Managing the Burden of Prurigo Nodularis: The Role of Emerging Therapies

Provided by Integrity Continuing Education, Inc.
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Faculty

April W. Armstrong, MD, MPH

Professor of Dermatology

Associate Dean of Clinical Research

Director, Psoriasis Program

University of Southern California

Los Angeles, California

Disclosures

Gil Yosipovitch, MD	
Relationship	**Manufacturer**
Consulting Fees	AbbVie, Bristol-Myers Squibb, Dermavant, Eli Lilly, Janssen Pharmaceuticals, Leo Pharma, Modernizing Medicine, Novartis, Ortho
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Learning Objectives

- **APPLY** clinical evidence and criteria to identify common symptoms and associated disease cycles that negatively affect quality of life in patients with prurigo nodularis (PN) to support earlier diagnosis
- **IDENTIFY** known factors involved in the pathogenesis of PN
- **UTILIZE** available guidance for the treatment of patients with PN
- **EVALUATE** clinical evidence supporting use of current and investigational agents for the management of PN

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Itching to Be Well Again: Understanding the Disease Burden of PN and Its Effect on QOL

Prevalence: PN by the Numbers

- Estimated prevalence: ~83,500 or 148/100,000 population

United States Prevalence Stratified by Age (Years)*					
	<15	**15–24**	**25–44**	**45–64**	**>65**
Number	2,919	16,914	38,076	30,164	79,635
Percentage	1.7	10.1	22.7	18.0	47.5

*Taken from NAMCS ICD-9 codes in 2015.

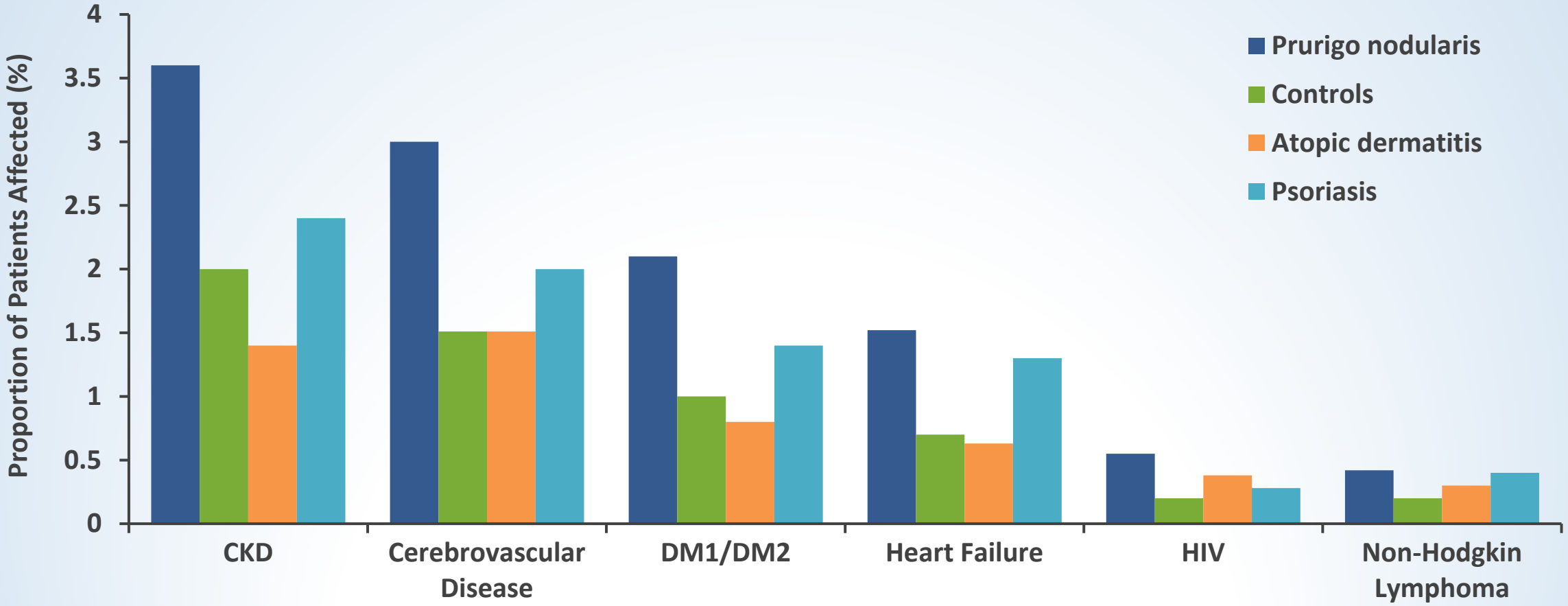
  - Prevalence by ethnicity: 3.4 times more common in African Americans
    - African Americans: 49.4%
    - White: 41.8%
    - Asian: 3.4%
  - By sex: Women 53%; men 47% per claims database of >24 million enrollees

ICD, International Classification of Diseases; NAMCS, National Ambulatory Medical Care Survey.

Boozalis E, et al. *J Am Acad Dermatol*. 2018;79:714-719; Huang AH, et al. *J Invest Dermatol*. 2020;140:480-483; Ständer S, et al. *JAAD Int*. 2020;2:28-30.

PN and Common Cutaneous and Systemic Comorbidities

PN may be observed with incidental metabolic, cardiovascular, and other comorbidities



CKD, chronic kidney disease; DM1/DM2, diabetes mellitus type 1 and 2; HIV, human immunodeficiency virus.

Huang AH, et al. *J Invest Dermatol*. 2020;140:480-483.

