CARA THERAPEUTICS

Capital Markets Day

February 16, 2023

Forward-Looking Statements

Statements contained in this presentation regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Examples of these forward-looking statements include statements concerning the Company's ability to successfully commercialize KORSUVA injection and Kapruvia, future revenue and profit share from sales of KORSUVA and Kapruvia, planned future regulatory submissions and potential future regulatory approvals, future product launches, the performance of the Company's commercial partners, including CSL Vifor, expected timing of the initiation, enrollment and data readouts from the Company's planned and ongoing clinical trials, the potential results of ongoing clinical trials, timing of future regulatory and development milestones for the Company's product candidates, the potential for the Company's product candidates to be alternatives in the therapeutic areas investigated and the potential for oral difelikefalin to address additional pruritic indications, the size and growth of the potential markets for pruritus management, and the Company's expected cash reach. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. These risks and uncertainties include the risks inherent in the launch of new products, including that our commercial partners, including CSL Vifor, may not perform as expected, risks inherent in the clinical and regulatory development of pharmaceutical products, and the risks described more fully in Cara Therapeutics' filings with the Securities and Exchange Commission, including the "Risk Factors" section of the Company's Annual Report on Form 10-K for the year ending December 31, 2021 and its other documents subsequently filed with or furnished to the Securities and Exchange Commission, including its Form 10-Q for the quarter ended September 30, 2022. All forward-looking statements contained in this presentation speak only as of the date on which they were made. Cara Therapeutics undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made, except as required by law.

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Today's Speakers

Christopher A. Posner
CEO, President and Director

Joana Goncalves, MD
Chief Medical Officer

Eric Vandal
SVP, Commercial

Joel Topf, MD, FACP
St. Clair Nephrology Research
Roseville, MI

Jennifer Scherer, MD, MS
NYU Langone Health
New York, NY

Raj Chovatiya, MD, PhD, FAAD
Northwestern University
Chicago, IL

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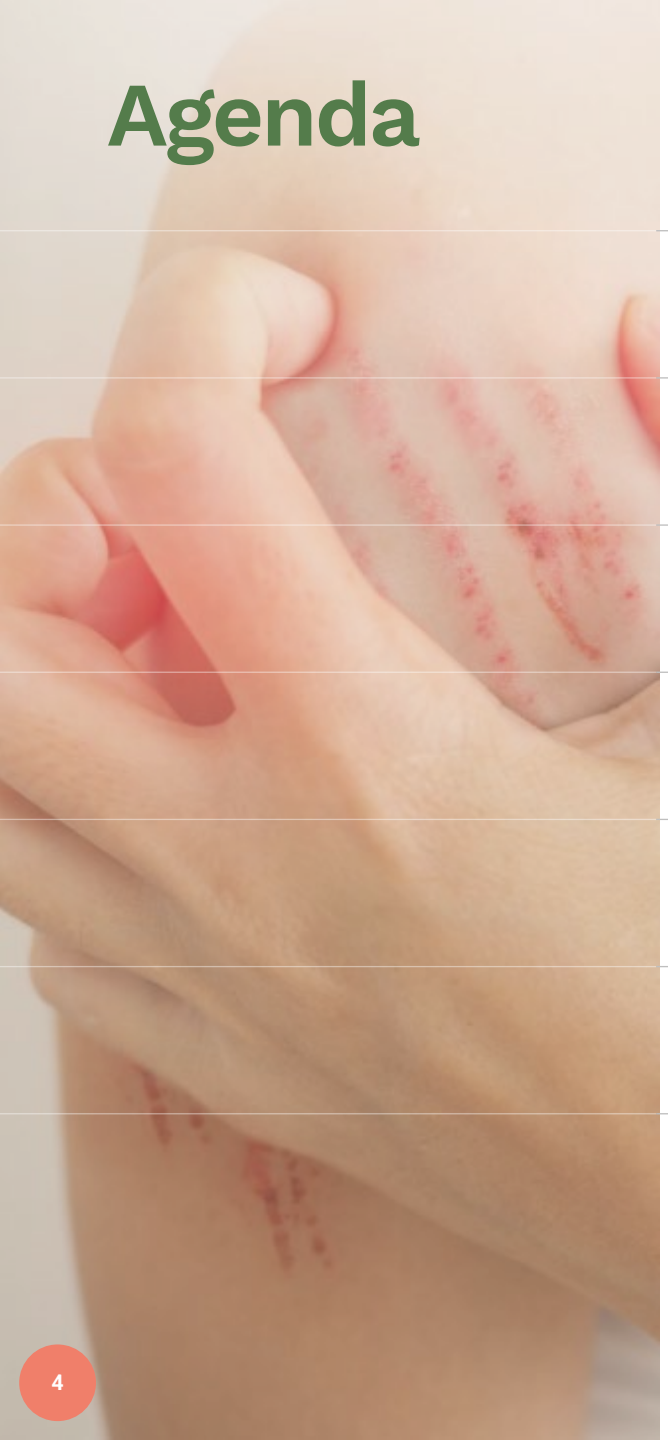

Agenda

1. **Introductory Remarks**
   Christopher Posner, CEO, President and Director, Cara Therapeutics
2. **Dialysis-Dependent CKD-aP: Spotlight on KORSUVA Injection**
   Joel Topf, MD, FACP, St. Clair Nephrology Research in Roseville, MI
   Eric Vandal, SVP, Commercial, Cara Therapeutics
3. **Pre-Dialysis CKD-aP: Assessing the Unmet Medical Need**
   Jennifer Scherer, MD, MS, NYU Langone Health in New York, NY
4. **Nephrology Q&A Session**
5. **Atopic Dermatitis: Segmenting the Market**
   Raj Chovatiya, MD, PhD, FAAD, Northwestern University in Chicago, IL
6. **Notalgia Paresthetica: Background & Trial Design**
   Raj Chovatiya, MD, PhD, FAAD, Northwestern University in Chicago, IL
   Joana Goncalves, MD, Chief Medical Officer, Cara Therapeutics
7. **Medical Dermatology Q&A Session**
8. **Closing Remarks & Management Q&A Session**

Oral difelikefalin is an investigational agent that has not been approved by the FDA. The efficacy and safety of oral difelikefalin has not been established.

Introductory Remarks

Christopher Posner, CEO, President and Director, Cara Therapeutics

Our Mission:

To be the leader in the treatment of chronic pruritus with a vision to transform the way pruritus is treated and improve the quality of life for millions of people who suffer.

Difelikefalin, a Pipeline in a Product

First-in-class selective and potent kappa opioid receptor agonist

Unique Chemical Structure and Features

- Synthetic peptide made of non-natural amino acids
- High hydrophilicity, high polar surface area and charge at physiological pH
- Does not readily cross the blood-brain-barrier

1

Attractive Pharmacology

- Highly selective and potent full agonist at KORs
- Does not produce classical mu opioid side effects (e.g., euphoria, addiction and respiratory depression)
- **Non-scheduled drug**

2

Differentiated MOA

- Acts on KORs on peripheral terminals of sensory nerves and immune cells
- Works downstream potentially as broad spectrum antipruritic

3

Strong Clinical Data in Multiple Therapeutic Areas

- IV formulation approved for CKD-aP in hemodialysis patients
- Oral formulation has shown positive clinical data in the treatment of chronic pruritus
  - CKD-aP in pre-dialysis patients
  - Atopic Dermatitis
  - Notalgia Paresthetica

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Focus on Moderate to Severe Chronic Pruritus

NEPHROLOGY

Advanced CKD Hemodialysis

APPROVED

~ 200K patients undergoing hemodialysis (HD) suffer from moderate-to-severe chronic pruritus

KORSUVA injection is the first-and-only product approved to help these patients.

Advanced CKD Pre-Dialysis

PHASE 3

~ 300K patients with stage 4-5 advanced CKD suffer from moderate-to-severe chronic pruritus

There are no approved therapies.

DERMATOLOGY

Atopic Dermatitis

PHASE 3

~ 3M mild-to-moderate patients with Atopic Dermatitis (AD) suffer from moderate-to-severe chronic pruritus

Chronic pruritus is one of the defining features of AD.

Notalgia Paresthetica

PHASE 2/3

~ 650K patients with Notalgia Paresthetica (NP) are in the care of a healthcare provider for moderate-to-severe chronic pruritus

There are no approved therapies.

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Dialysis-Dependent CKD-aP: Spotlight on KORSUVA Injection

Joel Topf, MD, FACP
Medical Director, St. Clair Nephrology Research
Assistant Clinical Professor of Medicine, Oakland University William Beaumont School of Medicine

Eric Vandal
SVP, Commercial, Cara Therapeutics

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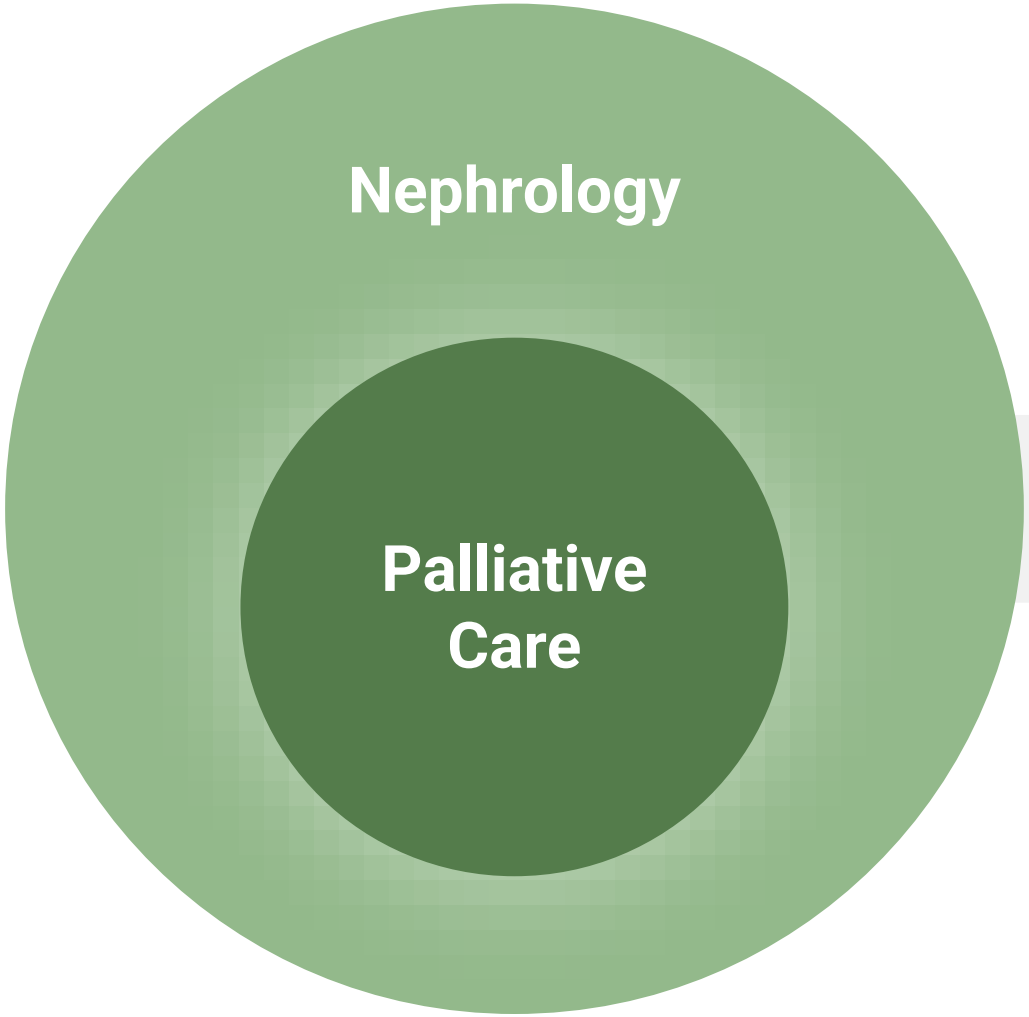
Pre-Dialysis CKD-aP: Assessing the Unmet Medical Need

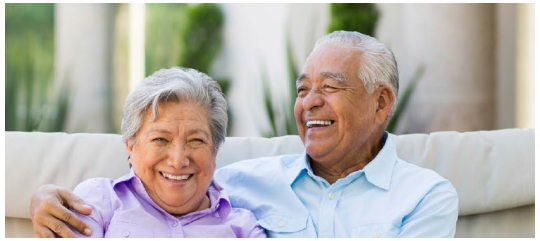
Jennifer Scherer, MD, MS
Assistant Professor, NYU Grossman School of Medicine
Director, Kidney CARES Program, NYU Langone Health
Medical Director, River Renal Dialysis Center

Kidney Palliative Care Clinical Model



KIDNEY CARES PROGRAM
AT NYU LANGONE NEPHROLOGY ASSOCIATES

Providing
Comprehensive
Advanced
Renal Disease and
ESRD
Support



Fan Fox and Leslie R. Samuels Foundation
Cambia Health Foundation

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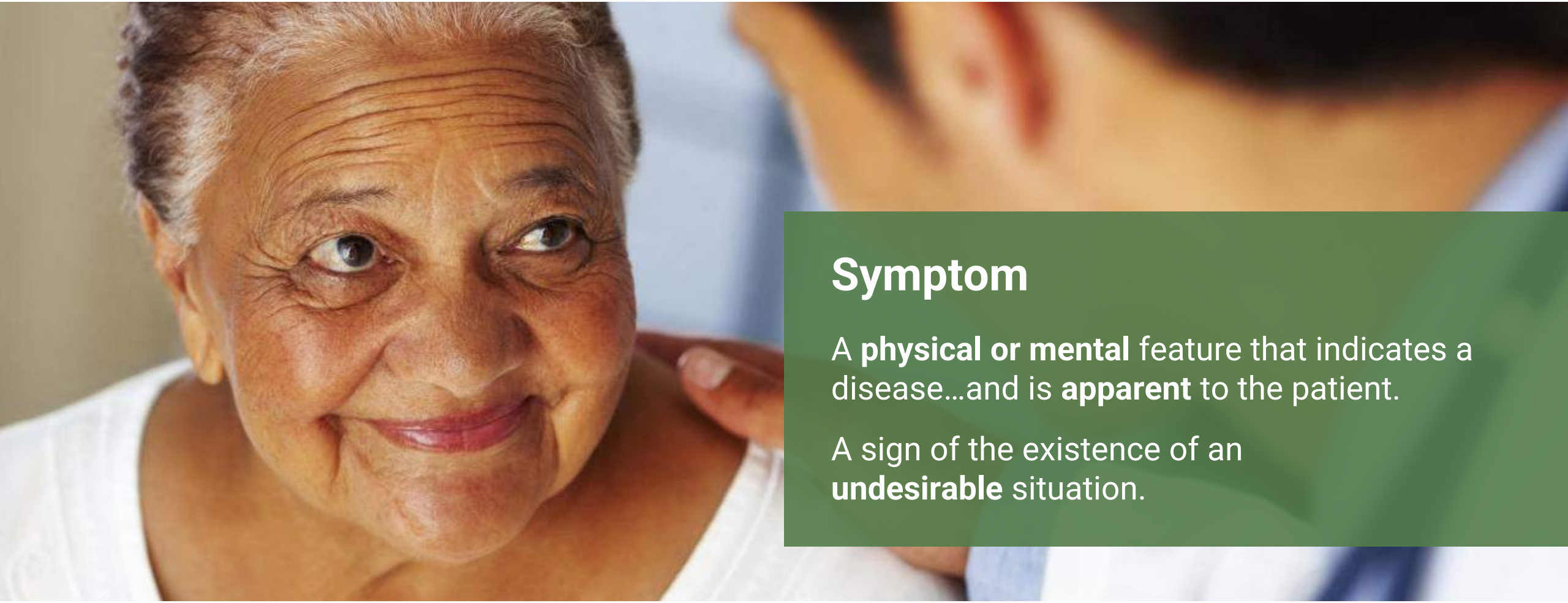
Why is CKD-aP Important?



