells you he's in crisis because he can't stop itching. He's driving his wife crazy because he can't sleep and is constantly scratching himself. The itching is so bad that he is unable to sit through an entire 4-hour dialysis session.

- He looks at you with a serious face and tells you that things are so bad that he is considering "giving up."

- What is your approach to this patient?


History of Pruritus:
• Duration
• Distribution - generalized versus localized, symmetric versus asymmetric
• Exacerbating/ameliorating factors
• Allergy and drug history
Physical Examination:
• Presence of scratch marks
• Rash or skin lesions consistent with dermatologic conditions other than UP
• Signs/systems of other systemic disease (e.g., liver disease)
Non-uremic causes of pruritus
Treat specific skin condition and/or underlying systemic cause of pruritus
Uremic Pruritus
Skin Care and Education:
• Apply emollients two to four times daily, especially after bathing, especially if xerosis present
• Encourage use of non-drying soap
• Keep nails short and clean
• Avoidance of scratching
Topical Agents:
• Given minimal risk of toxicity, use prior to systemic therapies
• e.g., capsaicin (for localized pruritus), pramoxine, gamma-linolenic acid
Dialysis Adequacy (Kt/V)
• If Kt/V < 1.4 or missing treatments, optimize dialysis adequacy
• Consider trial of daily hemodialysis for interested patients
Systemic Medications: gabapentinoids
• Initiate gabapentin at lowest appropriate dose and titrate according to efficacy and sided effects
• Good choice for UP concurrent with RLS and/or diabetic neuropathy
• Consider pregabalin if lack of efficacy with or intolerance to gabapentin
Other interventions to consider:
• Kappa-opioid agonists (where available)
• Acupuncture (for interested patients)
• UVB phototherapy
KDIGO

CONCLUSIONS

- CKD-aP is common; prevalence may be slowly decreasing over time
- Symptom severity varies by country
- Generally under-recognized and under-treated
- Some of the most used treatments lack data and are not recommended (i.e., anti-histamines)
- Gabapentin (+/- pregabalin) has the best evidence for efficacy
- Increased concern regarding abuse or misuse of gabapentinoids
- Gabapentinoid use in ESRD associated with increased hazard for AMS, falls, and fracture; the risk appears to dose-dependent
- Phase II/III trials of opioid modulators appear promising

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