Kidney Disease-Associated Pruritus
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Mark Lebwohl, MD, FAAD, Sara Combs, MD, FAAD, and J. Pedro Teixeira, MD, FAAD
Interviewed by Steven Chen, MD, FAAD

STEVEN CHEN, MD, FAAD: Welcome, everyone, back to another episode of *Dialogues in Dermatology*. Today, we're going to be talking about kidney-related pruritus, or itch. I am joined by three wonderful guests today and before I introduce them, just to mention, my name is Steven Chen. I am a dermatologist and an internist and I am so thrilled to talk about this, because this is such a common problem, either when I'm attending on medicine or on dermatology.—

--Today, our guests are Dr. Mark Lebwohl, who really does not need an introduction for the dermatology crowd, but I am going to give one anyway. He is a Professor of Dermatology and Dean for Clinical Therapeutics at the Icahn School of Medicine at Mount Sinai in New York and, of course, a former President of the American Academy of Dermatology. In addition to Dr. Lebwohl, I am also joined by Dr. Sara Combs, who is an Assistant Professor of Medicine and a practicing nephrologist and palliative care physician at the University of New Mexico.—

--And finally, joined by Dr. Pedro Teixeira, who is also an Assistant Professor of Medicine and a practicing nephrologist and critical care physician at the University of New Mexico. So first of all, welcome to all of you. Thank you so much for being here. I'm really excited to talk about this with all of you.

SARA COMBS, MD, FAAD: Thanks for having us.

MARK LEBWOHL, MD, FAAD: Delighted to be here.

STEVEN CHEN, MD, FAAD: Great. I'm going to jump right in with questions, just because I feel like I've got a lot to ask and I know that I am with three wonderful experts, so I don't want to

waste any time. The first thing I really want to know about, and maybe if it's okay, I'll direct this question to Dr. Teixeira. As a practicing nephrologist, I really think a lot about the things that cross over between the kidney and the skin, and obviously itch or pruritus is one of those things. But how big of a problem is this actually? How much should we be thinking about this in terms of population, in terms of epidemiology? How prevalent is this issue?

PEDRO TEIXEIRA, MD, FAAD: That's a great question, Dr. Chen. It's common. And importantly, it's more common than most nephrologists appreciate. The best data on the issue of the epidemiology of CKD-associated pruritus comes from a large study that nephrologists are likely familiar with but dermatologists might not be. It's called the DOPPS study, or the Dialysis Outcomes and Practice Patterns Study. It's a large, multinational observational cohort, with over 50,000 patients that was started actually back in the '90s, and so they've been tracking data on this topic since then.—

--Over 35,000 patients that have provided specifically information about pruritus. And in the most recent phase of this trial, phase 5 that was completed in 2015, they estimated about 35 to 40 percent or so of patients, by their metric, moderate to extreme pruritus. Any pruritus, even mild pruritus, the incidence goes up to about 70 percent. So most patients have at least some and a substantial minority have substantial pruritus.—

--In other studies, too, that are much smaller in size, reported similar incidence in the endstage kidney disease population, about 40 percent roughly speaking. And like I indicated, it's under-recognized. So a good three-quarters or so of the dialysis unit directors that were surveyed in this study underestimated the incidence of pruritus in their own patients. And so there's a substantial number of these patients that don't get any treatment whatsoever, in spite of having moderate to extreme pruritus.—

--These data from DOPPS that I mentioned are for hemodialysis patients. There's fewer data on peritoneal dialysis but it's about the same. Importantly, too, in terms of the significance of this condition is the impact on quality of life. Consistently, in study after study on the topic of CKD-associated pruritus, and certainly the dermatology crowd will probably be better aware of this than our nephrology crowd, but pruritus has a tremendous impact on quality of life. Multiple studies have shown that CKD-associated pruritus is associated with decreased both physical and mental quality of life, increased rates of depression, and of course has a tremendous impact on sleep.—

--There's actually really interesting data, too, implying that CKD-associated pruritus in endstage kidney patients may be an independent risk factor for mortality even, which is kind of somewhat mind-blowing. Of course. Those are observational data but nonetheless, I think the impact is significant.