Symptom

A **physical or mental** feature that indicates a disease…and is **apparent** to the patient.

A sign of the existence of an **undesirable** situation.

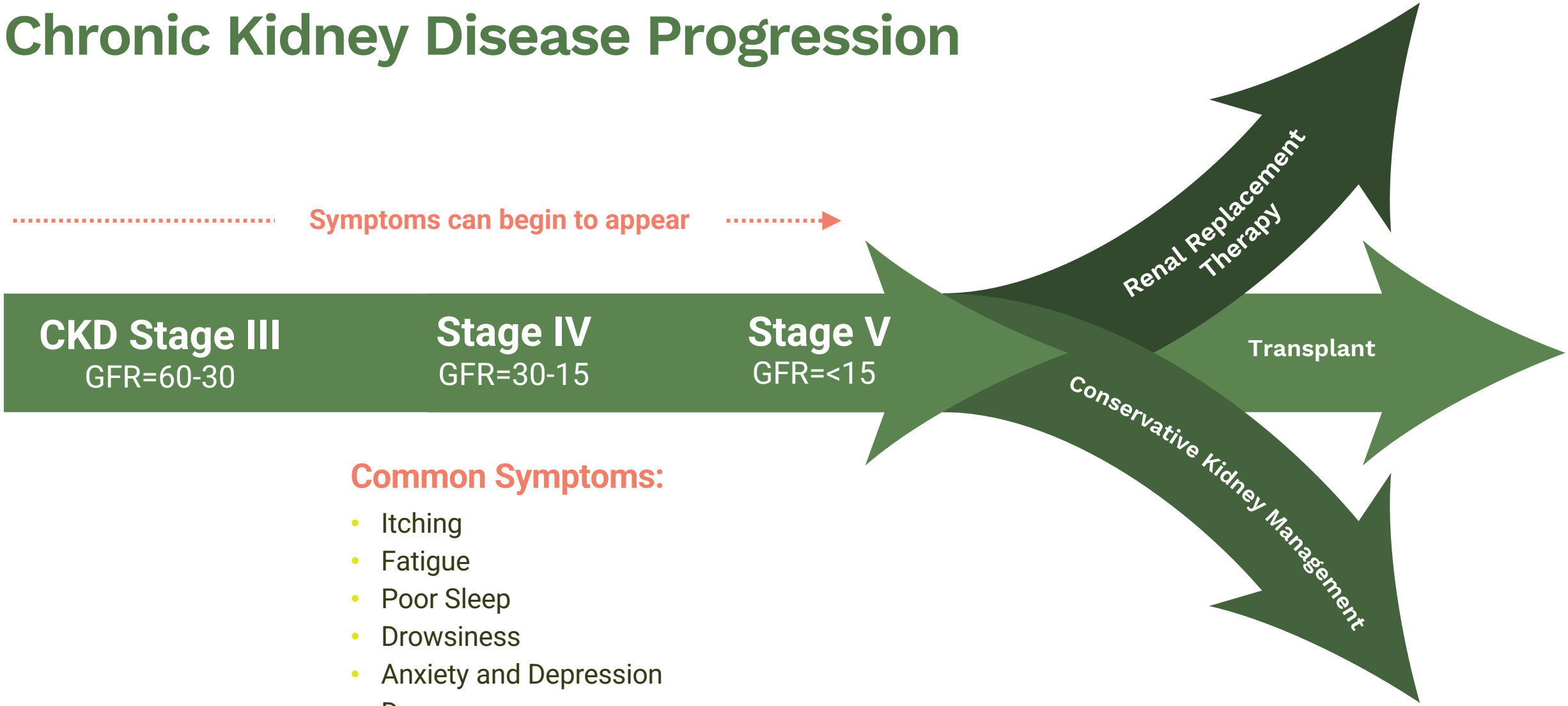
Patient Presentation

- 88-year-old male with coronary heart disease, hypertension CKD stage V, GFR=11 who has decided against dialysis.
- Referred for management of kidney disease with out dialytic therapies.
- On symptom assessment, he reports being mildly bothered by itch and poor sleep.
- However, during history, he was not able to sit still—scratching all four of his extremities intermittently.
- Upon further inquiry, his itch is worse than he had rated it on the survey and does state that he feels itch “most of the day” and this is what keeps him up at night.
- On exam, multiple excoriations and noticeable dry skin
- Did not want drug therapy, worried about interactions and said he doesn’t bother him enough

Patient Presentation – Continued

- Referred to dermatology and asked him to use lipid-based moisturizer.
- Came back in one month, no change, now more aware of how much the itch is impacting his day. Agreed to a trial of medication.
- Started gabapentin 100 mg every other day at night.
- Followed up in two weeks, sleep had improved, itch was only slightly better, but he was experiencing dizziness and drowsiness from the gabapentin, worried about falls, so it was discontinued.
- Managed his sleep with other interventions, itch was never able to be fully controlled.

Chronic Kidney Disease Progression



Common Symptoms:

- Itching
- Fatigue
- Poor Sleep
- Drowsiness
- Anxiety and Depression
- Dyspnea
- Sexual Dysfunction
- Pain
- Restless Legs Syndrome

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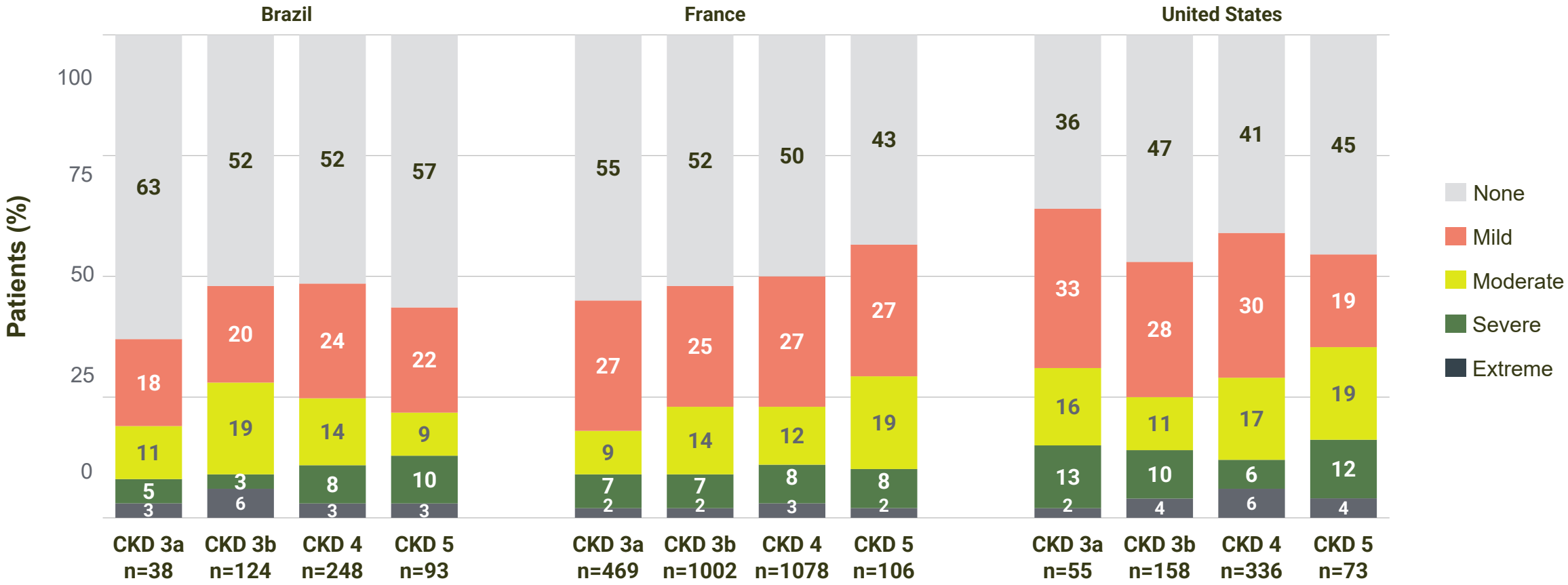
Pruritus Is a Common Issue Across Countries and CKD Stages

Pruritus was a common issue across countries and CKD stages (3–5) in the CKD Outcomes and Practice Patterns Study (CKDopps)



Sukul N, et al. *Clin J Am Soc Nephrol*. 2019;14:673-681.

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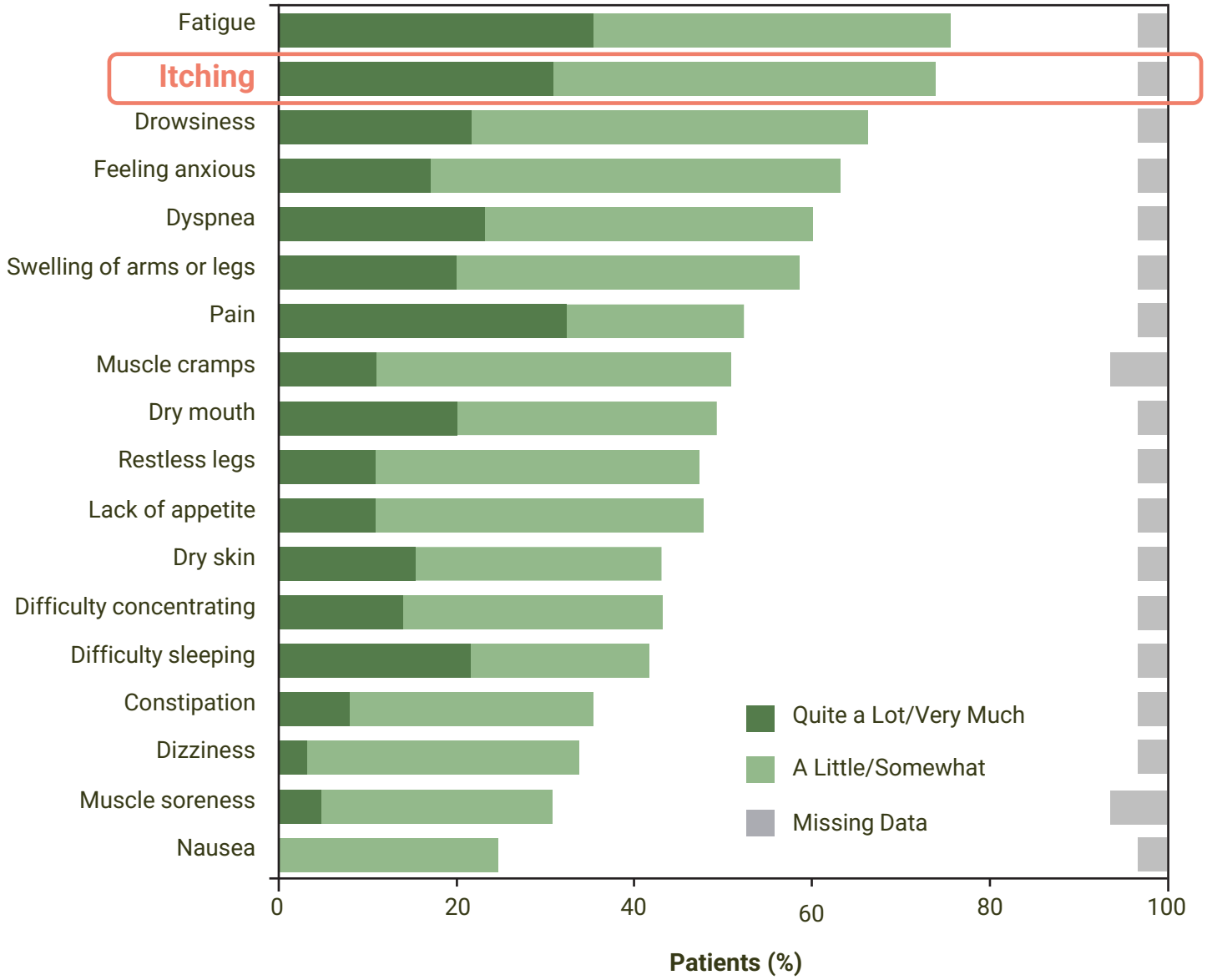
Pruritus is a Common Symptom in NDD-CKD Patients

Itching was the second most prevalent symptom among a cohort of patients with NDD-CKD stage 5 in the United Kingdom (n=66)

- 74% of patients reported itching
- 32% of patients were distressed “quite a lot” or “very much” by itching



Murtagh FEM, et al. J Pall Med. 2007;10:1266-1276.