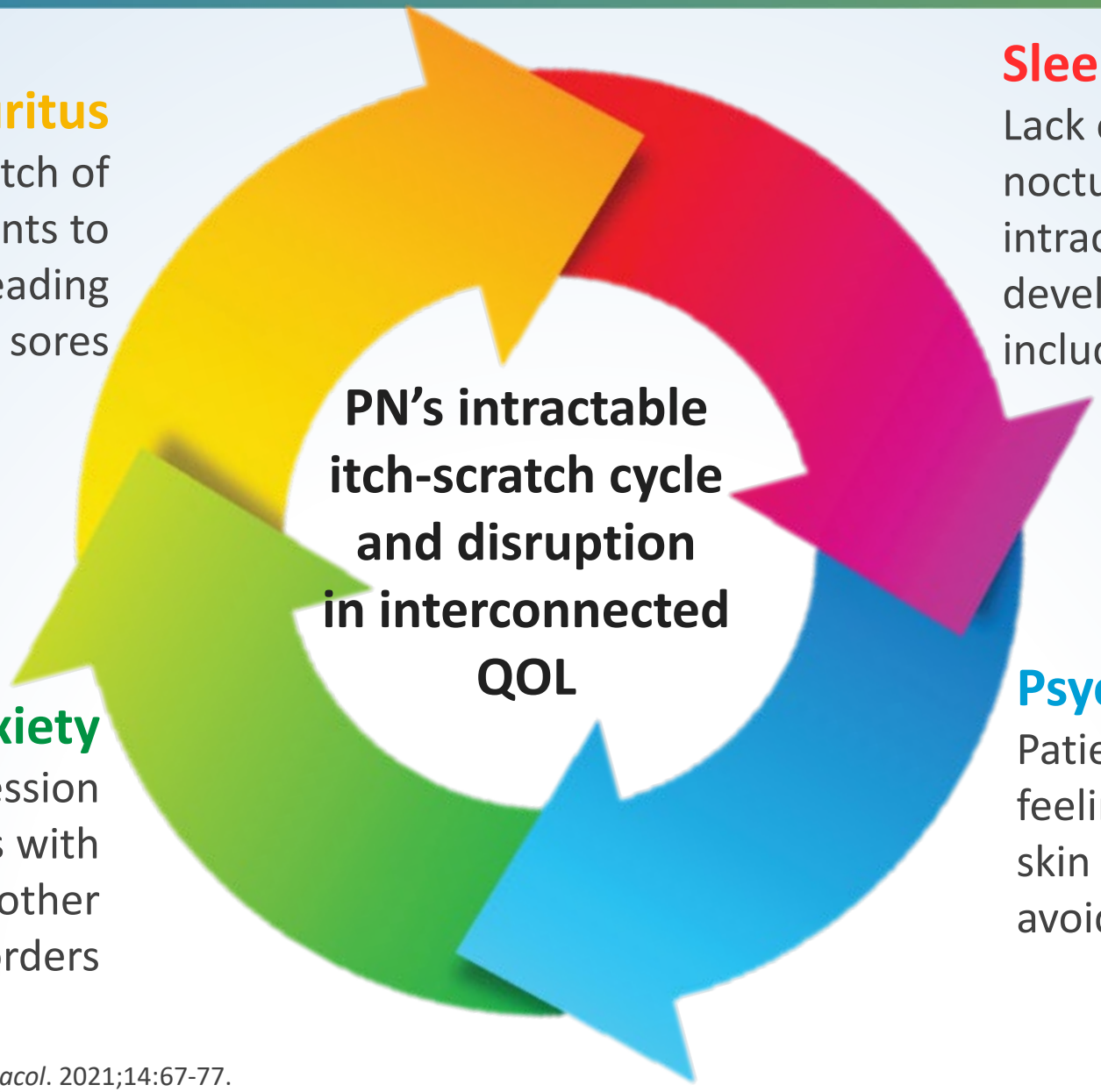
Itch + Scratch: A Vicious, Reflexive Cycle

Pruritus

Intense, relentless itch of PN causes patients to constantly scratch, leading to open, excoriated sores

Sleep Disturbance

Lack of sleep and frequent nocturnal awakenings due to intractable itch contribute to developing other diseases, including psychiatric conditions



Depression & Anxiety

Higher rates of depression and anxiety in patients with PN vs those with other inflammatory skin disorders

Psychosocial Difficulties

Patients with PN report feeling embarrassed by the skin nodules, causing them to avoid social interactions

QOL, quality of life.

Williams KA, et al. *Expert Rev Clin Pharmacol*. 2021;14:67-77.

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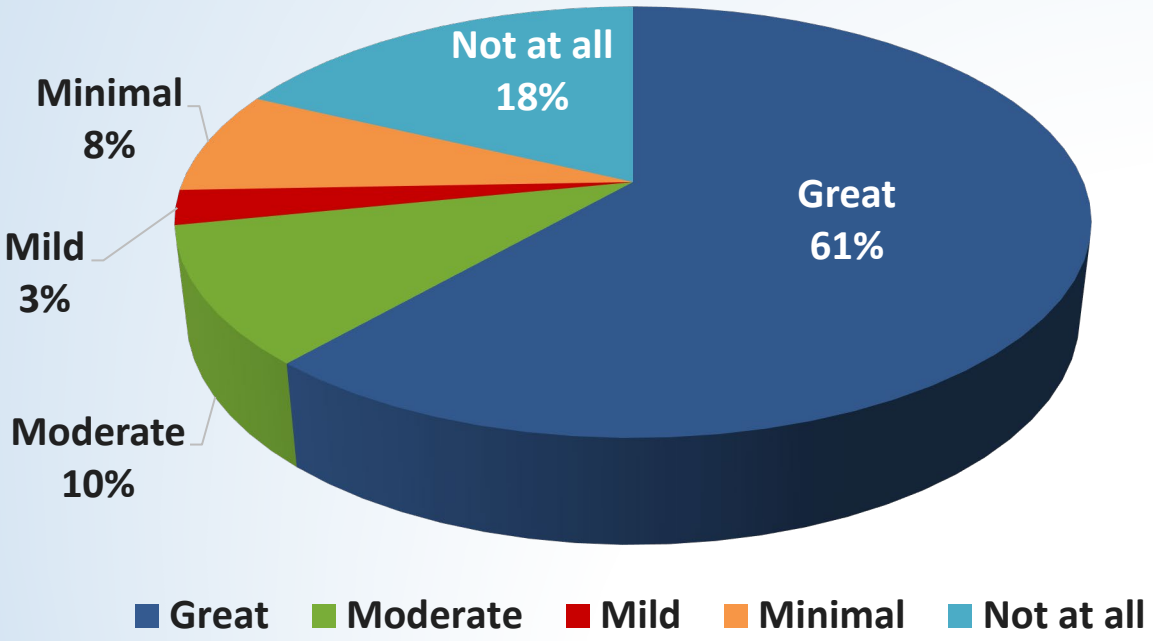
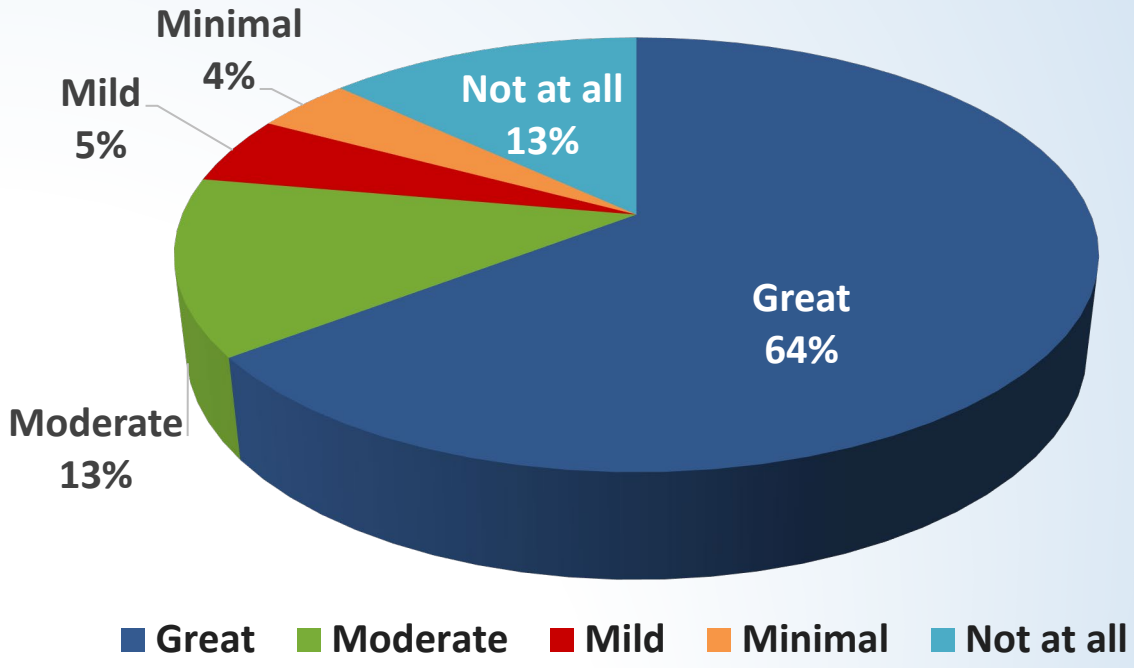
Impact of Itch on Sleep Disturbance