STEVEN CHEN, MD, FAAD: That's terribly for our dialysis patients and our endstage renal disease patients but that's a wonderful summary of the issue that's at large. If I can direct my next question to Dr. Combs, and obviously everyone should feel free to jump in, when I was taught about the issue of itch in our CKD patients, I often was told it's uremic pruritus, that it's all from uremia and it's all our endstage renal disease patients, which we've kind of touched on. Should I be thinking about this more in anyone with CKD, like early stage CKD? Should I be thinking about this only in those that are on dialysis? How broad of a risk group are we talking about here?

SARA COMBS, MD, FAAD: That's a great question, because I learned the same thing, too, in residency and in fellowship, to be honest with you. We have some pretty good quality data from something called CK-DOPPS, which is similar but just CKD patients not on dialysis, that suggests that about 25 percent of patients, CKD, are experiencing symptoms of pruritus. So I

think it's fair to say that even in our non-endstage kidney disease patients, we should certainly be thinking about this as something that burdens them.

MARK LEBWOHL, MD, FAAD: If I can ask Dr. Teixeira and Dr. Combs, how low a creatinine or how low a GFR is associated with pruritus? Because that's a question that has occurred to me as I see patients who I know have chronic kidney disease but their creatinines aren't that high.

SARA COMBS, MD, FAAD: I guess I would say that typically, the study data that's looked at the prevalence of pruritus in people with CKD, usually they stop looking at CKD stage 3. So usually, I think about it in our patients with CKD stage 3 and worse kidney function, so thinking about that GFR calculator rather than actual creatinine numbers. But I think it's possible that even people with better kidney function than that may have the symptom, it's just something that may not be very well studied.

MARK LEBWOHL, MD, FAAD: So what GFR is that about?

PEDRO TEIXEIRA, MD, FAAD: That would be stage 3 CKD is estimated GFR of 30 to 60, stage 4 is less than 30, and stage 5 is less than 15 or any dialysis requirement. I will say this is an interesting question. The caveat I would say to the question of kind of non-dialysis-associated CKD and pruritus is the treatment, I think we'll talk about treatment soon, the data or the treatments available for CKD-associated pruritus isn't tremendous, we don't have a ton of it.—

--But most of it is on the dialysis population, so I think like any condition, the less severe the disease is to some degree, the risk/benefit of treatments may be murkier, and I think it applies in this case, too, also because the data for how to address it in less severe forms of kidney failure aren't as strong.

SARA COMBS, MD, FAAD: If I may add one thing, is when they're thinking about prevalence in CKD patients, as I'm sure we'll discuss, but CKD-associated pruritus is a diagnosis of exclusion, so most people have done their due diligence to rule out other causes. That's not to say that something else may also be causing pruritus and we see it in these patients with CKD.

STEVEN CHEN, MD, FAAD: That's great foreshadowing for a question that I'm going to lob at Dr. Lebwohl in just a little bit. I think just to pause and just emphasize the point that you made, as a great reminder for myself as well, is that we can't anchor ourselves on just looking at a patient's creatinine. We really have to look at their glomerular filtration rate, their GFR, because we know creatinine changes so much just based on the patient's body habitus, their age, there are so many other factors that relate to that, that we have to take into account. It's not as simple as a greater or less than 1.0 or something as simple as that.—

--We've kind of talked around it, but one thing that I think is at least on my mind, if not on our listeners' mind, is the mechanism. What is the mechanism of CKD-related pruritus or itch? And I know this is a very complicated topic, so in no way am I expecting to have like the only mechanism defined, but at least a nice conversation would be great. Maybe, if it's okay, Dr. Teixeira and Dr. Combs, if you could start us off and then I would love, Dr. Lebwohl, if you don't mind sharing how it might differ from a typical pruritus patient that we think about, mechanistically speaking?

PEDRO TEIXEIRA, MD, FAAD: I would probably start by trying to emphasize what we don't think is playing a major role, at least in 2021, and this has undergone some evolution. So first, as some of the dermatology listeners may know better than certainly your average nephrologist, there are different types of itch nerve fibers. These are similar to pain fibers, pain and itch are related and they modulate each other, but they're not the same thing, of course. But these unmyelinated-type fibers that mediate itch, there's two major categories.—

--There's histaminergic fibers and then kind of a broad category, what's been described as polymodal, or maybe more relevantly non-histaminergic fibers. And these polymodal fibers use a variety of neurotransmitters to conduct their signals, including for example substance P, which is a commonly studied one, but it's not histamine. That latter category of non-histaminergic polymodal fibers are thought to be the primary mediators of uremic itch or CKD-associated itch, rather than the histamine fibers. And, of course, that has important implications for therapy.—