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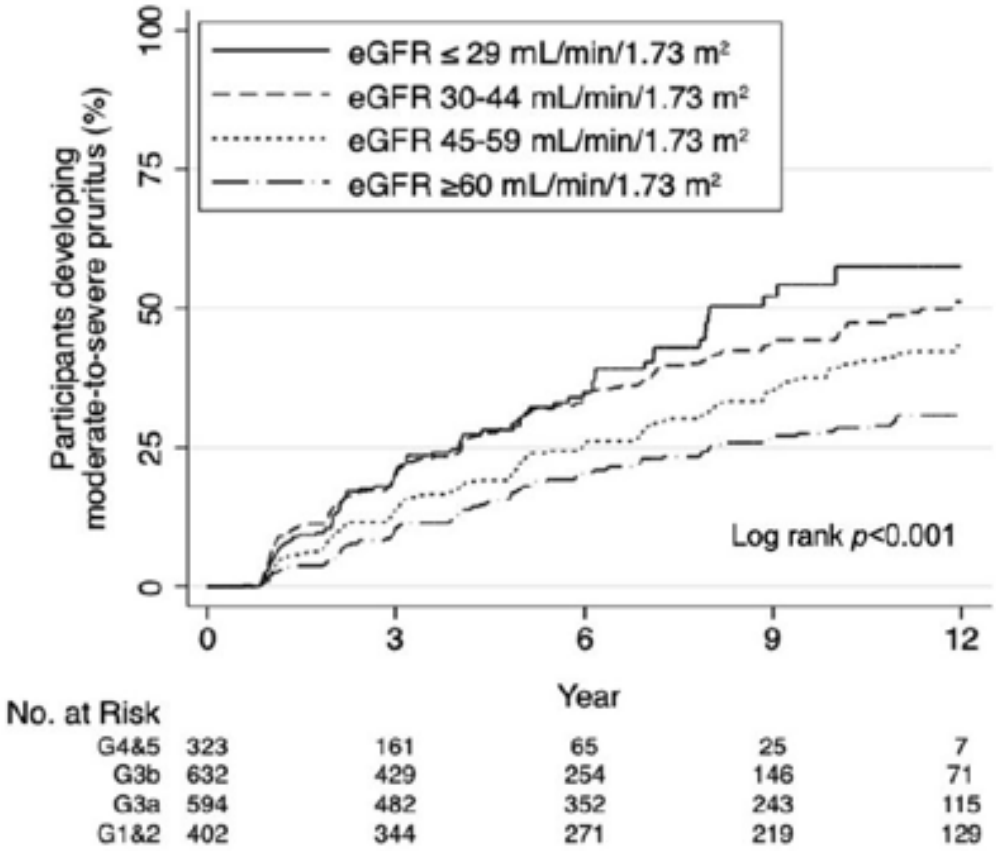
Incidence of Pruritus in NDD-CKD Patients



N=3685, mean eGFR=44ml/min^2

42% had Pruritus at Baseline

- Symptoms worsened by 1-2 points with each decrease of 5 ml/min/1.73m^2
- 1 in 4 CKD stage IV-V patients will develop moderate to severe pruritus in 4 years

Wulczyn K, Rhee E, Myint L, Kalim S, Shafi T. Incidence and Risk Factors for Pruritus in Patients with Nondialysis CKD [published online ahead of print, 2022 Dec 14]. Clin J Am Soc Nephrol. 2022;CJN.09480822. doi:10.2215/CJN.09480822

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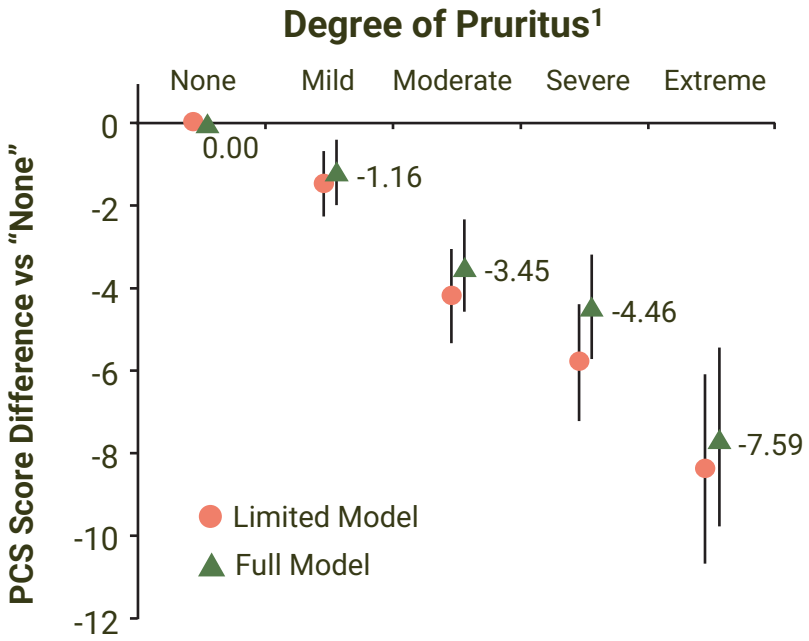
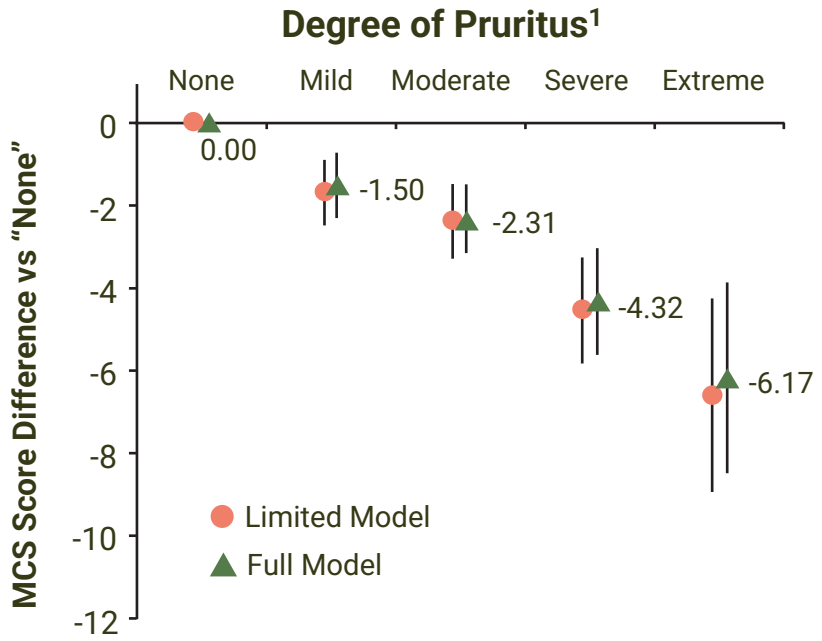
Physical and Mental Health Impact of Pruritus in NDD-CKD Patients

Pruritus severity is associated with reduced physical and mental health in NDD-CKD stage 3–5 patients[1]

- A 3- to 5-point change in Physical Component Score (PCS) or Mental Component Score (MCS) is considered clinically significant[2,3]





ERROR BARS REPRESENT 95% CI.

1. SUKUL N, ET AL. *CLIN J AM SOC NEPHROL*. 2019;14:673-681. 2. SAMSA G, ET AL. *PHARMACOECONOMICS*. 1999;15:141-155. 3. HAYS RD, WOOLLEY JM. *PHARMACOECONOMICS*. 2000;18:419-423.

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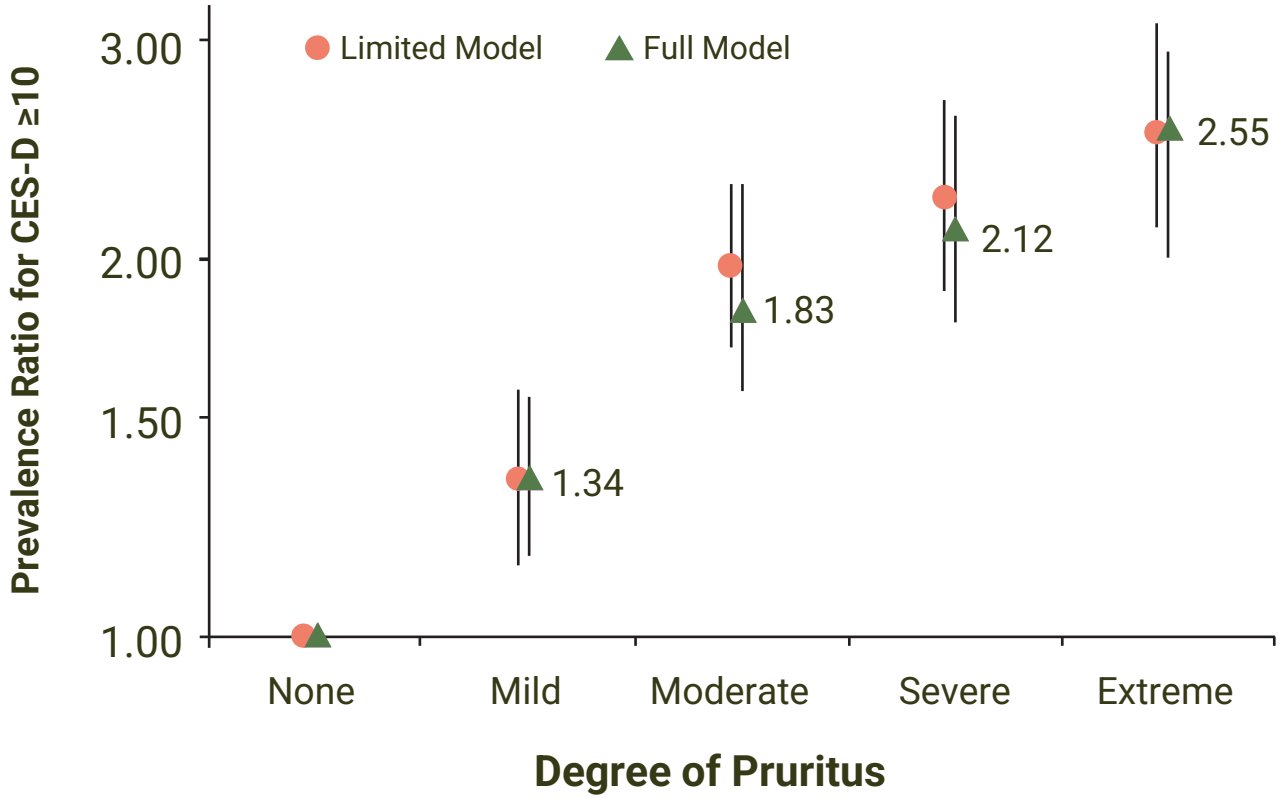
Depression and Pruritus in NDD-CKD Patients

- Symptoms of depression increase with pruritus severity in NDD-CKD stage 3–5 patients
- Patients with moderate-to-extreme pruritus are 1.8–2.5 times more likely to experience symptoms of depression



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CES-D, CENTER FOR EPIDEMIOLOGIC STUDIES DEPRESSION SCALE.

SUKUL N, ET AL. CLIN J AM SOC NEPHROL. 2019;14:673-681.

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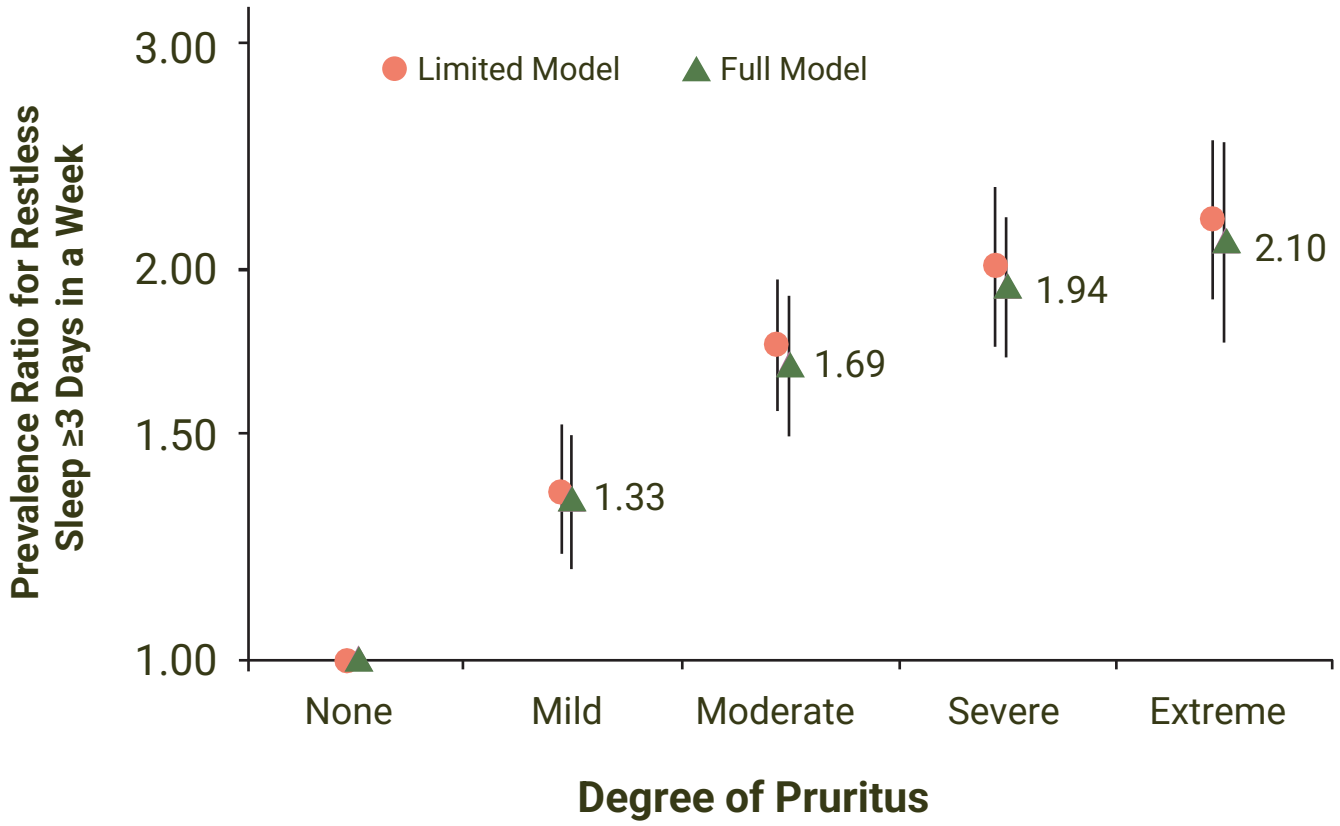
Sleep Quality and Pruritus in NDD-CKD Patients

- Frequency of restless sleep increases with pruritus severity in NDD-CKD stage 3–5 patients
- Patients with moderate-to-extreme pruritus are ~1.7–2.1 times more likely to have restless sleep



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SUKUL N, ET AL. CLIN J AM SOC NEPHROL. 2019;14:673-681.

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Multifactorial Pathogenesis Proposed for Pruritus in CKD

Implicated toxins[1-5]

Vitamin A, aluminum, calcium, phosphorus, magnesium

Abnormalities related to uremia

Peripheral neuropathy

Abnormal nerve conduction[1,3,5-6]

Pattern of cutaneous innervation
Nerve conduction studies

Imbalanced mu- and kappa-opioid receptor activity[1-5, 7]

↑ endorphins
(mu-opioid agonist)

↓ dynorphins
(kappa-opioid agonist)

Endogenous opioid dysregulation

Immune system dysregulation

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;87:685-691. 3. Wang H, Yosipovitch G. Int J Dermatol. 2010;49:1-11. 4. Kuypers DRJ. Nat Clin Pract Nephrol. 2009;5:157-170.
5. Patel TS, et al. Am J Kidney Dis. 2007;50:11-20. 6. Zakrzewska-Pniewska B, Jędras M. Neurophysiol Clin. 2001;31:181-193. 7.Phan NQ, et al. Acta Derm Venereol. 2012;92:555-560. 8. Kimmel M, et al. Nephrol Dial Transplant. 2006;21:749-755.

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CKD-aP Treatment Options

Barriers to Identification

- Related to kidney disease or a separate chronic systemic condition
- Other possible causes
- Widely variable clinical presentations
- Under reported

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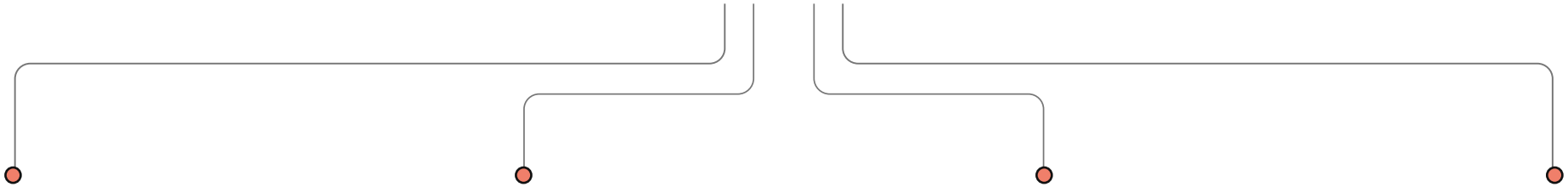
How Do We Treat Pruritus in CKD Patients?