Sleep disturbance effect studied in patients with PN vs AD

Extent pruritus disturbs sleep (PN)
N=39



Extent pruritus disturbs sleep (AD)
N=81



AD, atopic dermatitis.

Gwillim EC, et al. *Acta Derm Venereol*. 2021;1010:adv00424.

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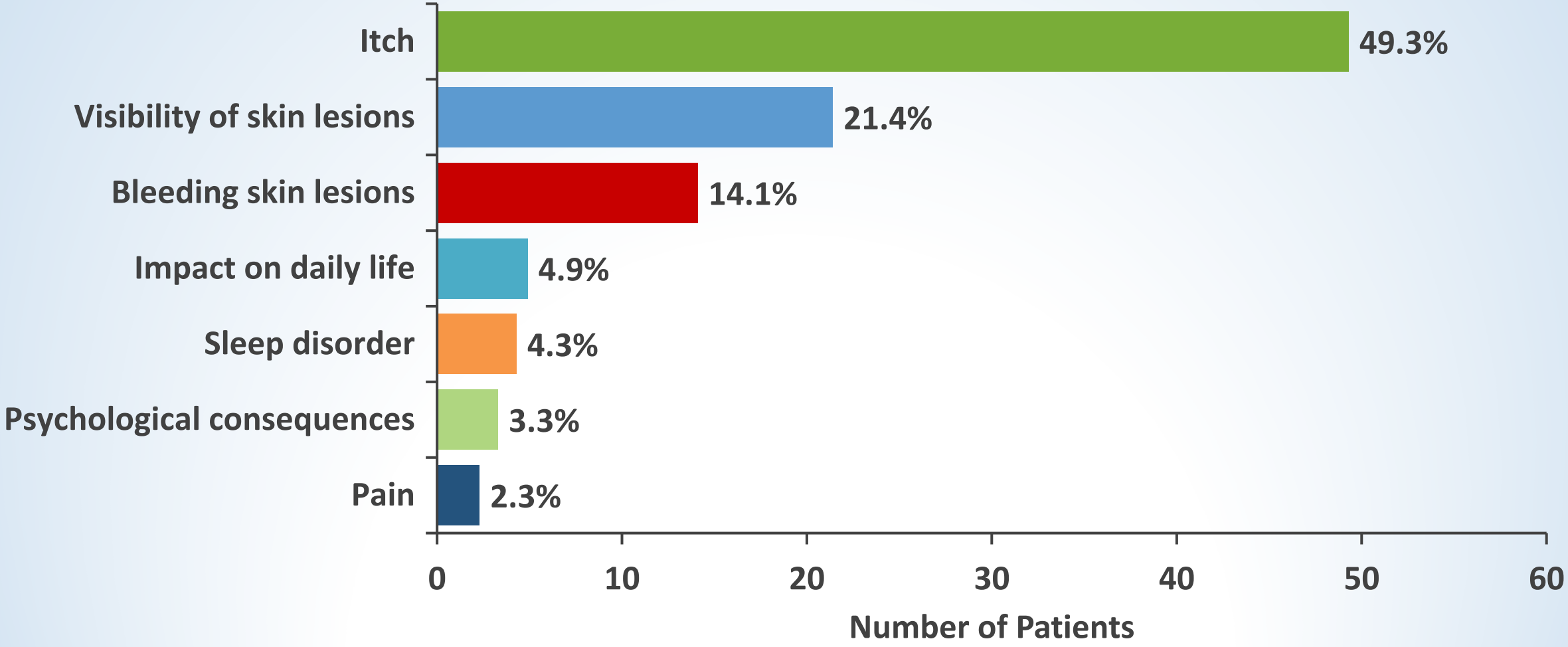
Itch the Most Bothersome Disease Burden

Most bothersome symptom identified by PN patients in 12 European countries (N=509)



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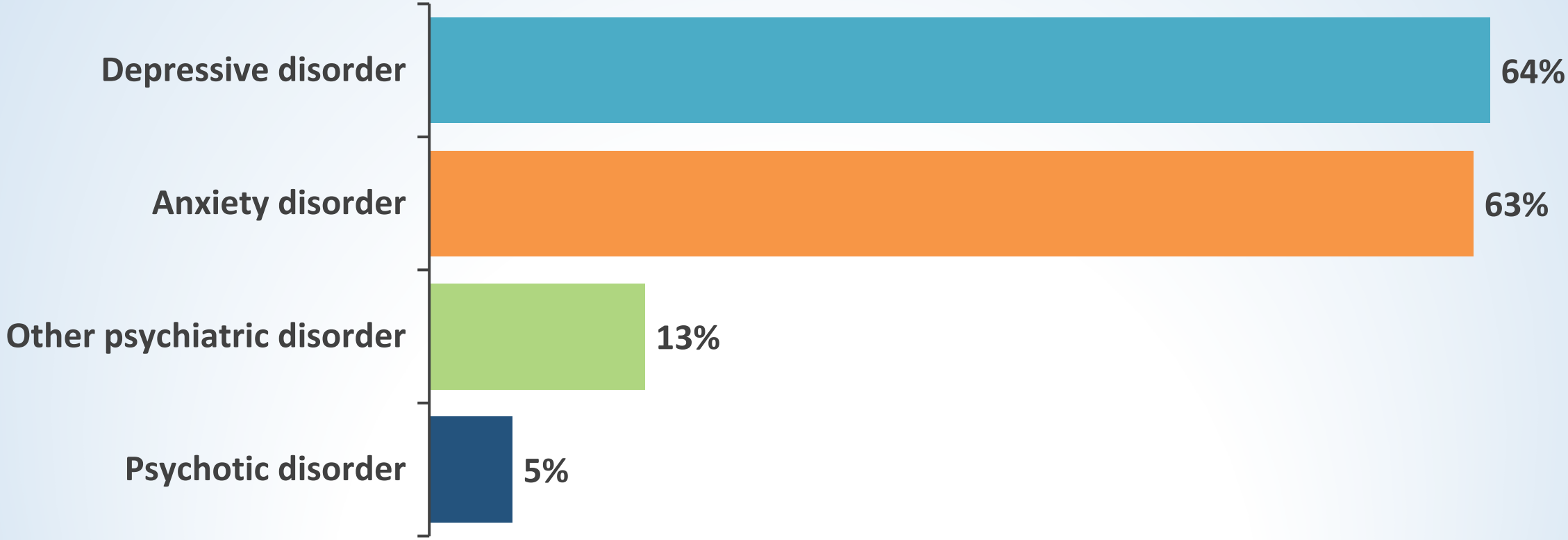
Pereira MP, et al. *J Eur Acad Dermatol Venereol*. 2020;34:2373-2383.