--The other kind of old school thought about CKD-associated pruritus is that it relates to hyperparathyroidism and hyperphosphatemia and what nephrologists call mineral bone disease in kidney disease. And there's definitely some studies, some correlations that could be found. But the highest quality data, which again comes from that DOPPS study, do not actually show an independent relationship, an independent correlation between hyperphosphatemia or, for example, hyperparathyroidism and itch.—

--And so I think an emerging idea is that those are probably not the primary mediators of itch in most patients, even though one of the most commonly held beliefs by nephrologists, I don't know about the dermatology world, but by nephrologists. And so setting those two kind of things aside, three different types of theories or mechanisms have been implicated recently, and all of these have some degree of potential treatment implications. So first and foremost, probably the one that we have the least treatment for right now is the inflammatory kind of component of CKD-associated pruritus.—

--Again from the DOPPS study, one of the things that did predict intensity of pruritus in that large cohort, was CRP levels. In addition, a kind of correlative of that was low albumin is associated with an increased risk, independently associated increased risk of pruritus, as well. In the nephrology realm, hypoalbuminemia is a profound global prognostic indicator, patients with low albumin just do poorly and die more, to be blunt. And it's thought that part of that is part

of this kind of malnutrition, inflammation kind of complex or syndrome that's typical of patients with endstage kidney disease.—

--There's also an interesting phenomenon that patients who have kidney disease after transplant, in other words they get a kidney transplant and then they redevelop some degree of chronic kidney disease, which is pretty common, for a given level of kidney dysfunction post transplant, those patients tend to have less severity of pruritus and it's probably because their anti-rejection medications are somewhat addressing maybe this inflammatory component of pruritus.—

--There's some interesting case reports, very minimal data to be honest, but some interesting case reports and case series about using inflammatory modulators that the dermatologists would be more familiar with, for example, I have to look at the name because we definitely don't prescribe these in nephrology, but dupilumab.—

STEVEN CHEN, MD, FAAD: That's in every dermatologist's back pocket.

PEDRO TEIXEIRA, MD, FAAD: --It's interesting. Again, case report level data, still very kind of exploratory stuff, but interestingly that's an IL-4 modulator of some sort. For example, I believe there's some case reports of using that for refractory pruritus. The second kind of newer concept is the idea that CKD-associated pruritus may be more of like a neuropathic process. There's some really interesting old data from decades ago, looking at immunohistochemistry of patients with endstage kidney disease.—

--And they show that the ones that develop pruritus have an abnormal distribution of these neurofibers and that they actually distribute to the epidermis. My understanding is that in normal skin, these neurofibers kind of terminate in the dermis rather than the epidermis. So there's some abnormal architecture of these nerve fibers. And then probably most compellingly, in

terms of this neuropathic mechanism, is the fact that the most effective drugs that we have, at least readily available today, our treatment options may be changing, but the most effective drugs that have been shown to have consistent benefit are indeed GABAergic agents, like gabapentin and pregabalin.—

--And so that certainly supports it. Other studies have shown interesting correlations between actual neuropathy symptoms or even EMG nerve conduction studies defined neuropathy, correlations between that and pruritus, as well, which supports that mechanism. And then finally, probably the newest kid on the block mechanistically would be the opioid receptor system and an imbalance in opioid receptors. It's been known for a long, long time that mu opioid receptor agonists, so these are your generic opioids like morphine, tend to aggravate pruritus and that can cause pruritus as a side effect or worsen it in patients who already have pruritus.—

--More recently, it's been appreciated that kappa opioid agonists can mitigate pruritus, have an opposite effect. And it's thought that there may be an imbalance in some patients between these kind of two opioid receptor systems that could be contributing. Some newer data, actually I think this is just the past year, showed that kappa opioid receptor expression in the skin of patients with CKD-associated pruritus is decreased, which would kind of fit with that theory, as well.—

--Indeed, as we'll talk about later, there's some newer agents, newer drugs on the block have been showing promise for treatment, as well, that again kind of proof is in the pudding, showing that this mechanism may be something we can target for therapy, as well.

STEVEN CHEN, MD, FAAD: Great, thank you for that. Dr. Lebwohl, I'm curious first of all if you have anything to add to what Dr. Teixeira just shared about mechanism?