- Establish treatment goals with the patient
- Keep skin hydrated, keep cool
- Start with topical/least systemic effects: lotions/creams/ointments
- Can add medicated lotion (Pramoxine) or topical steroids
- Off-label use of Gabapentinoids
- Second line agents such as off-label paroxetine, sertraline
- Regular and consistent reassessment

Limitations of Current Treatments



Overall limited

Often recommended algorithms do not provide relief

Patients often experience side effects

Clinical situation often makes you more worried about side effects, especially around fall risks for older adults.

Key Takeaways

- Pruritus is a common and burdensome condition for CKD pre-dialysis patients
- Pruritus can impact CKD patients' physical and mental health
- Current treatment options are off-label and have limitations
- There is a significant unmet need for a new therapy to treat pruritus in CKD pre-dialysis patients

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Atopic Dermatitis: Segmenting the Market

Raj Chovatiya, MD, PhD, FAAD
Assistant Professor of Dermatology, Director of the Center for Eczema and Itch, Medical Director of the Clinical Trials Unit
Northwestern University Feinberg School of Medicine

Clinical Case

John is a 35-year-old with atopic dermatitis

- Present since childhood and he feels it's getting worse over time
- He recalls being covered with thick, red scaly patches on his face, neck, arms and legs when he was younger
- These days he notes mostly dry skin as an adult and occasional small pink patches on his hands, wrists, ankles, and feet
- He experiences itch constantly and hasn't sleep well in years (this has gotten worse)
- His AD gets in the way of his work as delivery driver
- His current regimen includes 2 antihistamines, 2 topical steroids, 1 topical calcineurin inhibitor, occasional oral steroids, occasional oral antibiotics

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Is This “Severe” AD?

What Does “Severe” AD Actually Mean?

- Large plaques
- Hand and foot involvement
- Erythema and lichenification
- High body surface area
- ↑↑↑ Itch, sleep issues
- Asthma, seasonal rhinosinusitis, food allergies
- Getting worse over time
- Unable to go to work
- Topical vs. systemic treatment
- Skin not clear after treatment

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The Heterogeneity of AD

AD Severity is a Multi-layered Concept

- Lesion distribution
- Lesion morphology
- Extent
- Intensity
- Symptoms
- Long-term course
- Burden
- Comorbidities
- Treatment choice
- Treatment response

Chovatiya R, Silverberg JI.. J Drugs Dermatology. 2022;21(2):172–6.

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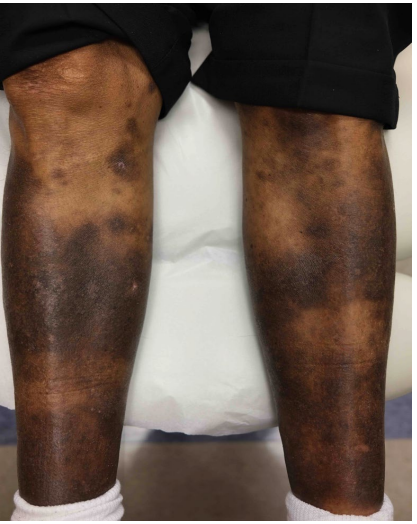
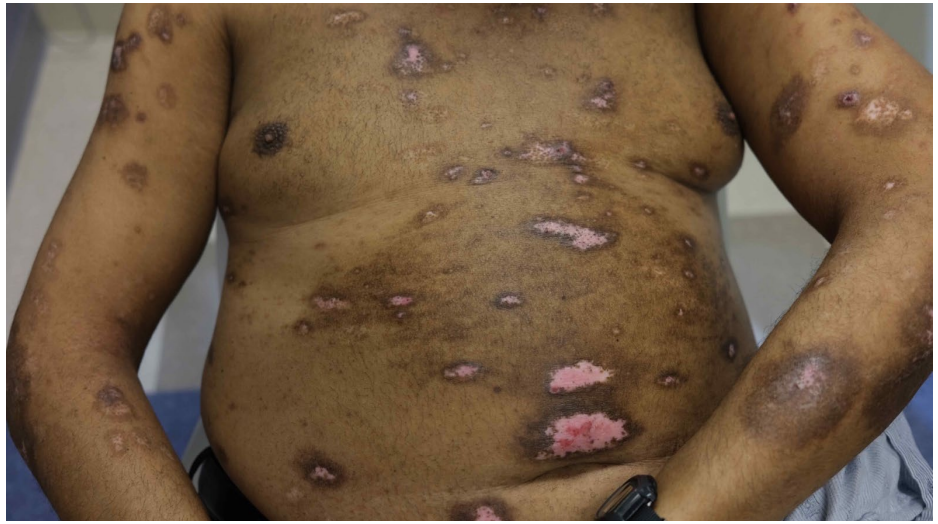
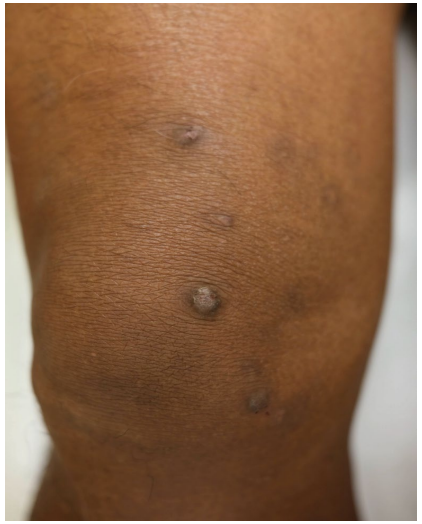
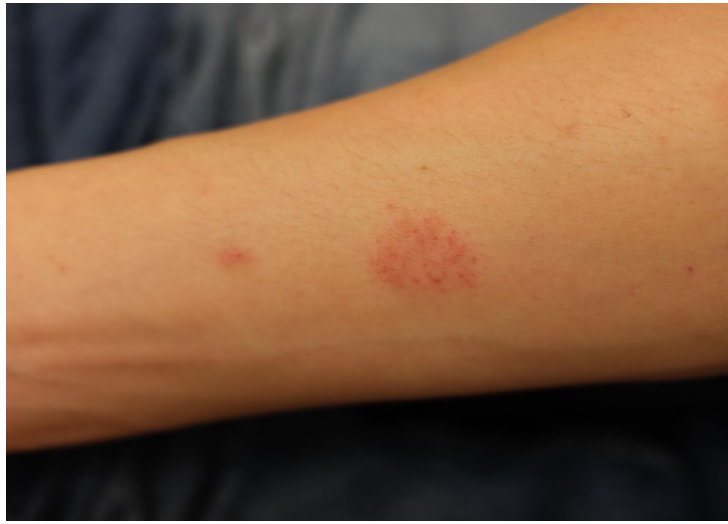
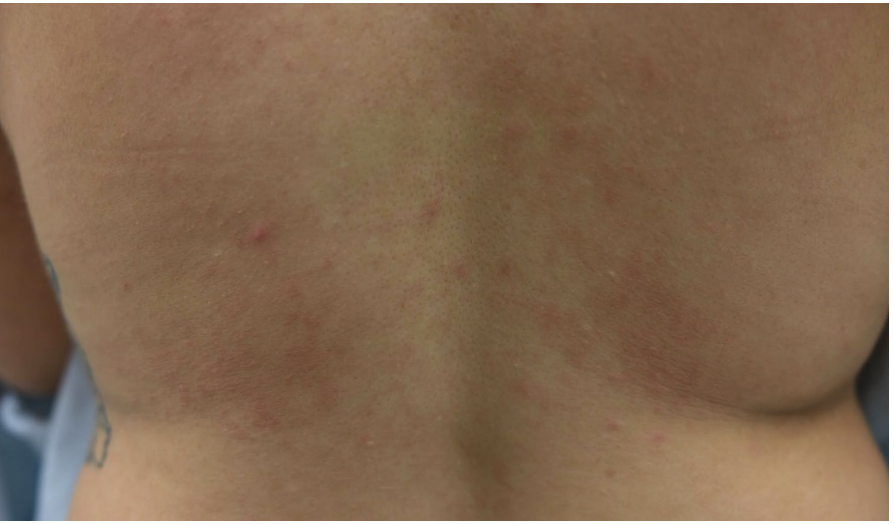
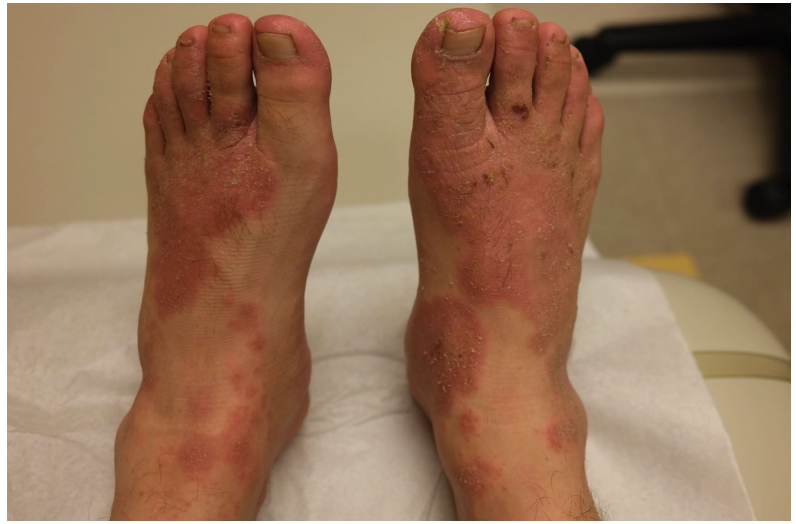
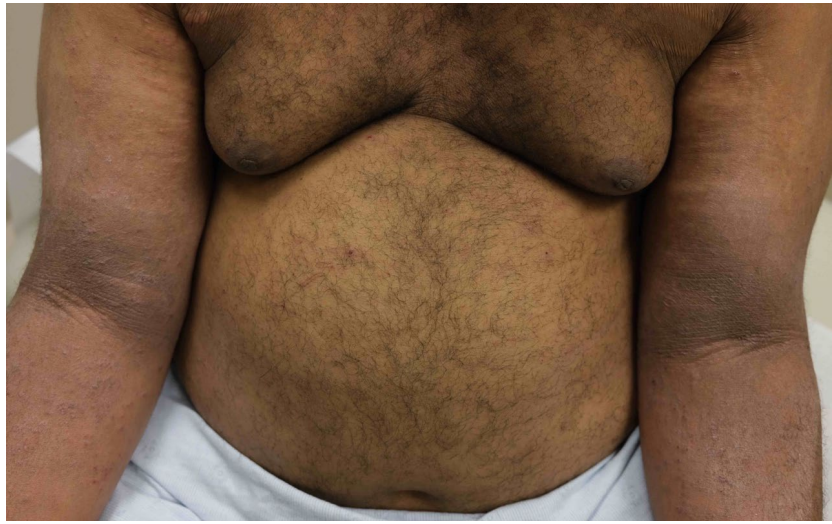
Despite Our Best Efforts, AD is Not One-size Fits All

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Clinical Descriptions of AD

Understanding Severity Requires Multiple Perspectives

Patient

Long-term course:
Onset, recurrence, persistence, flares

Symptoms:
Itch (and more)

Burden:
Quality-of-life

Clinician

Morphology:
Common and uncommon phenotypes

Intensity:
Redness, edema, excoriation, lichenification

Extent:
Total body skin exam

Combined

Comorbidities:
ROS, PMHx

Treatment Selection and Response:
Shared-decision making

Chovatiya R., Silverberg J.I. J Drugs Dermatol, 2022
Chovatiya R., Silverberg J.I. JAAD, 2022

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Severity is Often Assessed from the Clinician Perspective

Patient

Long-term course:
Onset, recurrence, persistence, flares

Symptoms:
Itch (and more)

Burden:
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Physicians and Patients Rate AD Severity Differently

Disparities exist between patients' and physicians' ratings of AD severity

Physician- vs. patient-reported severity of atopic dermatitis

Physician-reported severity	Patient-reported severity, *n*			Row total, *n* (%)
	Mild	Moderate	Severe	
Mild	134	39	2	175 (25.8)
Moderate	99	270	35	404 (59.6)
Severe	4	34	61	99 (14.6)
Column total, *n* (%)	237 (35.0)	343 (50.6)	98 (14.5)	678 (100)

Severity ratings were discordant in about **one-third of patients**

Wei W, et al. Am J Clin Dermatol. 2017;18:825–835

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The Signs of AD Don’t Tell the Whole Story

Patients with mild or moderate AD may experience persistent, bothersome symptoms

Itch

- Patients with mild AD may still experience severe itch[1]

Quality of Life

- Over one-third of adults with mild AD report lifestyle limitations[2]

Mental Health

- 27% of patients with mild AD report significant anxiety/depression[3]
- Patients with mild AD may report similar mental health burden as patients with moderate or severe AD[4,5]

1. Chovatiya R, et al. *Ann Allergy, Asthma Immunol*. 2021;127:83–90.e2. 2. Silverberg JI, et al. *Ann Allergy Asthma Immunol*. 2018;121:340–347. 3. Simpson EL, et al. *JAMA Derm*. 2018;154:903–912.
4. Eckert L, et al. *J Am Acad Dermatol*. 2017;77:274–279. 5. Whiteley J, et al. *Curr Med Res Opin*. 2016;32:1645–1651.