PN and Common Psychiatric Comorbidities

Most common psychiatric comorbidities identified in PN patients in (N=288)
44% had at least 1 psychiatric comorbidity, most common noted below



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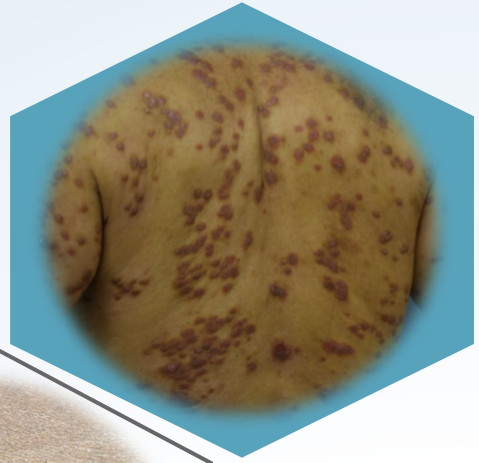
Han J, et al. *J Clin Aesthet Dermatol*. 2021;15:53-58.

Diagnosis and Distinctives: PN Phenotypes, Differentials, and Diagnostic Criteria

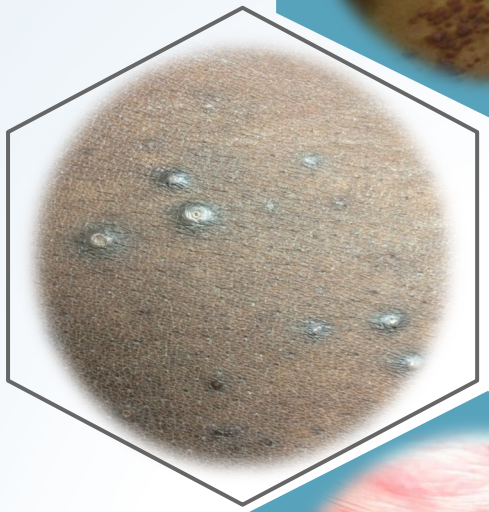
What PN Can Look Like

PN with extensive body involvement

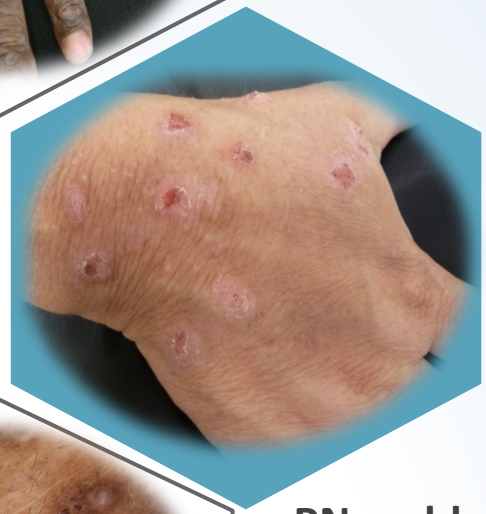


PN in AD in African Americans

Hyperkeratosis on top of PN lesions: less intensive scratching

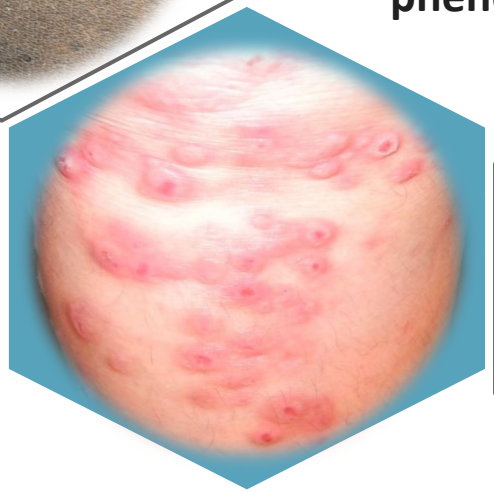


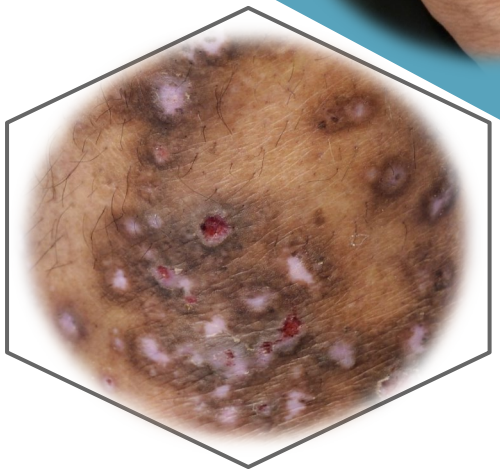
Prurigo Nodules of multiple etiologies may display different phenotypes



Excoriations on top of PN lesions: more intensive scratching

Pink nodules without hyperpigmentation in white skin





PN on black skin may have hyperpigmentation surrounding nodules

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Common Differential Diagnoses

- Many dermatologic conditions can be confused with PN
  - Hypertrophic lichen planus
  - Multiple keratocanthomas
  - Perforating disorders
  - Bullous pemphigoid
  - Insect/arachnid bites
  - Scabies

And many more!!

Elmariah S, et al. *J Am Acad Dermatol.* 2021;84:747-760.

PN Diagnostic Criteria From EADV

PN a clinical diagnosis of exclusion; No definitive lab tests

Disease State	Criteria	Comment
Core symptoms (major criteria)	1. Chronic pruritus ≥6 weeks 2. History and/or signs of repeated scratching (eg, excoriations and scars) 3. Localized or generalized presence of multiple lesions	• All symptoms must be present for a diagnosis of PN • Pruritus must be present and should be the initial sign • Localized: one affected area such as lower leg or lower arm or initial singular lesions do not meet diagnostic criteria
Range of manifestations	1. Nodular type 2. Plaque type 3. Umbilicated type	Patients must present with ≥1 clinical manifestation of chronic PN. It is sufficient to diagnose patients as chronic PN without including subtype

EADV, European Academy of Dermatology and Venereology.

Pereira MP, et al. *J Eur Acad Dermatol Venerol.* 2018;32:1059-1065.