MARK LEBWOHL, MD, FAAD: If you go back about 40 years now, Barbara Gilchrist showed in an incredibly impressive study that broadband UVB treatments, and there's about 30 treatments, given 2 or 3 times a week, dramatically improved uremic pruritus. And specifically, if you treated half the body, both sides got better. That led to a theory that there is a circulating itch factor that might be responsible for uremic pruritus and that light inactivates that itch factor.—

--Move forward 30 years and no one has broadband anymore. We actually saved a unit, so we actually have it. We still use it for uremic pruritus, it always works. Narrowband UVB almost doesn't work at all. So all of us now have narrowband. And I remember hearing colleagues say, "Phototherapy doesn't work." Well, that's because you're using narrowband, narrowband doesn't work. So there must be something about the other wavelengths of light in broadband UVB that treat whatever that itch factor is.—

--Then go forward a few more years and we discover that there is an itch cytokine called IL-31. And then a couple years go forward, and we find that IL-31 is increased in patients with uremic pruritus. But the disappointment which is coming is that nemolizumab, which is an anti-IL-31 cytokine, did not work for uremic pruritus. So that theory sounded great, until the nemolizumab study was published.—

--The story about the mu and kappa opioid receptors is clearly substantiated by the observation that difelikefalin works in uremic pruritus and that study was published in the *New England Journal of Medicine*. And until now, short of broadband UVB, which almost nobody has anymore, we really need a drug for uremic pruritus and this looks like it's going to be it.

STEVEN CHEN, MD, FAAD: Can I ask, just kind of going down that path a little bit, Dr. Lebwohl, if someone comes in to you with pruritus and they have CKD, and we've talked about

the need to rule out other causes of pruritus, do you mind just briefly taking me through your approach to that patient? What do you rule out? What do you try first? What do you reach for?

MARK LEBWOHL, MD, FAAD: So the causes of pruritus are so numerous that we have an organized approach. I'm going to tell you right now, as Dr. Combs said, it's a diagnosis of exclusion. Our diagnoses of causes of pruritus are also diagnoses of exclusion. In fact, when you go through the whole algorithm, you end up with usually it's an elderly patient, we call it pruritus of the elderly, or what was called Willan's pruritus. And that is I call it a wastebasket diagnosis because when everything else is thrown away, that's what you're left with.—

--So one of the early things is uremic pruritus. And basically, if I see that a patient's GFR is reduced, then I will assume that that is the diagnosis, and I usually will treat them. Now, you want to exclude other things like scabies. And let me tell you, scabies can last years. And warn all my colleagues out there, I've been approached a couple of times in my career to testify against dermatologists, which I did not do, because they missed the diagnosis of scabies, which frankly is really easy to miss.—

--And despite all those know-it-alls who say, "Oh, it's so obvious. You get little burrows between the fingers, the distribution," they're full of it. It is not an easy diagnosis. And we often will simply do a trial of either permethrin or ivermectin. And if that doesn't work, then we assume that it's not scabies. Along the way, many other things. There are liver causes of itching, so we always do get bloods. By the way, one of the number one causes is medications.—

--So, for example, published is calcium channel blockers. In my experience, it's hardly ever the cause. Published much more is ACE inhibitors. And basically, if somebody is on a drug that ends in "pril," that's an ACE inhibitor: enalapril, lisinopril, captopril. And switching them to an ARB is an easy switch. But ACE inhibitors are kininogen ACE blockers, so they increase kinins. So they actually make every cause of itch worse.—

--Now, if somebody is on an ACE inhibitor, we'll switch them, that's the first thing we do. Then we go through our algorithm, which includes scabies. It also includes bullous pemphigoid in elderly patients. And there's an outbreak of bullous pemphigoid because of peptidyl dipeptidase inhibitors. Drugs that end in "gliptin" are very common causes of bullous pemphigoid. And the funny thing about it is that most of them don't have bullae, at least early in the course, they just itch.—

--So we'll look at their drug list, which is very important. If the drug list doesn't substantiate that, we often will then look for either serologic or immune deposition evidence in the skin by immunofluorescence of bullous pemphigoid. So with the skin biopsy, we usually do two. If there is a bullae, we certainly will biopsy that but often there isn't. So we'll do a skin biopsy for immunofluorescence. And we often will even do a BP180 and 230, just to see if there's any evidence of bullous pemphigoid.—

--Now again, when the patient has a reduced GFR, I don't even go that far. I usually will simply treat them for uremic pruritus. And right now, the treatment is broadband UVB, which by the way can make bullous pemphigoid worse. So you want to make sure they don't have bullous pemphigoid. But most of the time when they have a reduced GFR, it is uremic pruritus.