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Understanding Severity Requires Both Patient & Clinician Perspectives

Patient

Long-term course:
Onset, recurrence, persistence, flares

Symptoms:
Itch (and more)

Burden:
Quality-of-life

Clinician

Morphology:
Common and uncommon phenotypes

Intensity:
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Combined

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Treatment Selection and Response:
Shared-decision making

Chovatiya R., Silverberg J.I. J Drugs Dermatol, 2022
Chovatiya R., Silverberg J.I. JAAD, 2022

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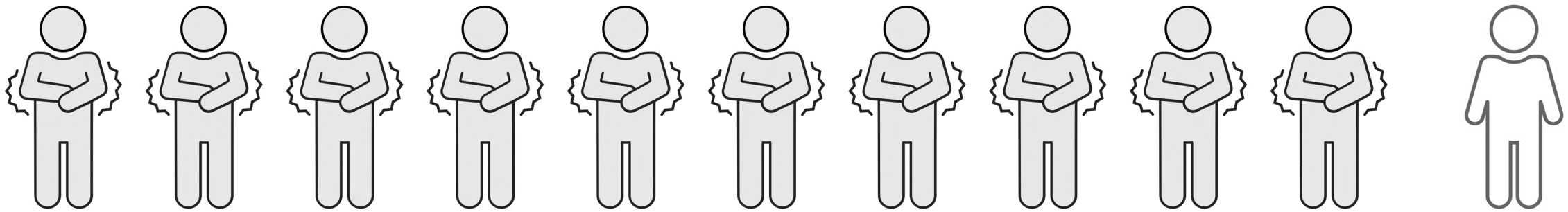
Itch Presents a Daily Challenge for AD Patients

9 out of 10 Patients with AD Complain of Daily Itching



Dawn A, et al. *Br J Dermatol*. 2009;160:642–644

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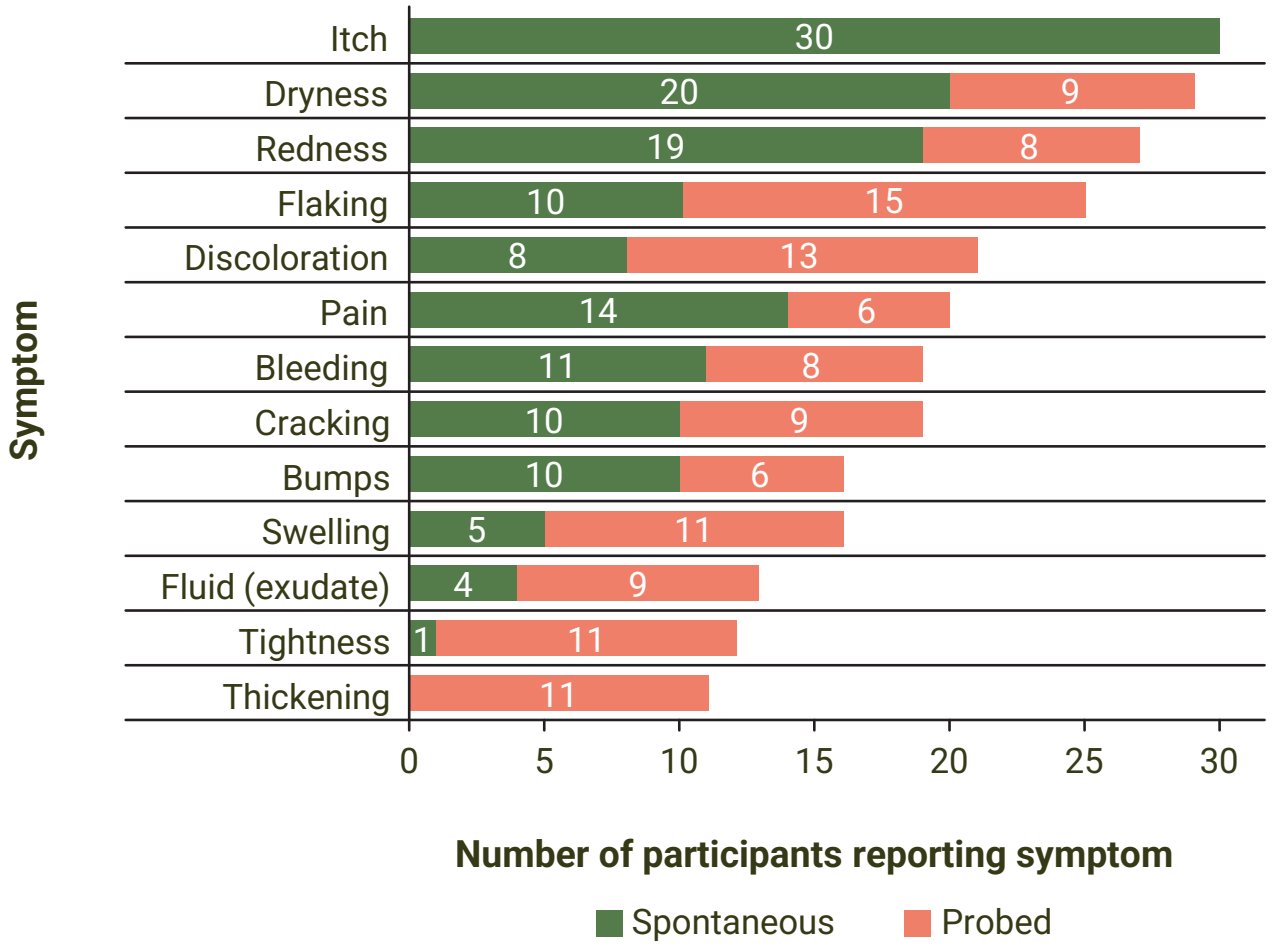
Itch is the Most Prevalent Symptom in AD



- Up to **100%** of AD patients spontaneously report itch[1,2]
- **60%** of AD patients report their itch is severe to very severe[3*]

Adapted with permission from Hall R, et al.[1]

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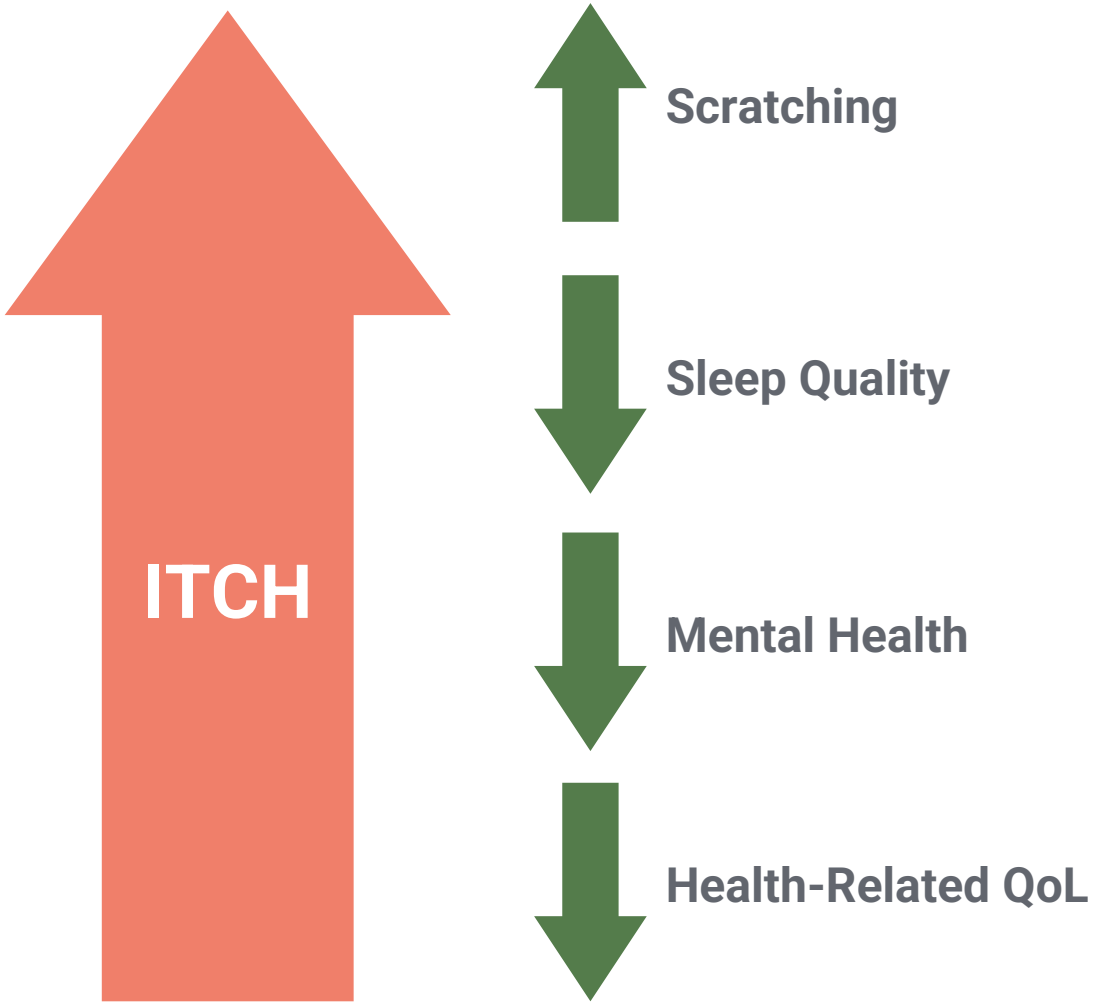
Pruritus Drives Quality of Life Impairment in AD

- Patients with AD spend up to 14% of their sleep time scratching[1]
- Increased pruritus is correlated with reduced sleep quality[2] and decreased QoL in patients with AD[3,4]
- Severe itch is associated with impaired mental health[1]



1. Bawany F, et al. *J Allergy Clin Immunol Pract*. 2021;9:1488–1500. 2. Kaaz K, et al. *Acta Derm Venereol*. 2019;99:175–180.
3. Kong TS, et al. *Ann Dermatol*. 2016;28:321–326. 4. Huet F, et al. *Acta Derm Venereol*. 2019;99:279–283. 5. Silverberg JI, et al. *Ann Allergy Asthma Immunol*. 2018;121:340-347

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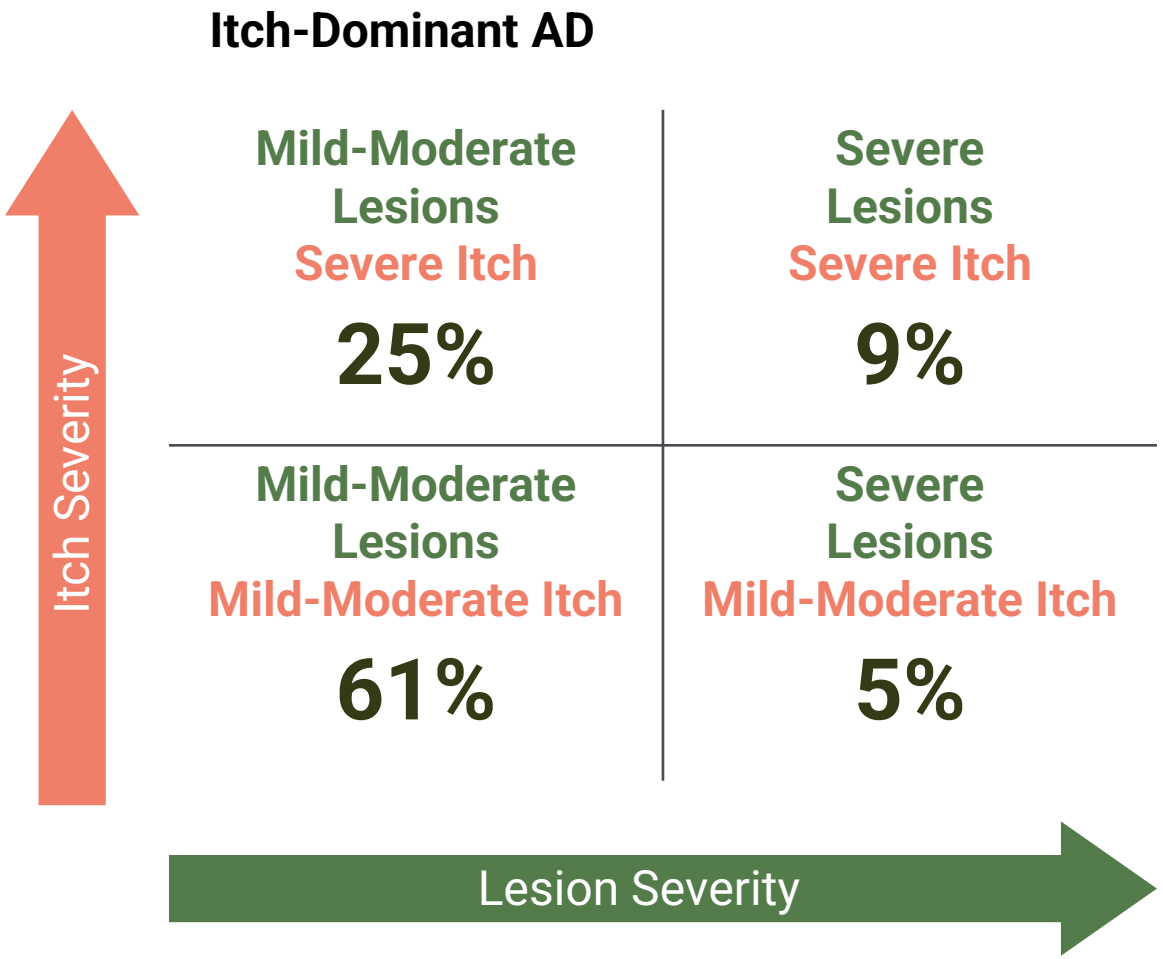
Itch Defines Important Clinical Subtypes of AD – Especially Mild-Moderate Lesions

- A recent study categorized patients with AD according to lesion severity and average itch intensity[1]
  - 592 adults with mild-severe AD undergoing standard-of-care treatment over a two-year period
  - Mild-moderate itch and lesions (MI-ML), mild-moderate itch and severe lesions (MI-SL), severe itch and mild-moderate lesions (SI-ML), and severe itch and lesions (SI-SL)
- Most patients had **mild-to-moderate lesions** and matching **mild-to-moderate itch** severity[1]
- The second most common subset had **mild-to-moderate lesions** with **severe itch** (itch-dominant AD)[1]



1. Chovatiya R, et al. *Ann Allergy Asthma Immunol*. 2021;127:83–90.e2.

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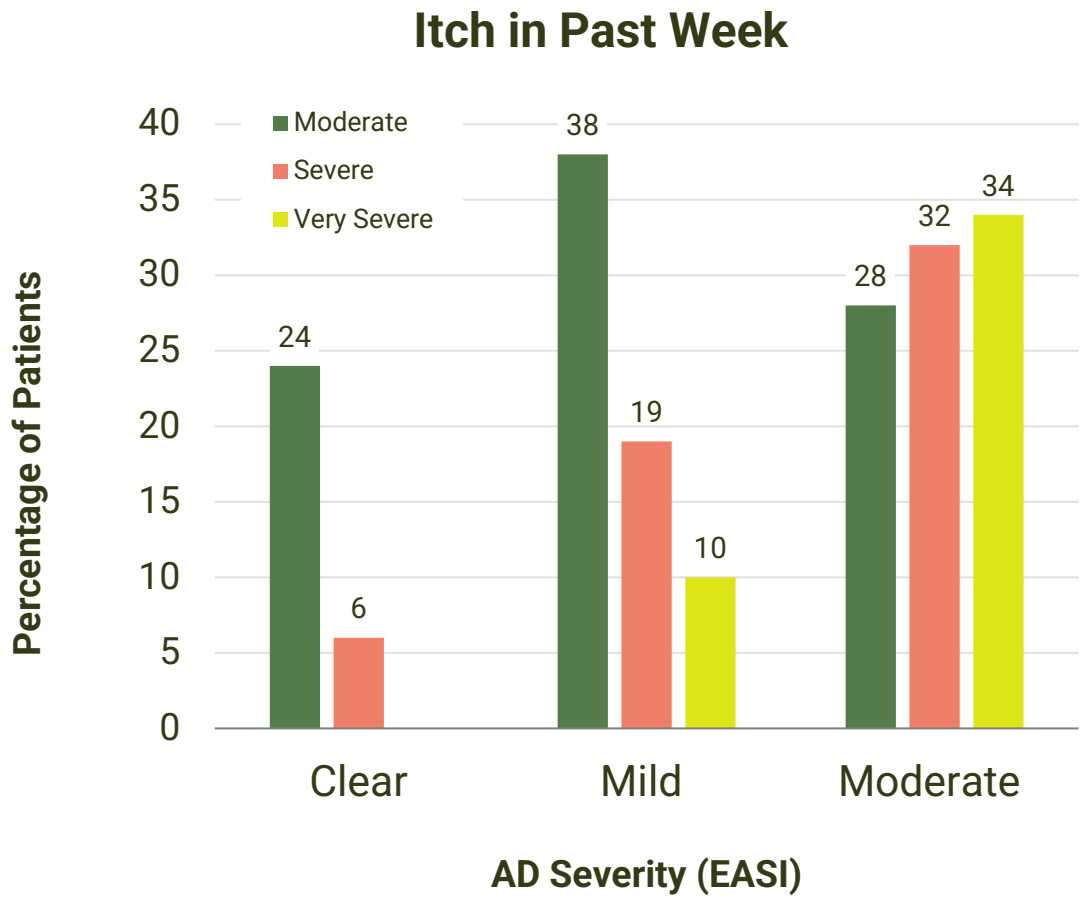
Lesional Severity is not Directly Proportionate to Itch

- Itch is present across all spectrums of AD[1]
- Moderate to severe pruritus is very common in patients with mild to moderate lesions[1]
- Pruritus is also common in AD patients with clear skin[1]



EASI, Eczema Area and Severity Index.