PN Diagnostic Criteria From EADV *(continued)*

Associated Criteria	Comment
1. Signs	• Lesions distributed on areas of the skin accessible to scratching • Lesions symmetrically distributed • Normal or lichenified skin between lesions • Excoriations and scars may be present • Face and palms rarely affected • Lesions are persistent
2. Symptoms	• Pruritus precedes skin lesions • Pruritus might be accompanied by burning, stinging, pain, and other sensations • Signs of chronicity: continuous high-intensity pruritus; alloknesis, hyperknesis, spreading of lesions
3. Function	• Impaired QOL • Sleep loss due to pruritus • Absence from work • Obsessive-compulsive behavior

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Pereira MP, et al. *J Eur Acad Dermatol Venerol.* 2018;32:1059-1065.

PN Diagnostic Criteria From EADV *(continued)*

Associated Criteria	Comment
4. Emotions	• Depression • Anxiety • Anger • Disgust • Shame • Helplessness
5. Pathophysiology	• Neuronal sensitization toward itch induced by chronic pruritus and development of chronic itch-scratch cycle • Etiology of chronic pruritus might be dermatologic, systemic, neurologic, psychiatric/psychosomatic, multifactorial, or can be idiopathic • Presence of other specific skin lesions may point to a concomitant skin disease

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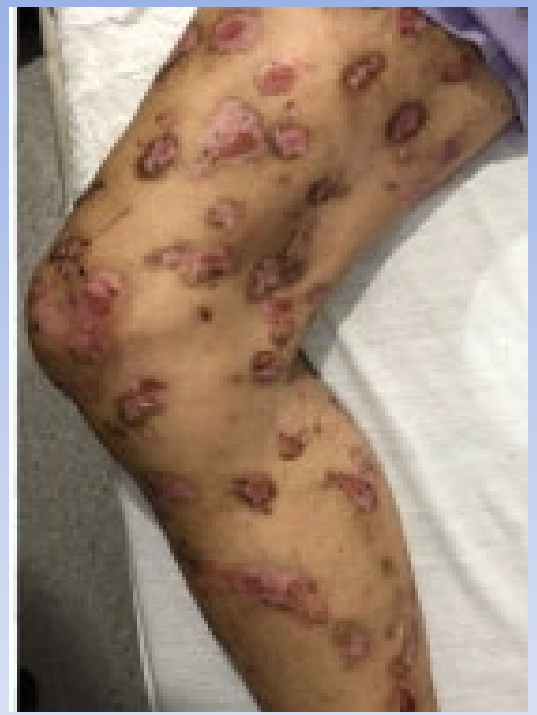
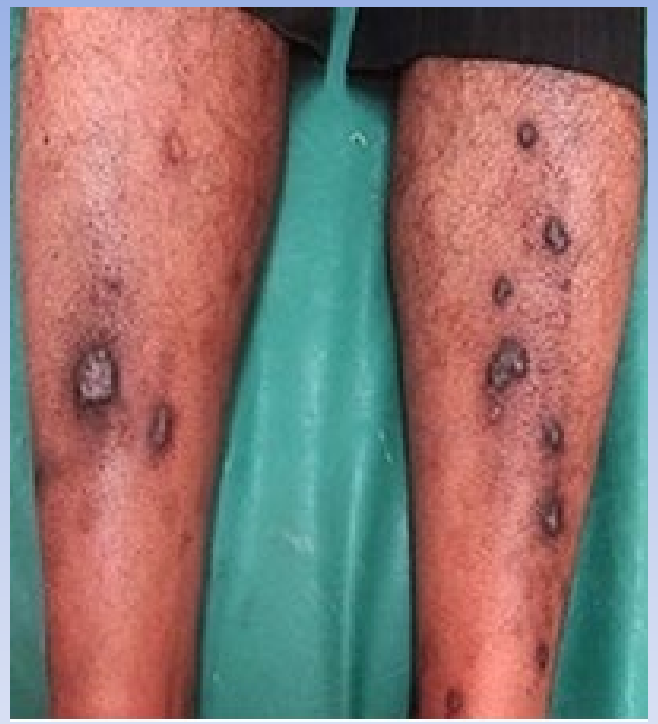
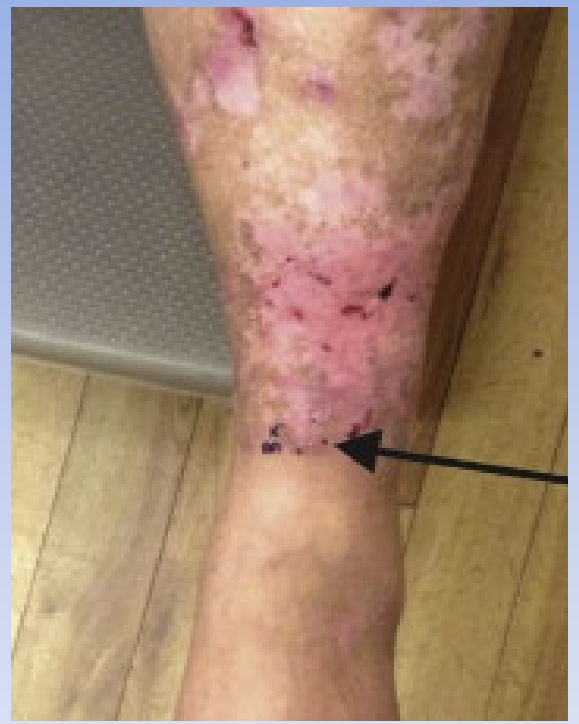
Pereira MP, et al. *J Eur Acad Dermatol Venerol.* 2018;32:1059-1065.

Difficult Differentials That May Need Skin Biopsy

Most cases of PN can be clearly delineated by phenotype and clinical exam; these diseases can mimic PN and may require skin biopsy







Left: Blistering disease, pemphigoid nodularis; **Middle:** Hypertrophic lichen planus; **Right:** PN and keratocanthomic squamous cell carcinoma, arrow shows area of biopsy that turned out to be PN.

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Ankad BS, Beergouder SL. *Dermatol Pract Concept.* 2016;6:3:9-15; Jedlowski PM, et al. *JAAD Case Reports.* 2020;6:3-5; Tan CH, Tey HL. *Int J Dermatol Venereol.* 2020;3:239-241.

Diagnostic Workup

Variable	Potential Workup Evaluation/Test
Initial visit (treatment can be initiated)	• Clinical examination for any signs of any type of skin disease • If PN is determined, assess severity – Extent of PN (number and firmness of lesions) – Pruritus intensity (mild, moderate, severe) – Disease burden (QOL, sleep disturbance, anxiety/depression)
Dermatologic tests to consider if PN is uncertain	• H&E histology staining if underlying dermatosis is suspected • Direct immunofluorescence to exclude autoimmune blistering diseases if patient reported blisters and/or erythemas/blisters were found • PCR for mycobacteria if histology finds granulomatous inflammatory infiltrate
Systemic laboratory tests	• Complete blood cell count with differential • Liver function tests • Renal function tests • Thyroid function tests • Diabetes assessment • Screen for HIV and hepatitis B and C
Psychological	• Assess for depression, anxiety • Psychiatric evaluation if skin-picking disorder is suspected

H&E, hematoxylin and eosin; HIV, human immunodeficiency virus; PCR, polymerase chain reaction.