STEVEN CHEN, MD, FAAD: That's so helpful to hear. You're right, I don't think about reaching for broadband, I think about narrowband because that's just what everyone has, that's so helpful to know. And you heard it here first, "pril" and "gliptin," you need to be on the lookout for those drugs. Dr. Combs, can I ask you from a nephrologist point of view, what do you feel, and I don't want to put you on the spot and make you speak for all nephrologists everywhere but I am going to, what do you feel like is low hanging fruit that nephrologists should be doing for their patients who are itchy, before they get referred to dermatology?—

--Meaning, what do you think could be done before the dermatologists, like Dr. Lebwohl or myself or anyone else who is listening from dermatology, before they get to our door, what are the things that you hope your colleagues would do?

SARA COMBS, MD, FAAD: There's a couple things. So first is just to keep in mind is that most of us who are treating endstage kidney disease patients who are on hemodialysis, which is the majority of folks who are getting some modality of dialysis with endstage kidney disease, we're usually seeing our patients at chairside in the dialysis unit. And so our dermatologic exam probably is a bit cursory. And many of our patients are not excited to stay after and go into an exam room for an examination.—

--So I guess I would say low hanging fruit is that particularly us, living in the southwest, is that all of our patients have very dry skin. And so xerosis is even more common in patients with CKD. So I usually start with education about avoiding drying skins, avoiding drying lotions, making sure folks are trimming their nails. And then aggressive emollient use, like three or four times a day. And then after that, I think making sure that there's particularly the infestation issue is ruled out.—

--I trained in Denver, there is a huge problem with bedbugs, so you're talking about scabies, bedbugs, there is a huge problem, which is also an enormous pain and drop in cash dollars to get rid of. And so those are the two sort of low hanging fruits that I try to help rule out, before moving onto the next things.

MARK LEBWOHL, MD, FAAD: I do want to say that the things that were described, like scabies, bedbugs, atopic dermatitis we didn't mention, they all have skin lesions. So you can make the diagnosis from the appearance of the skin lesions. Where it becomes tricky is a patient who doesn't have primary skin lesions, just excoriations. And there are things we haven't even spoken about. There's actually a wonderful review in the *British Journal of Dermatology*,

the British Association of Dermatologists published a very long article, with many very useful tables.—

--And part of their workup, for example, would be a chest x-ray. So I'm going to just say again, if a patient tells me that they have fever and weight loss, I'm going to worry about a lymphoma causing itch. But if the patient comes in and I'm looking for a cause of itching and I stumble upon a reduced GFR, that is going to be my working diagnosis.

STEVEN CHEN, MD, FAAD: And we talked about it earlier, and I'll just pose this to all of you, where do GABAergics and those other kind of modalities fall in our treatment algorithm? It sounds like something that I've learned already is broadband UVB is such a helpful treatment for this, but let's assume that I can't get broadband UVB because I can't find a center that offers that modality of phototherapy. What are the other things we should reach for? In my back pocket, it's always gabapentin is kind of a, I don't want to say no-brainer, but just more and more, as we see more and more itch, where we just kind of try to treat the nervous system, as opposed to any circulating itch factor. That's always been on the tip of my tongue in terms of something to suggest. What else should we be thinking about?

SARA COMBS, MD, FAAD: Well, I'll just say that I agree with what you're saying, Dr. Chen, gabapentinoids would be, if I'm thinking about pharmacologic therapy, the first thing that I would definitely pull out of my pocket, particularly given that it can treat many other symptoms that patients with CKD or endstage kidney disease suffer from, like restless leg syndrome or neuropathic pain. So I'm always a huge fan of trying to hit many birds with one stone when prescribing a medication particularly that there might be concerns about side effects.—

--I don't think that we have access to broadband phototherapy here and so it's not something that I've ever been able to prescribe. And sometimes because the risks are so low, if a patient is interested, I'll talk to them about using acupuncture therapy, which there's conflicting data about

but it's certainly going to cause very little harm. But those are sort of the first steps of what I'll try.