1. Chovatiya R, et al. Ann Allergy Asthma Immunol. 2021;127:83–90.e2

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Itch Severity Is Only Weakly to Moderately Correlated with Lesional Severity and Extent

Itch severity	Spearman correlations (rho)				
	EASI	O-SCORAD	BSA	vIGA-AD	vIGA-AD × BSA
NRS worst itch	0.61	0.60	0.56	0.32	0.53
NRS average itch	0.61	0.62	0.57	0.40	0.56
SCORAD itch	0.53	0.50	0.49	0.39	0.48

1. Chovatiya R, et al. *Ann Allergy Asthma Immunol*. 2021;127:83–90.e2.

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Patients with Severe Itch and Milder Lesions May Not Be Adequately Treated

% of patients initiated advanced systemic therapy for their AD

- Severe Itch - Severe Lesions: 57.8% - 66.7%
- Mild Itch - Severe Lesions: 53.9% - 57.7%
- Severe Itch – Mild Lesions: 30.8% - 32.0%

1. Chovatiya R, et al. *Ann Allergy Asthma Immunol*. 2021;127:83–90.e2.

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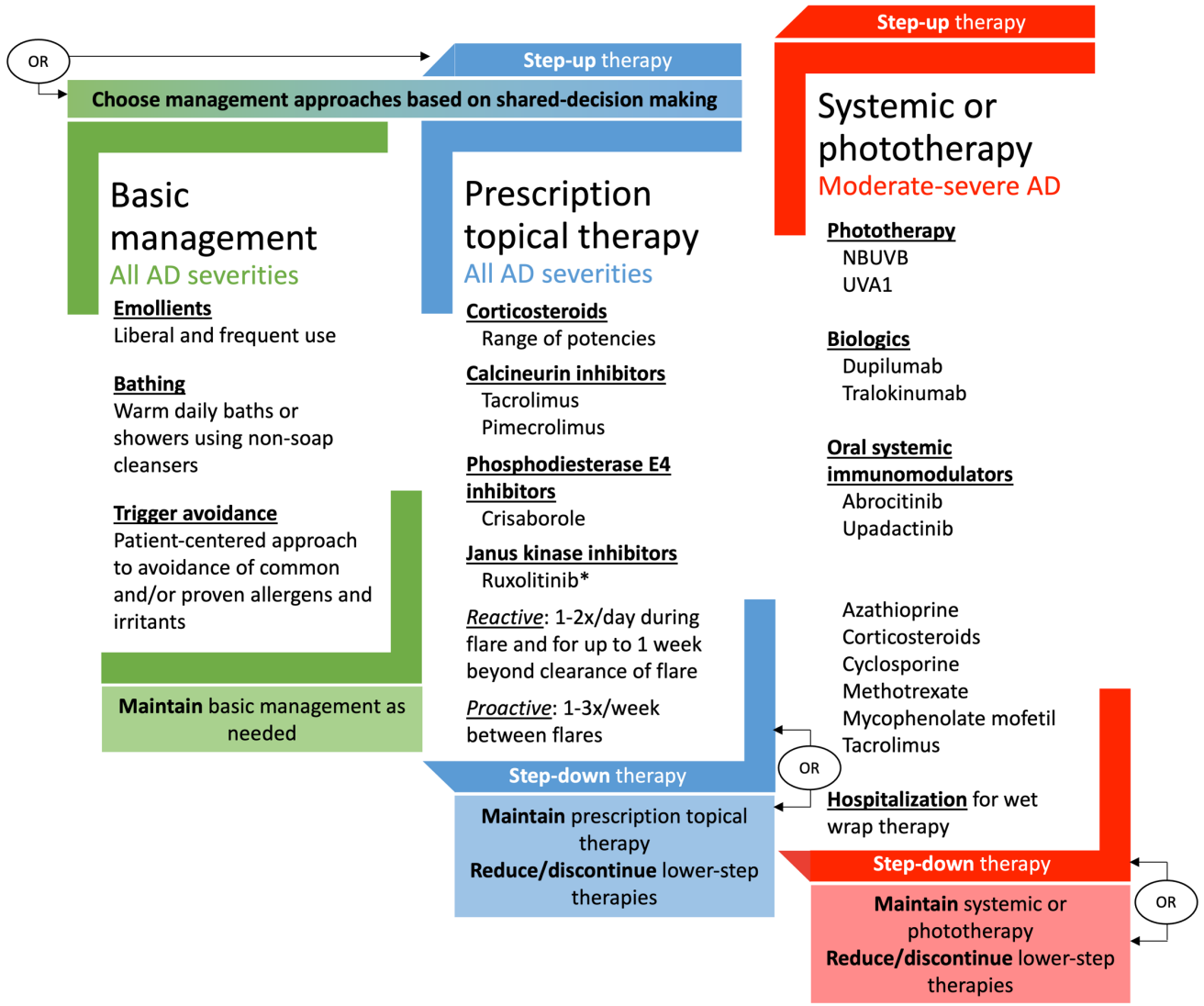
Does This Have Implications for Treatment?

Heterogeneous Clinical Domains Contribute to a Dynamic and Stepwise Treatment Approach

Issues with this Approach:

- Differences in criteria
- Different treatments at different steps
- No singular definition of severity



Chovatiya R, Silverberg JI. Iatrogenic Burden of Atopic Dermatitis. Dermatitis. 2021; Publish Ahead of Print.

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Where Does this Leave Itch-Dominant Patients?

- Highly pruritic patients experience a high QoL impact[1]
- Increased itch triggers and flares are characteristic of patients with itch-dominant AD[1]
  - Avoidance of all itch triggers may not be possible
- Patients with itch-dominant AD are frequently only treated with topicals[1,2]
- Step-up therapy may be required for disease control in patients with itch-dominant AD[1]
  - Less than one-third patients with severe itch and mild-to-moderate lesions are treated with systemic therapies

1. Chovatiya R, et al. *Ann Allergy Asthma Immunol*. 2021;127:83–90.e2. 2. He H, et al. *J Allergy Clin Immunol*. 2021;147:1369–1380.

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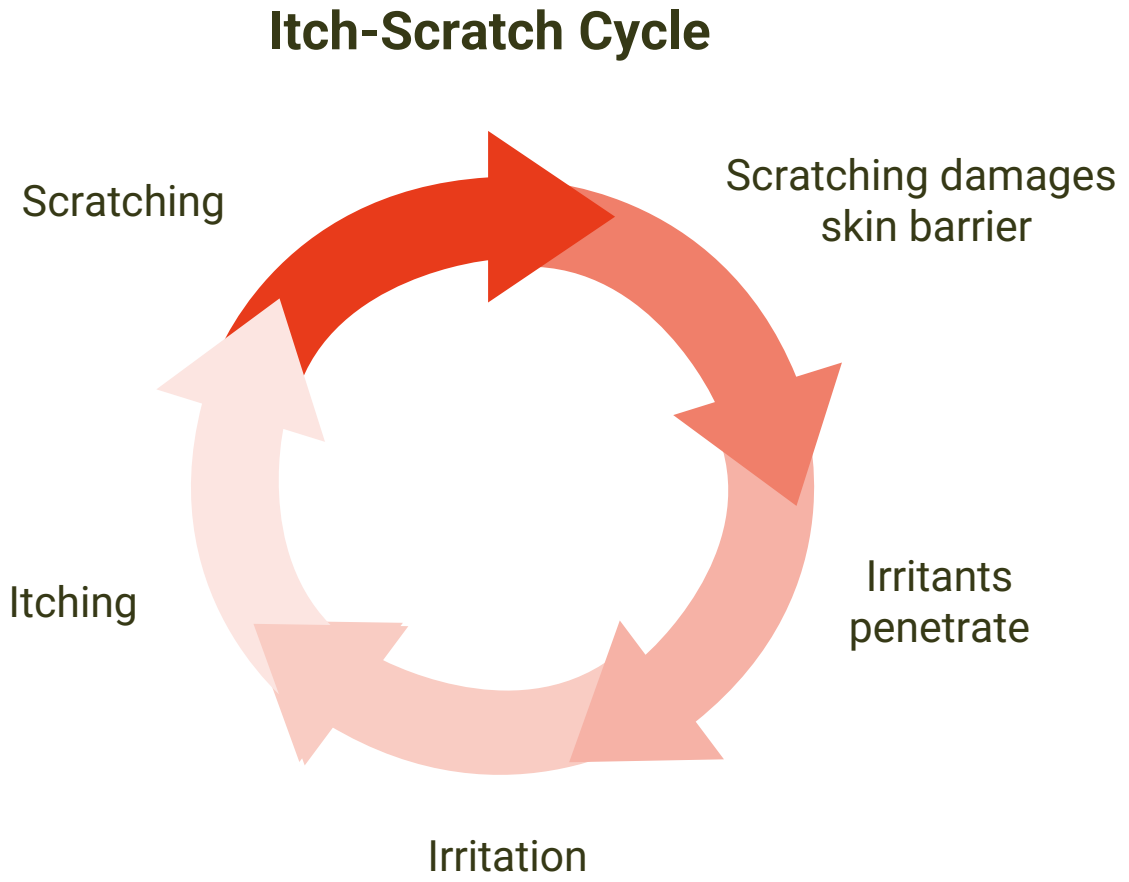
Could Itch-Targeting Systemic Agents Be Appropriate for Itch-Dominant Patients?

- Topical agents may not be sufficient to control itch, especially in nonlesional skin
- Alleviating itch may:[1,2]
  - Stop the itch-scratch cycle, thus reducing skin damage and potential for microbial infection
  - Improve sleep
  - Improve QoL



1. Pavlis J, Yosipovitch G. *Am J Clin Dermatol*. 2018;19:319–332. 2. Alexander H, et al. *Br J Dermatol*. 2020;182:1331–1342.

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Key Takeaways

- AD is a common but heterogeneous inflammatory skin condition that **cannot be fully evaluated by clinician assessment alone**

- Evaluation of lesions and itch together reveal clinically relevant subsets of disease – namely **itch dominant AD**

- The next generation of AD treatments should be designed to selectively **target and treat relevant disease pathways**

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Notalgia Paresthetica: Background

Raj Chovatiya, MD, PhD, FAAD
Assistant Professor of Dermatology, Director of the Center for Eczema and Itch, Medical Director of the Clinical Trials Unit
Northwestern University Feinberg School of Medicine

Etiologies of Chronic Pruritus

Defined as an unpleasant sensation of the skin that provokes the urge to scratch, with symptoms present for more than 6 weeks[1]

Inflammatory pruritus

- Atopic dermatitis
- Psoriasis
- Lichen planus
- Prurigo nodularis

Neuropathic

- Notalgia paresthetica
- Brachioradial pruritus
- Post-herpetic neuralgia

Systemic pruritus

- Chronic kidney disease
- Primary biliary cholangitis
- Hyperthyroidism

Other etiologies of pruritus

- Pruritus in elderly
- Drug-induced (checkpoint inhibitors[2])
- Pruritus of unknown origin

1. Weisshaar E, et al. *Acta Derm Venereol*. 2019;99:469-506.
2. Allegra A, et al. *Biomedicines*. 2021;9:2.

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Characteristics of Neuropathic Pruritus

- Neuropathic pruritus – pruritus caused by neuronal or glial damage, which plays a role in pruritic signal transduction[1]
- The prevalence of pruritus in the general population varies from 8% to 38% worldwide, with lifetime prevalence ranging from 23% to 26%[2]
  - Neuropathic pruritus represents approximately 8% of total cases of chronic pruritus[3]
- Most often accompanied by sensory damage experienced as pain, allodynia, paresthesia, hyperesthesia, or hypothesia[1,4]
  - Peripheral and central sensitization of nerve fibers induces alloknesis, common in neuropathic itch
  - Patients may also experience burning, tingling, and stinging
- Neuropathic pruritus can be caused from local nerve fiber compression, or localized or generalized nerve fiber degeneration affecting different neuronal structures in the PNS or CNS[1]

CNS, central nervous system; PNS, peripheral nervous system.

1. Misery L, et al. *Nat Rev Neurol*. 2014;10:408-416. 2. Mollanazar NK, et al. *Curr Dermatol Rep.* 2015;4:20-29 3. Rosen JD, et al. *Dermatol Clin*. 2018;36:213-224. 4. Yosipovitch G, Samuel LS. *Dermatol Ther*. 2008;21:32-41.