Elmariah S, et al. *J Am Acad Dermatol.* 2021;84:747-760; Ständer HF, et al. *J Am Acad Dermatol*. 2020;82:460-468.

Severity Assessment

Severity of Chronic Nodular Prurigo Using Investigator Global Assessment (IGA) Scale

Score	Category	Description
0	Clear	No nodules
1	Almost Clear	Rare, flattened lesions with no more than 5 dome-shaped, palpable nodules (approximately 1–5 nodules)
2	Mild	Few, mostly flattened lesions, with small number of dome-shaped, palpable nodules (approximately 6–19 nodules)
3	Moderate	Many lesions, partially flattened and dome-shaped, palpable nodules (approximately 20–100 nodules)
4	Severe	Abundant lesions, majority are dome-shaped, palpable nodules (more than 100 nodules)

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Ständer HF, et al. *J Am Acad Dermatol*. 2020;82:460-468.

Case Study Introduction

Case Study: Ashley, 39-Year-Old Female*

Patient complaint and presentation	• Ashley presents complaining of itchy nodules on her arms, legs, and back • She thinks it may be a worsening of AD • But also recently completed an eco tour of the Amazon Rainforest and thinks she may have picked up parasites
Medical history	• AD diagnosed at 5 years old
Impact on QOL	• Intense and persistent itching, burning – Itching started before bumps appeared and has lasted 7 weeks • Unable to sleep for more than 3 hours at a time because of itch • Feels anxious, avoiding intimacy with her husband because of embarrassment
Current therapies	• Topical corticosteroid, when needed, for AD flare

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*This is a standardized case study; not a real patient.

Case Study: Physical Exam and Lab Findings

Physical exam	• ~25 dome-shaped, palpable nodules • 2 excoriated papules in reachable extensor areas • Evidence of scarring • HEENT, normal • BMI, normal
Lab findings	• CBC with differentials • Liver function tests • Thyroid panel • eGFR • HbA1c **All within normal limits**

BMI, body mass index; CBC, complete blood count; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HEENT, head, eyes, ears, nose, and throat.

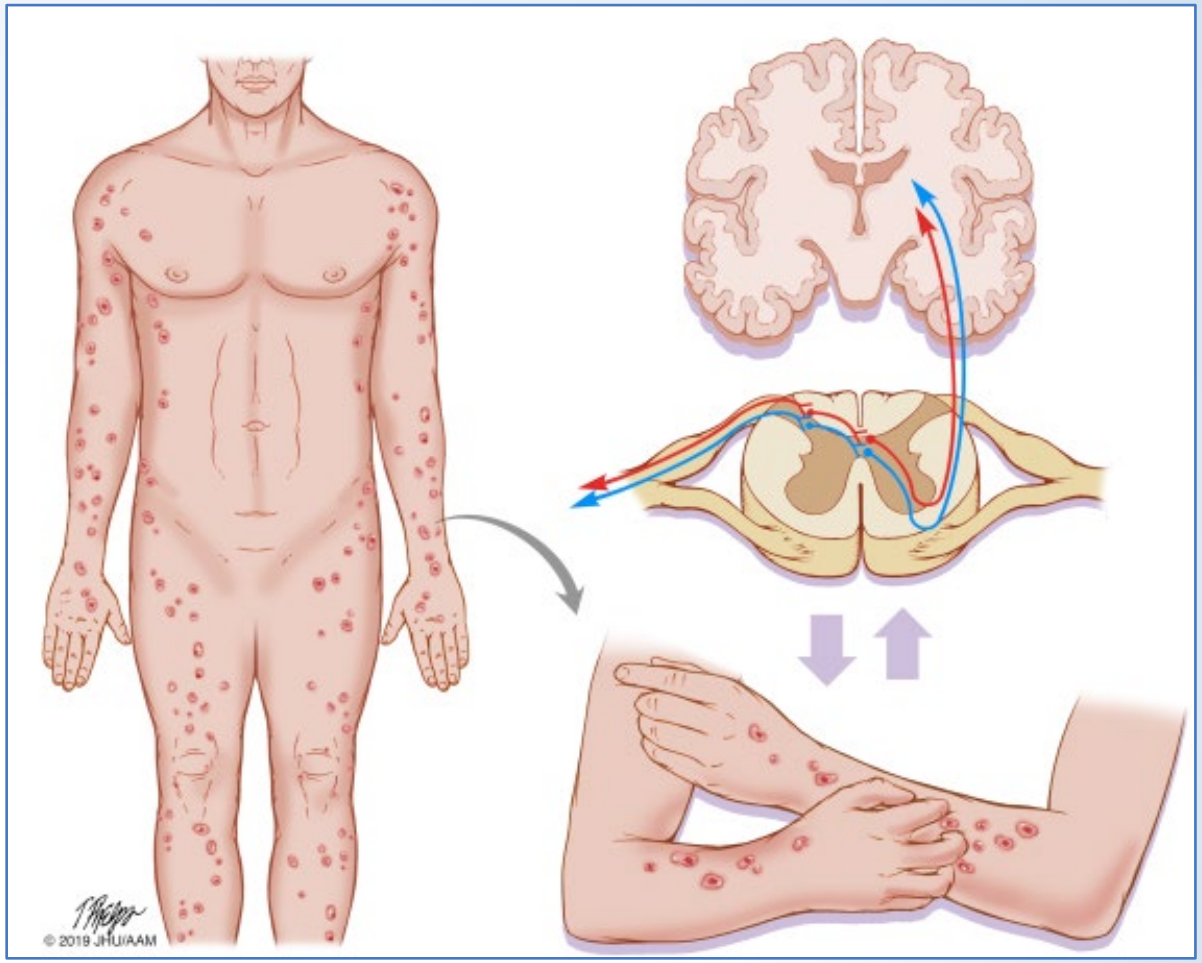
Questions and Discussion

- How do you know this ***is not*** a worsening of AD?
- Would you do H&E histology staining, PCR, or skin biopsy to determine if she contracted something in the Amazon rainforest?