MARK LEBWOHL, MD, FAAD: So I will say broadband UVB, which we use now because we don't have a lot of options. I'd love to hear your experience with gabapentin but mine hasn't been great. The broadband UVB, think about it, a patient is being dialyzed several times a week and now you're adding two or three more visits to the hospital. It's murder on them. You have to think about that. It's not an easy treatment, which is why I'm excited about the prospect of us getting a new drug that actually works and doesn't have to involve the patient coming back multiple times a week for months.

STEVEN CHEN, MD, FAAD: You bring up a good point. I reach for gabapentin often but it's never been the magic bullet that takes away the itch completely. It's always just that usually what my patients tell me is that maybe it takes the edge off of the itch and it makes it a little bit more bearable, but it's never been one to completely take it away. Can I just, for the sake of putting it out there, antihistamines, is there a role for antihistamines in the treatment of CKD-related pruritus?

MARK LEBWOHL, MD, FAAD: Amen, no.

STEVEN CHEN, MD, FAAD: Alright, great, perfect. The reason I want to just put it out there is because I see so many people reach for those, for any kind of pruritus. And I feel like I'm always teaching my residents, you have to think about the mechanism. If it's not histamine-related, it doesn't make sense to reach for an antihistamine. So alright, you heard it here. Everyone agrees, antihistamines maybe not as helpful. And then before we talk about the new stuff, one thing that we always think about is repurposing medications, and Dr. Teixeira mentioned dupilumab as a potential option. Dr. Lebwohl, what do you think about dupilumab for the treatment of this?

MARK LEBWOHL, MD, FAAD: So we have used dupilumab for many causes of itch. We've published its use for pruritus of the elderly. We know that it's been used for, of course it's approved for atopic dermatitis, but it's used in severe hand dermatitis. It's used in nummular dermatitis. There are many itchy conditions that respond to it. I am not aware that uremic pruritus responds to it. By the way, even bullous pemphigoid, there are many reports of it responding to dupilumab.

STEVEN CHEN, MD, FAAD: Yeah, dupilumab, actually this is a personal aside, that's actually one of my favorite treatment modalities for checkpoint inhibitor-induced pruritus and bullous pemphigoid, which is a whole other episode. So we've talked around it a lot already, but let's talk about the new agents that we might have at our disposal that's exciting, because it may actually allow us to treat this without forcing the patient into the clinic two or three times a week, and may actually be a little bit more effective than something that just takes the edge off.—

--So this is to all of you. What should we be looking for in the future? What should we be excited about in terms of, and what's the data behind it, in terms of new treatments for uremic pruritus?

MARK LEBWOHL, MD, FAAD: So that *New England Journal of Medicine* article is very convincing, which showed a statistically significant drop in worsened itch numerical rating scale that is as impressive as anything we have right now. We desperately need a treatment for this and that one is coming.

SARA COMBS, MD, FAAD: So the drug is a mouthful to say, difelikefalin, I think, I don't know, the trade name is Korsuva. It was the KALM-1 study, I think like 300 patients, and the primary outcome, like Dr. Lebwohl was saying, is a numeric rating scale improvement in 3 or greater and it was statistically significant and clinically significant, or improvement in 3 or greater, and it was a significant response. And so I have a lot of colleagues that were PI's on that study locally

and it was a life-changing drug for patients and then they had to stop taking it, which is a huge shame.—

--But the expectation is that I think it's being fast tracked through the FDA, that it may be approved later this year. So we're hopeful that we might be able to prescribe it for our patients. This is only who are receiving hemodialysis would receive it three times a week.

STEVEN CHEN, MD, FAAD: Is there any other kind of critical information you want our listeners to know about that new medication? I know that obviously we have a lot more to learn about it before it's like fully available for anyone to prescribe. But thinking about toxicity data, thinking about efficacy data, thinking about who is going to prescribe it, will it be the nephrologist or the dermatologist who is going to be reaching for this, what do you all foresee?

SARA COMBS, MD, FAAD: It's marketed as a peripherally-acting kappa agonist. And so the side effects, they look not bad at all, in terms of the neurologic side effects or other side effects. It seems like it's a pretty good outcome there in terms of side effects. And it is going to be something that will be given at the end of dialysis, for hemodialysis patients. And so it's going to be on the onus of the nephrologist to prescribe this medication in order for it to be given successfully.—

--And I think we're not really sure how that is going to go, how it's going to be covered by what they call this bundle of dialysis patients, or if it's going to be an individually-covered medication. I think all of that is still sort of in contention. But this is definitely going to be a nephrology-driven medication for the hemodialysis patients, at least for now I think.