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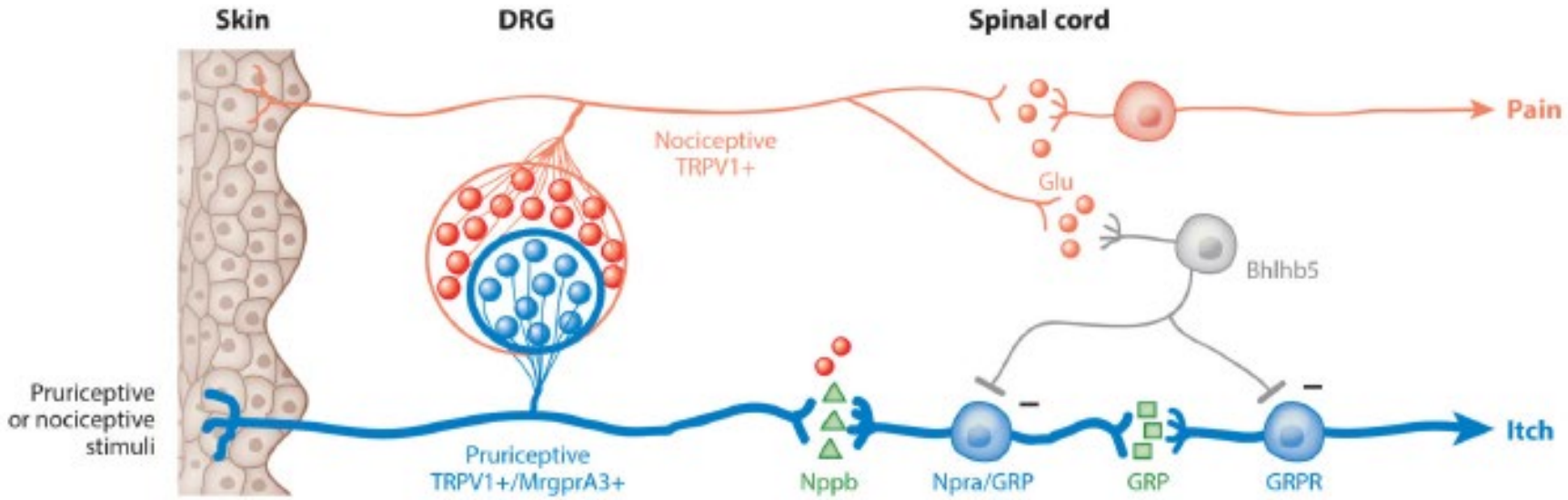
Transmission of Itch Signals from the Skin to the Brain



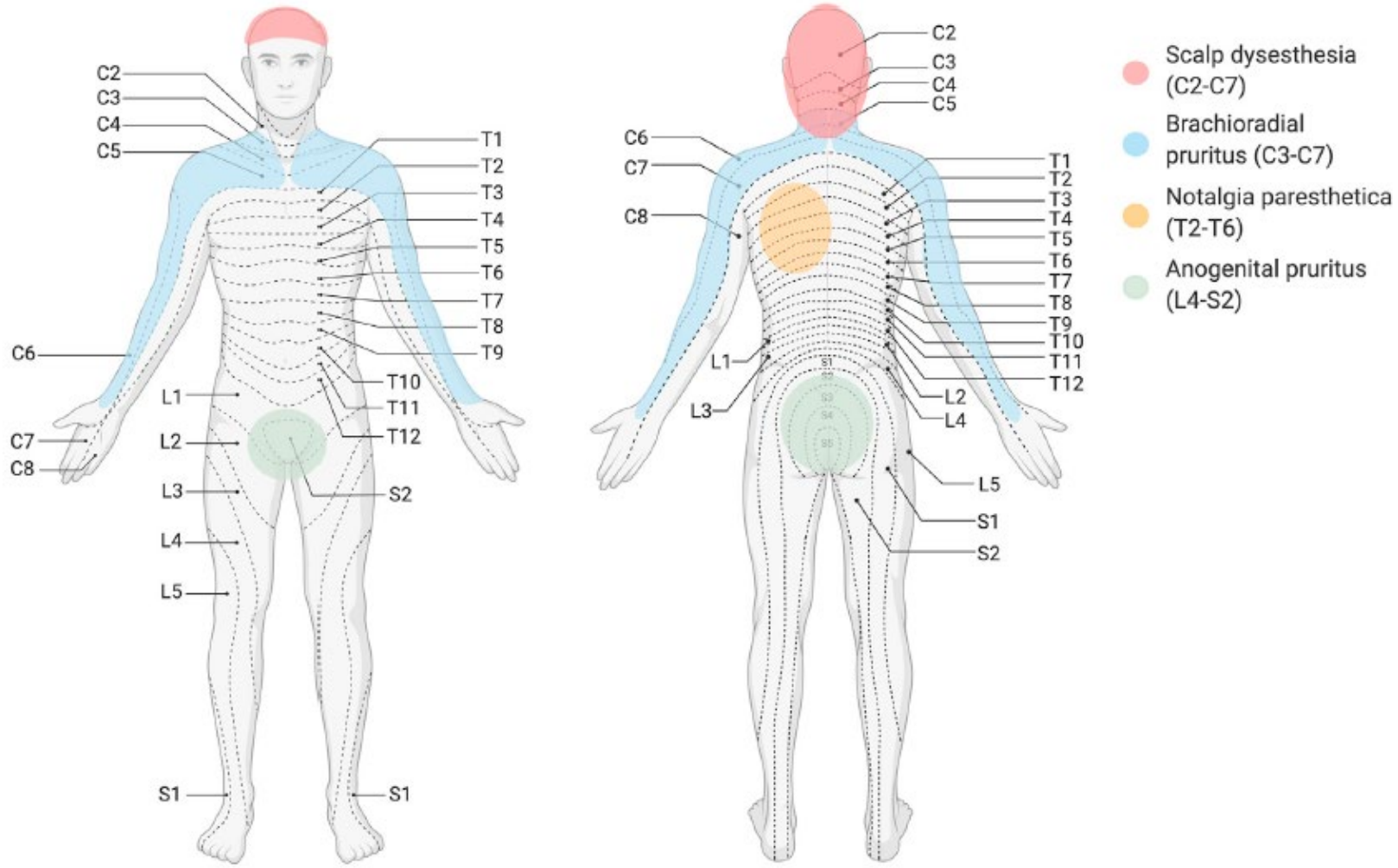
- Itch signals are transmitted by both itch & pain sensitive neurons from periphery into the dorsal root ganglia (DRG)[1]
- From the DRG, the signal is carried through various interneurons within the spinal cord[1,2]
- Itch signals are then processed in the thalamus and parabrachial nucleus in the brainstem[2]
- Trauma to the spinal cord or spinal nerves can alter itch transmission[3]

Republished with permission from *Annu Rev Biophys*, Han L, Dong X, 43, 2014.

GRP, gastrin-releasing peptide; MrgprA3, mas-related G-protein-coupled receptor member A3; Nppb, natriuretic polypeptide b.

1. Liu T, Ji R. *Pflugers Arch*. 2013;465:1671-1685. 2. Dong X, Dong X. *Neuron.* 2018;98:482-494. 3. Roh YS et al. *J Am Acad Dermatol.* 2022;86(1):1-14

Pathogenesis of Neuropathic Itch Disorders



C, Cervical; L, Lumbar; T, Thoracic

Roh YS et al. *J Am Acad Dermatol.* 2022;86(1):1-14.

Clinical Case

Jane is a 55-year-old with chronic pruritus

- Itch for the past 2 years on the upper back
- Never had an issue with skin / itch in the past
- Rarely able to focus during the day or sleep well at night
- Tried a variety of over-the-counter treatments marketed as “anti-itch” but generally experienced dryness or irritation
- Has seen several specialists, including one who told her that the itch is “in her head”
- Has tried five different topical corticosteroids without any improvement
- The most recent treatment she tried was prescription oral medication that made her drowsy and lose focus in her work as an accountant

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What is Notalgia Paresthetica (NP)?

- NP is a common, yet under-recognized neuropathic itch disorder[1]
- May be caused by damage to the cutaneous branches of the dorsal rami of the thoracic spinal nerves (T2-T6)[2]
- May present to a range of specialists due to variable symptoms but most commonly seen by dermatologists[3]
- Resistant to many commonly used anti-pruritic therapies such as anti-histamines and topical corticosteroids[3]

1. Ellis C. *Dermatol Pract Concept*. 2013;3:3-6 2. Pereira et al. Curr Opin Neurobiology 2022, 75:102573. 3. Ansari et al. Journal of Dermatological Treatment 2019: 1-10..

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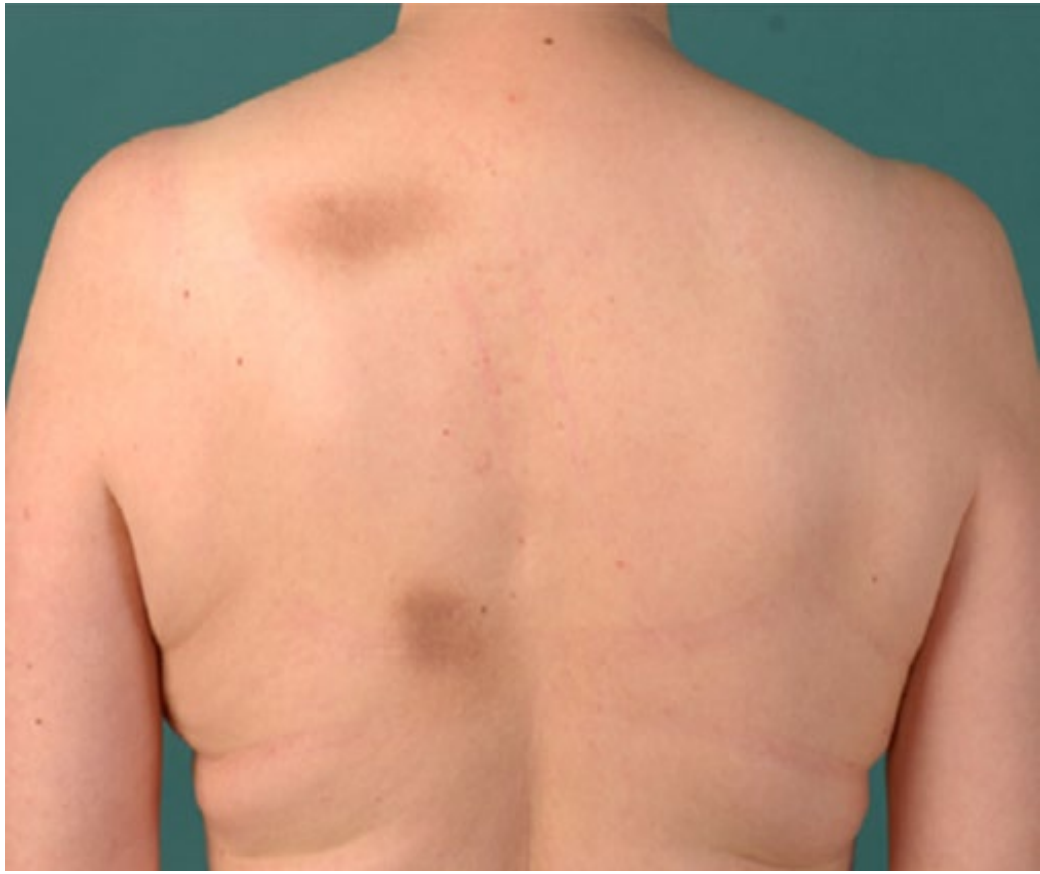
Clinical Presentation

- Characterized by recurrent, localized itching in the interscapular and paravertebral regions[1]
- May be accompanied by pain, tingling, burning, or other hyperesthesias or parethesias[2]
- Excessive scratching leads to hyper- or hypo-pigmentation or lichenification[2]
- More common in women[2]
- Mean age of onset 50-60 years[2]



1. Ellis C. *Dermatol Pract Concept*. 2013;3:3-6 2. Howard et al. Int Journal of Derm 2018;57: 388-392.

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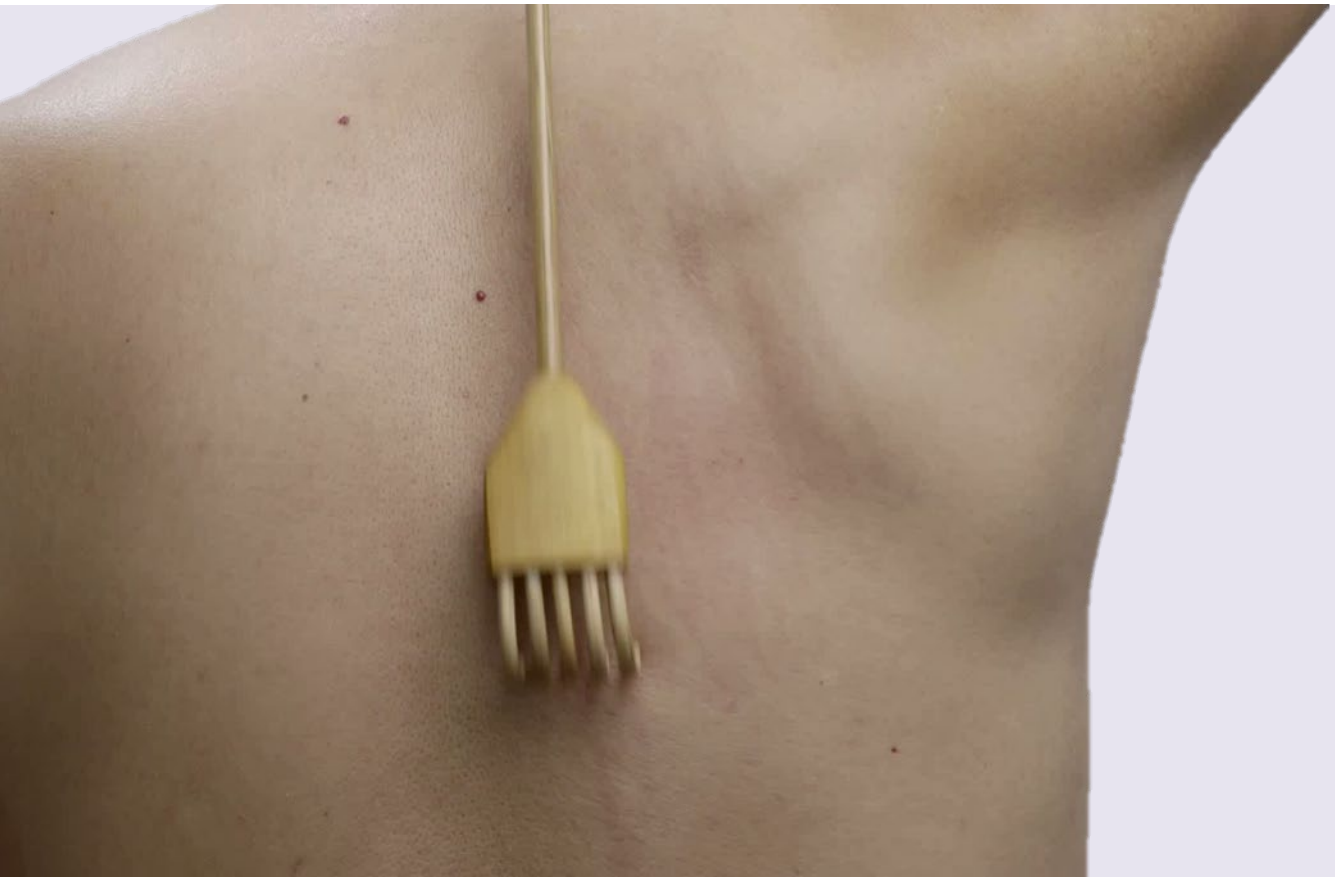
Impact of Itch in NP Patients

- Itch in NP is bothersome and may affect emotions, mood, or self-care practices (needing back scratchers at home or when traveling)[1]

- Some patients report difficulty sleeping or staying asleep, although sleep may be less disturbed in NP compared to other neuropathic itch conditions[1,2]

1. Bacci et al. JAAD Int 2022;8:94-101. 2. Lipman et al. JAAD Int 2020;2:96-97.

Limitations to Treatments



- There are no approved therapies for NP and no professional guidelines
- Current off-label therapies have little evidence and have tolerability limitations
- Application site makes topicals impractical in most cases

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Current Off-Label Treatment Options