Pathogenesis: Neural-Immune Dysregulation and Neural Sensitization

Neural-Immune Dysregulation: Type 2 Immune Response

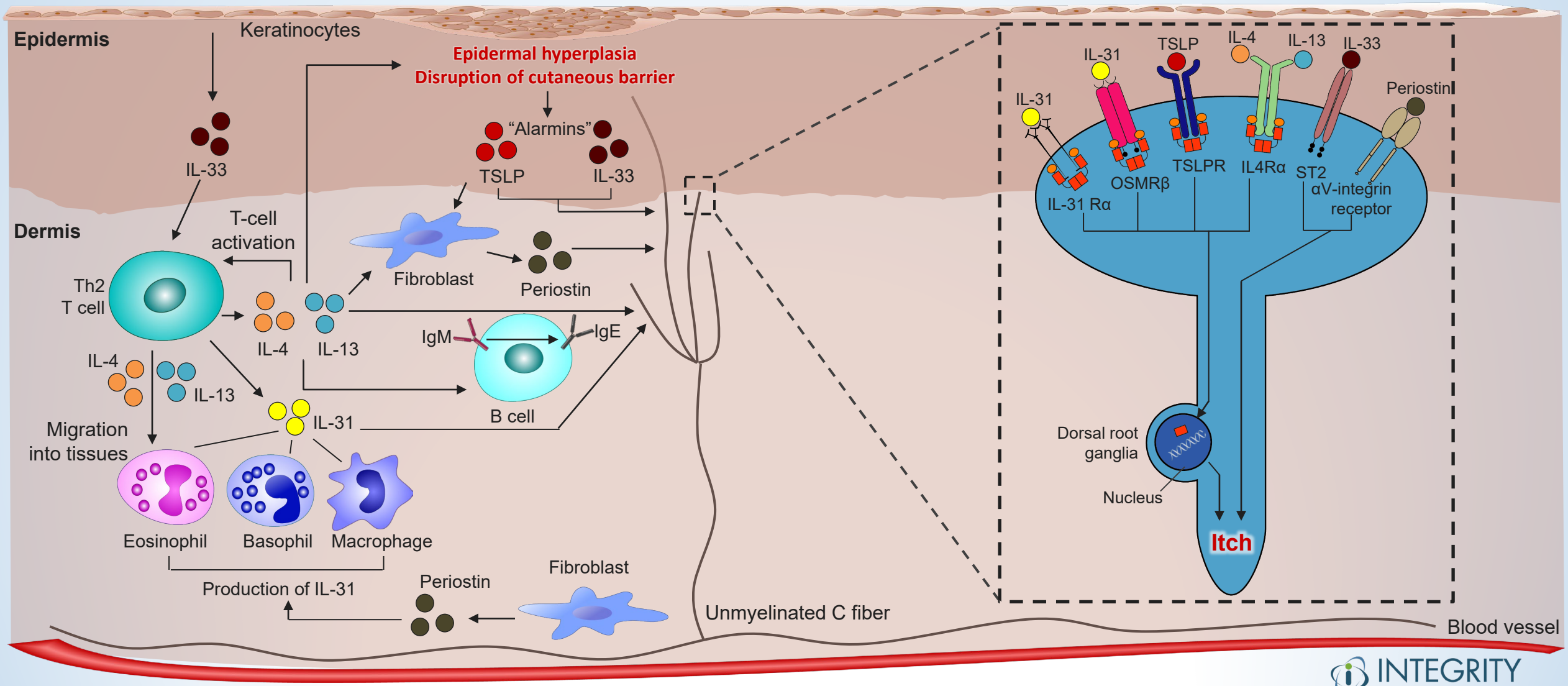
- PN nodules caused by dysregulation of cross-talk between immune and neural systems, propagating itch-scratch cycle
  - Inflammatory Th2 cytokines increased
    - Mainly: IL-4/IL-13, IL-31
  - Neuropeptides increased
    - Mainly: CGRP; SP
- Hypersensitivity of nerve fibers
  - At peripheral and spinal levels



CGRP, calcitonin gene-related peptide; IL, interleukin; SP, substance P; Th2, T-helper 2 cells.

Szöllősi AG, et al. *Front Pharmacol*. 2022;13:745658; Williams KA, et al. *J Am Acad Dermatol*. 2020;83:1567-1575.

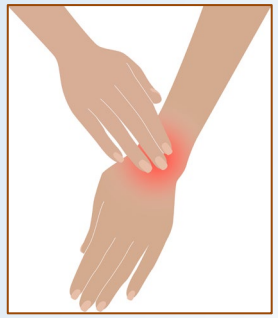
Cells and Cytokine Pathways in Neural-Immune Dysregulation



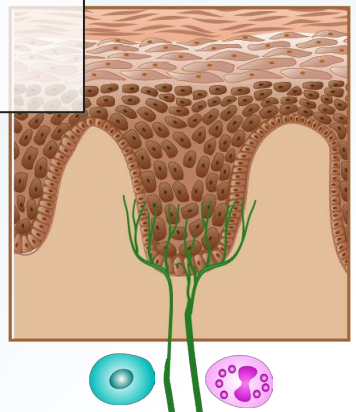
Ingrasci G, et al. *Exp Dermatol.* 2021;30:1208-1217.

Pathways of Neural Sensitivity

- Inflammation (NGF, PGE2, Artemin, etc.)
- Abnormal innervation induced by inflammation/scratching
- PAR-2 activation
- Lack of Merkel cells

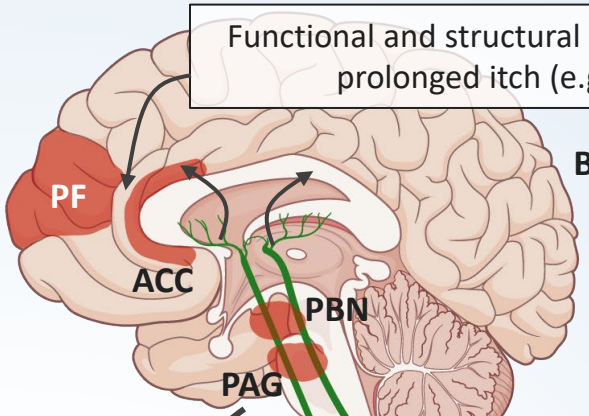


Skin



Functional and structural changes caused by prolonged itch (e.g., PF, ACC)

Brain



Attenuation of descending inhibitory pathway

Descending inhibitory pathway

Upregulation of itch-related receptors and molecules (Substance P, BDNF, etc.)

DRG

Spinothalamic/spinoparabrachial tract

Dysfunction of the inhibitory circuits (BhIhb-5 neurons, NPY neurons)