MARK LEBWOHL, MD, FAAD: The typical side effects that you worry about with opioids did not occur. It's not addictive. There's no respiratory depression. I think that a lot of the concern, when you realize it's an opioid receptor, again it's very specific, it's the kappa opioid receptor

and so it is not dangerous. The other point, which I agree with, it's going to be given by nephrologists because it's given IV. But there is an oral preparation currently under study for notalgia paresthetica and hopefully it will work for a lot of pruritic conditions.

PEDRO TEIXEIRA, MD, FAAD: It's being developed as a possible treatment, we talked previously about the kind of dearth of treatment options for non-dialysis CKD patients and pruritus. It's being potentially developed as an oral agent for CKD-associated pruritus for kind of those pre-dialysis patients who obviously have less access to IV medications.

SARA COMBS, MD, FAAD: Or patients on PD, and I think they're in phase 2 trials right now for that.

STEVEN CHEN, MD, FAAD: So it sounds like obviously to start, nephrology will certainly be running the show in terms of the medication. But stay tuned for the possibility of broader availability across specialties. I guess the crux of the question is, how can dermatologists be the most helpful in this first phase, in terms of partnering with nephrology? Because if nephrologists are the ones dosing it, how can we be helpful? Is it just the suggestion of using this medication? Is it to help with the exam of ruling out other causes? How do you foresee us being the most helpful to partner with you in nephrology?

PEDRO TEIXEIRA, MD, FAAD: I think it's probably the latter. So there may be some of the former, too, we'll have to see how this gets adopted. The good news about dialysis treatment in the United States is it's basically a socialized healthcare system, to some degree, like everyone has access. And so to the degree that a lot of our care is protocolized, this may potentially become a protocolized part of care for dialysis patients, as well, so that may increase uptake. But we'll have to see how it goes. Obviously, the FDA approval is step one and that hopefully will be forthcoming soon.—

--And then indeed, I think probably the most important role of a dermatologist in the care for our patients with pruritus will be to help us sort out if there's something we're missing, patients with abnormal skin exam beyond just sort of clear signs of kind of secondary excoriations. For most of us, and I speak probably for most nephrologists, in saying we're not that great at skin findings. We'll probably refer those patients to you guys, as well. I think that's going to be a big part of the role.

SARA COMBS, MD, FAAD: I would say clearly, nephrologists do not excel at recognizing the impact or importance of the symptom and how much it is burdening our patients. And so any gentle reminder that it's present and that a new medication is out is always welcome.

STEVEN CHEN, MD, FAAD: And I think that's great, to highlight something that Dr. Lebwohl reminded all of us earlier, is that really a lot of the things in the differential diagnosis come with skin lesions and come with rash. And so those are all the things that we love to see in dermatology clinic. So certainly I can only speak for myself when I say I welcome the referrals, to help think about our CKD patients, so that we can hopefully get them the best care possible.—

--That about wraps it up from my end. Is there anything else that any of you would like to share with our listeners before we end our episode today?

MARK LEBWOHL, MD, FAAD: I just have a question that had intrigued me. You mentioned dupilumab for the pemphigoid associated with immune checkpoint inhibitors. How effective has that been for you?

STEVEN CHEN, MD, FAAD: I don't know if we're allowed to talk about this on this episode. But it's been quite effective. We're studying it now. We're trying to put together our own kind of case series. I'll say that in every patient I've used it in so far, it's been at least moderately successful.

Almost everyone that I've used it in, I've been able to stop all other kind of adjunctive measures, so it's been really good.

MARK LEBWOHL, MD, FAAD: And even if they have bullae?

STEVEN CHEN, MD, FAAD: Yes, even if they have bullae. And it gets better quick. So to wrap up, just really quickly wanted to of course thank our wonderful guests today, Dr. Teixeira, Dr. Combs, and Dr. Lebwohl, for being with me today to discuss CKD or kidney disease-related pruritus. I have been so honored to be joined by three experts in their respective fields as we talk about this really important issue that affects so many of our patients. Thank you so much for your time today. And I hope everyone listening learned as much as I did on this episode of *Dialogues in Dermatology*.