- Often resistant to multiple therapies
- Conventional antipruritic therapies (i.e., antihistamines, topical corticosteroids) show poor effect
- Capsaicin and gabapentin commonly used treatments by dermatologists
- Other anecdotal off-label therapies:
  - Topical anesthetics
  - Tacrolimus
  - Intralesional steroids
  - Botulinum toxin A
  - Oxcarbazepine
  - Amitriptyline
  - Surgical decompression
  - Paravertebral local anesthetic blocks
  - Transcutaneous electrical nerve stimulation (TENS)
  - Electrical Muscle Stimulation (EMS)
  - UV-B
  - Spinal manipulation
  - Physical therapy
  - Osteopathic manipulative therapy
  - Acupuncture
  - Cryotherapy

Source: Howard et al 2017 International Journal of Dermatol 57, 388-392

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Key Takeaways

- Notalgia Paresthetica is common, yet under-recognized and under-diagnosed
- Pruritus is bothersome to patients and may impair normal activities
- Treatment is challenging
  - Traditional anti-pruritic therapies are ineffective
  - Off-label therapies like capsaicin and gabapentin are effective in some patients but may have tolerability limitations
- There is a need for additional safe and effective therapies

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Pruritus in Notalgia Paresthetica: Trial Design

Joana Goncalves, MD
Chief Medical Officer, Cara Therapeutics

Difelikefalin for Pruritus in Notalgia Paresthetica (NP)

Estimated >650K patients currently treated for NP[1, 3-5]

No FDA-approved treatments; off label treatments are either ineffective or have tolerability issues[2]

Oral difelikefalin demonstrated strong anti-pruritic effect in patients with NP in the Phase 2 POC KOMFORT Study

Oral difelikefalin was well-tolerated with a consistent safety profile

Positive interaction with FDA paved the path for the NP clinical development program

1. Pereira P. et al., Acta DV 2018 ; 98:82-88; 2. Howard M et al. Notalgia paresthetica: a review for dermatologists. Int J of Derm. 2017. 388-392. 3. US Census Bureau 2020 population projection; 4. Mollanazar N.K. et al., Acta Clin Croat 2018; 57:721-725; 5. Syneos Health qualitative primary research of US dermatologists, Feb 2022; 5. Syneos market research and Apollo claims database

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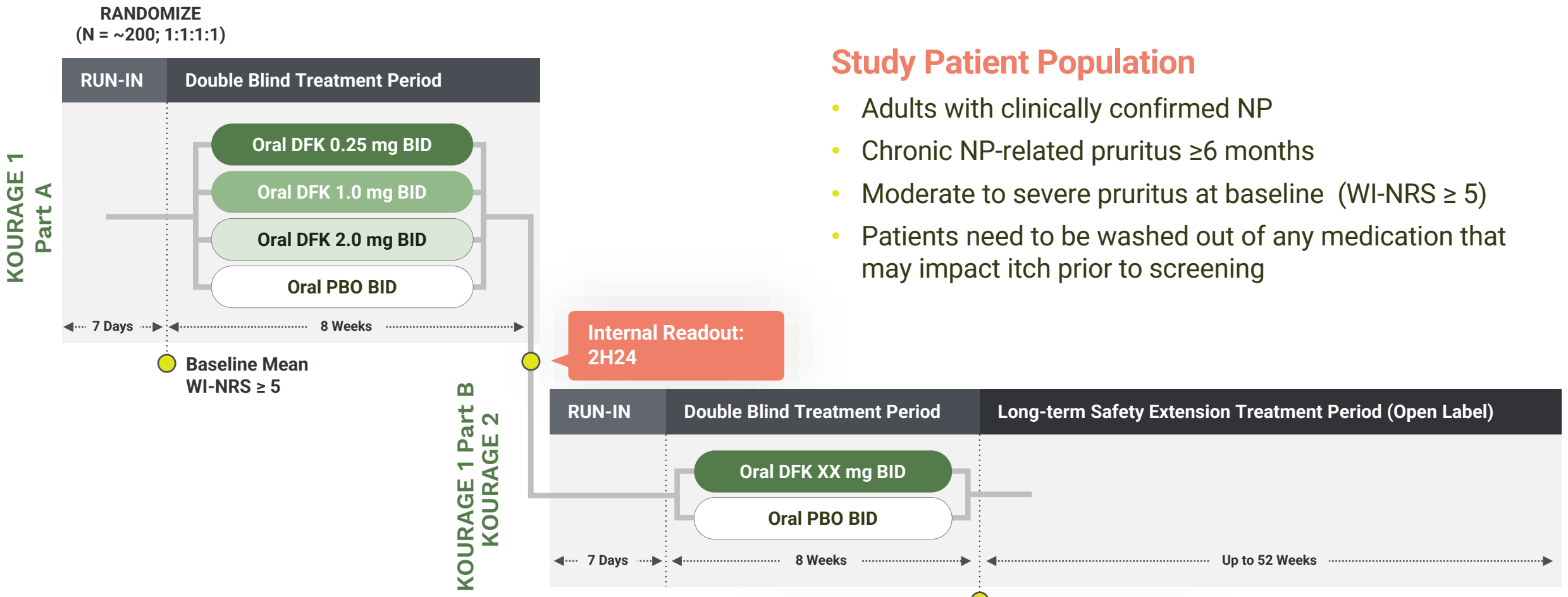
KOURAGE 1 & 2 : Phase 2/3 Study Design in NP



Study Patient Population

- Adults with clinically confirmed NP
- Chronic NP-related pruritus ≥6 months
- Moderate to severe pruritus at baseline (WI-NRS ≥ 5)
- Patients need to be washed out of any medication that may impact itch prior to screening

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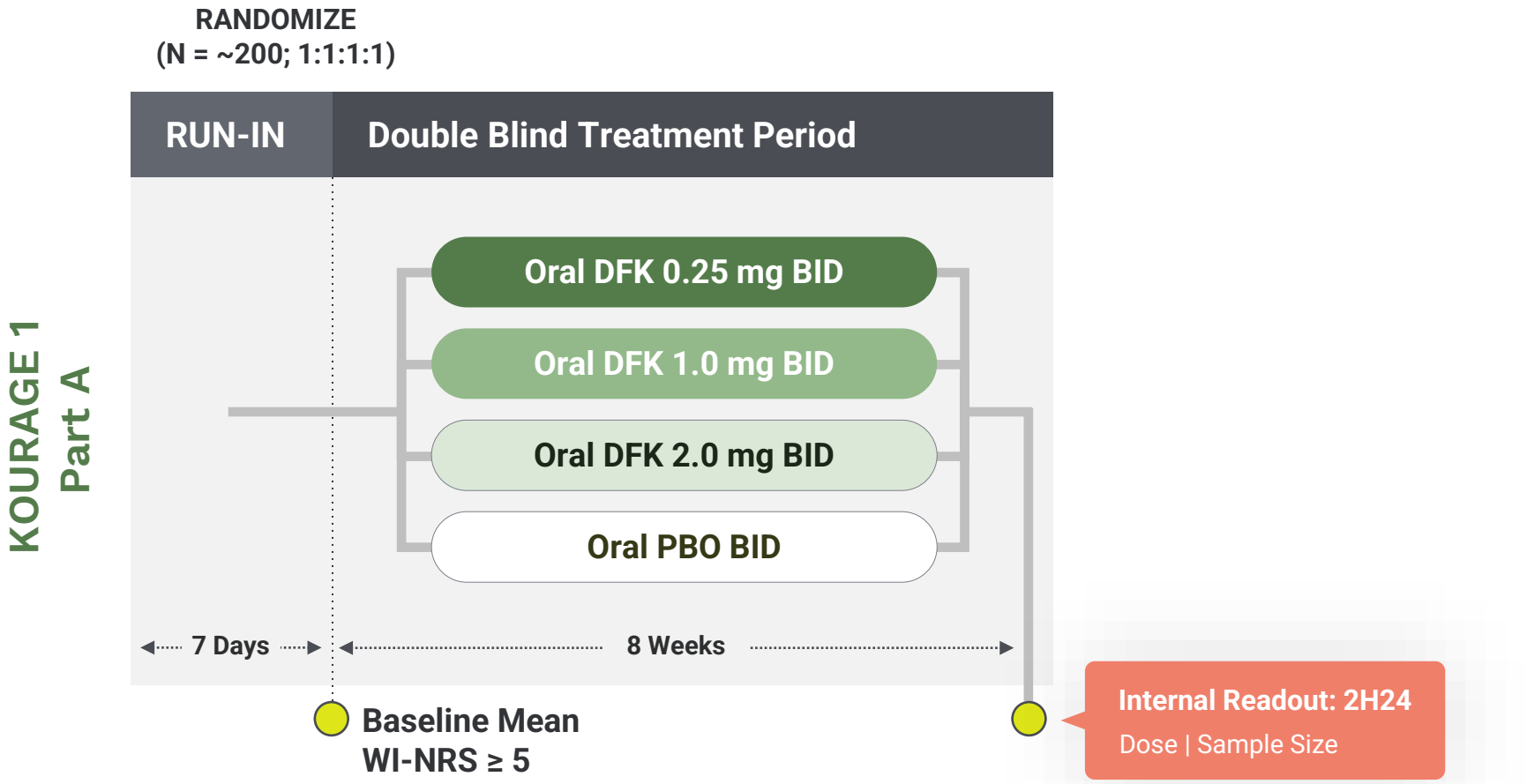
KOURAGE 1 Part A : Study Design



Criteria

- % of subjects with ≥4-point improvement from baseline in WI-NRS score at Week 8
- Safety assessments

Information

- Dose
- Sample size

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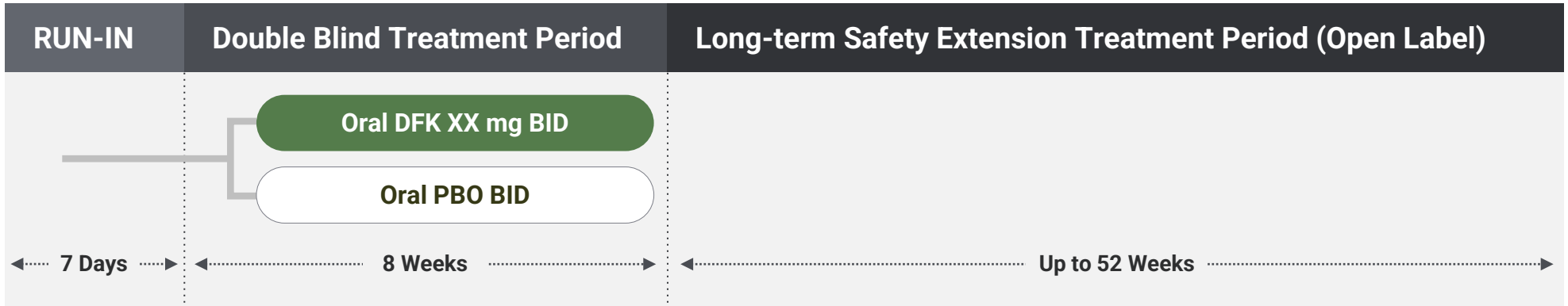
KOURAGE 1 Part B and KOURAGE 2 : Study Design

KOURAGE 1 Part A

READOUT
Informs dosing & sample size



PRIMARY ENDPOINT
% of subjects with ≥4-point improvement from baseline in WI-NRS score at Week 8

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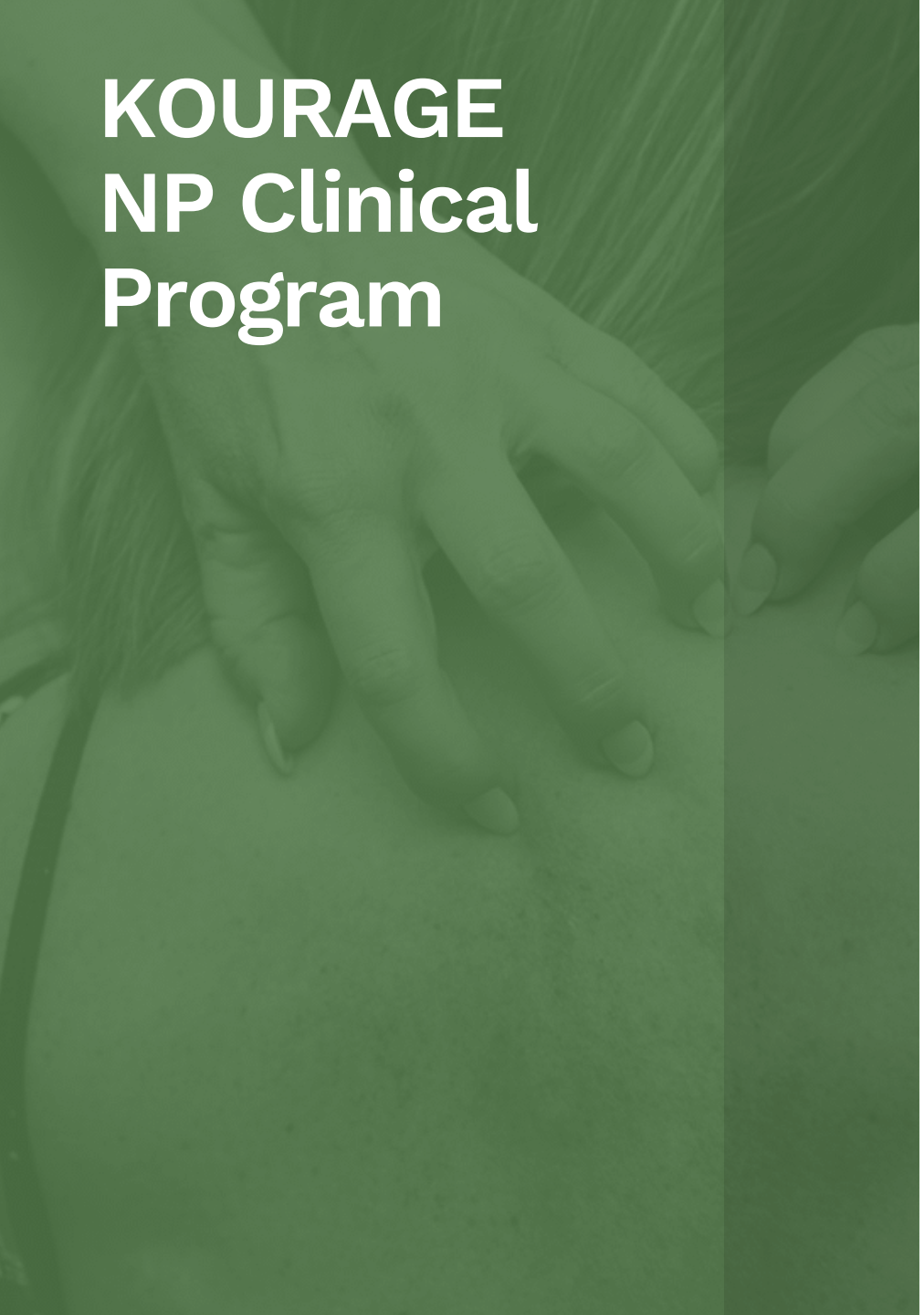
KOURAGE NP Clinical Program



- Address the unmet need where there are no approved treatments and current therapies have limitations.
- The program is designed to enhance operational efficiency and to progress as rapidly as possible.
- Execute on study designs with the greatest likelihood of success.

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Thank You