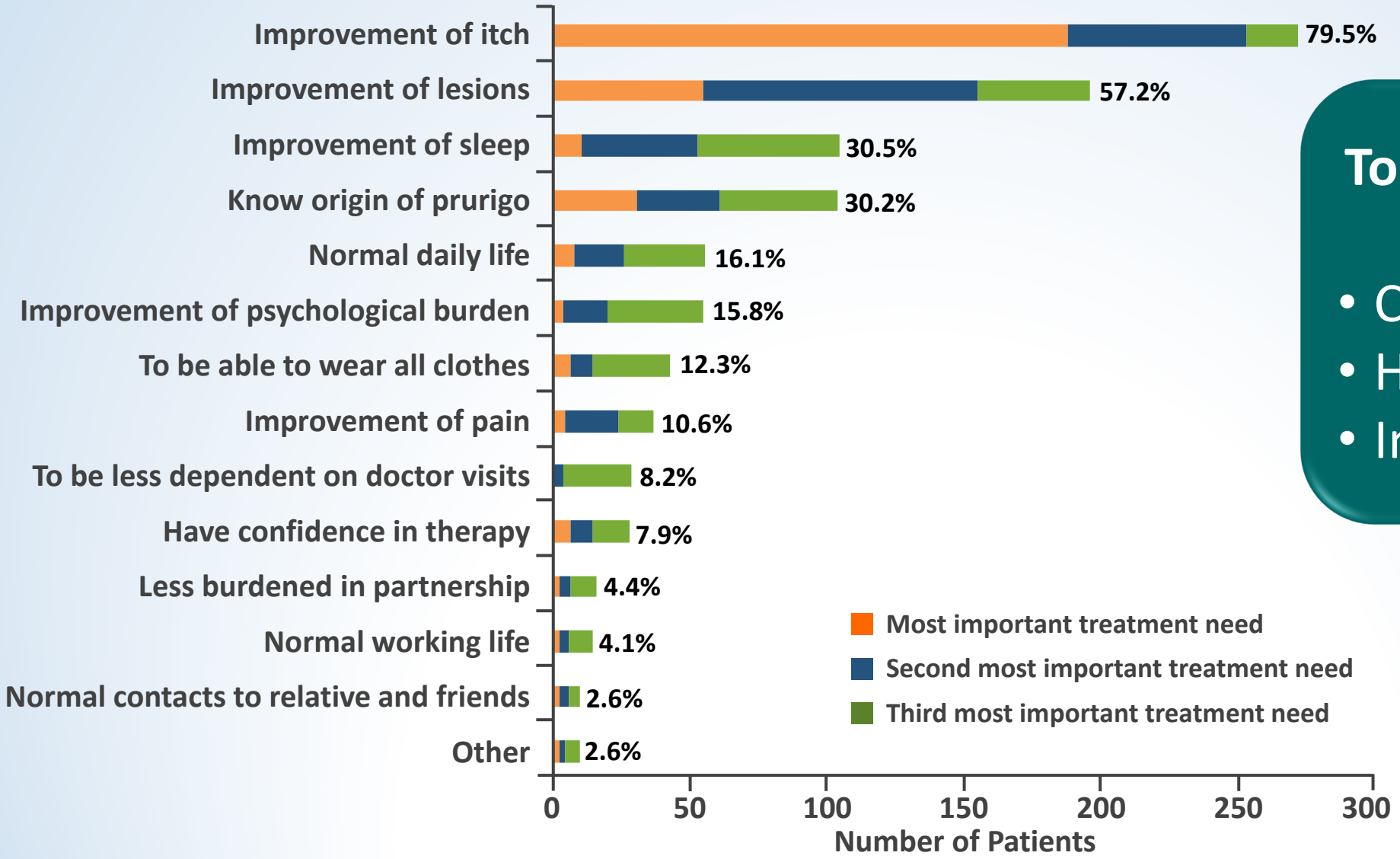
Spinal cord

ACC, anterior cingulate cortex; BDNF, brain-derived neurotrophic factor; DRG, dorsal root ganglion; NPY, neuropeptide Y; PAG, periaqueductal gray matter; PAR, protease-activated receptor; PBN, parabrachial nucleus; PF, prefrontal area.

Yosipovitch G, et al. *J Allergy Clin Immunol.* 2018;142:1375-1390.

Current and Emerging Treatments

Goals of Therapy From the Patient Perspective



Top 3 Patient Goals

- Control the itch
- Heal skin lesions
- Improve sleep

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Pereira MP, et al. *Acta Derm Venereol.* 2021;101:adv00403.

AAD Guidelines: Treatment Approaches in Therapeutic Ladder

Neural

Cannabinoids	**Tier 4**	JAK/STAT inhibitors Mycophenolate mofetil
Kappa/Mu opioid receptor antagonists Thalidomide	**Tier 3**	Azathioprine Dupilumab (anti-IL-4Rα) Nemolizumab (anti-IL-31)
NK_1 receptor antagonists High-dose gabapentinoids Antidepressants (SNRI → SSRI → TCA) Low-dose gabapentinoids	**Tier 2**	Cyclosporine Methotrexate Narrowband UVB/PUVA phototherapy
Topical ketamine/amitriptyline/lidocaine Topical capsaicin	**Tier 1**	Intralesional corticosteroids (<10 lesions)/cryotherapy Topical calcipotriol Topical calcineurin inhibitors Topical corticosteroids

Immunologic

AAD, American Academy of Dermatology; JAK, Janus kinase; NK1R, neurokinin 1 receptor; PUVA, psoralen plus ultraviolet light A; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; STAT, signal transducer and activator of transcription; TCA, tricyclic antidepressant; UVB, ultraviolet B-ray.

Elmariah S, et al. *J Am Acad Dermatol.* 2021;84:747-760.

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One FDA-Approved Treatment for PN

- Dupilumab approved by FDA for PN on September 29, 2022
- 1st approved treatment for PN
- Indication from PI: “For the treatment of adult patients PN”
  - Dosing: Initial dose two 300-mg injections; then 300 mg Q2W
- Approved based on findings from phase 3 LIBERTY-PN PRIME and PRIME 2 trials recently released
  - PRIME (NCT04183335) presented at 2022 EADV annual meeting, September 7–10
  - PRIME 2 (NCT04202679) presented at 2022 AAD annual meeting, March 25–29

Full publication of results expected soon

FDA, Food and Drug Administration; PI, prescribing information; Q2W, every other week.

FDA press release. September 29, 2022. www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-prurigo-nodularis; Yosipovitch G, et al. AAD 2022 Annual meeting. LBA S026; Yosipovitch G, et al. Presented at 2022 EADV Annual Meeting. Abstract 3583.

Remaining Unmet Needs in PN Treatment

- Several treatments used off-label (eg, topical corticosteroids, UV light therapy, immunosuppressive agents, and neuromodulators), but ***inadequate control is common*** in moderate-to-severe PN
- Current SOC of nonapproved therapies are limited by ***insufficient efficacy***, common AEs, and toxicities
- No treatments have yet been tested in PN that is ***secondary*** to endstage renal disease or neuropathic disease

AEs, adverse events; SOC, standard of care.

Systemic Treatments in Phase 2/3 Clinical Trials

Drug Names*	Mechanism of Action	Route	Trial Names† / ID # / Phase	No. Pts.	Study Completion
Nalbuphine ER	Opioid κR agonist/μR antagonist	PO	PRISM / NCT03497975 / Ph3	360	Feb 28, 2023
Nemolizumab	IL-31Rα inhibits IL-31	SC	NCT04501679 / Ph3 NCT04501666 / Ph3 NCT04204616 / Ph3 NCT05052983 / Ph3	274 270 450 100	May 17, 2022 Sep 1, 2022 Jan 31, 2023 Aug 31, 2023
Vixarelimab	Oncostatin-M Rβ inhibits IL-31 pathway	SC	NCT03816891‡ / Ph2	230	July 30, 2023

*Listed in alphabetical order; †If assigned; ‡Phase 2 trial, all others are phase 3.
ER, extended release; κR, kappa receptor; PO, by mouth; Rα, receptor alpha; Rβ, receptor beta; SC, subcutaneous; μR, mu receptor.

Source: ClinicalTrials.gov, August 16, 2022, using filters for prurigo nodularis, recruiting, active not recruiting, completed, and phase 3.

Phase 3 Clinical Trials for Dupilumab

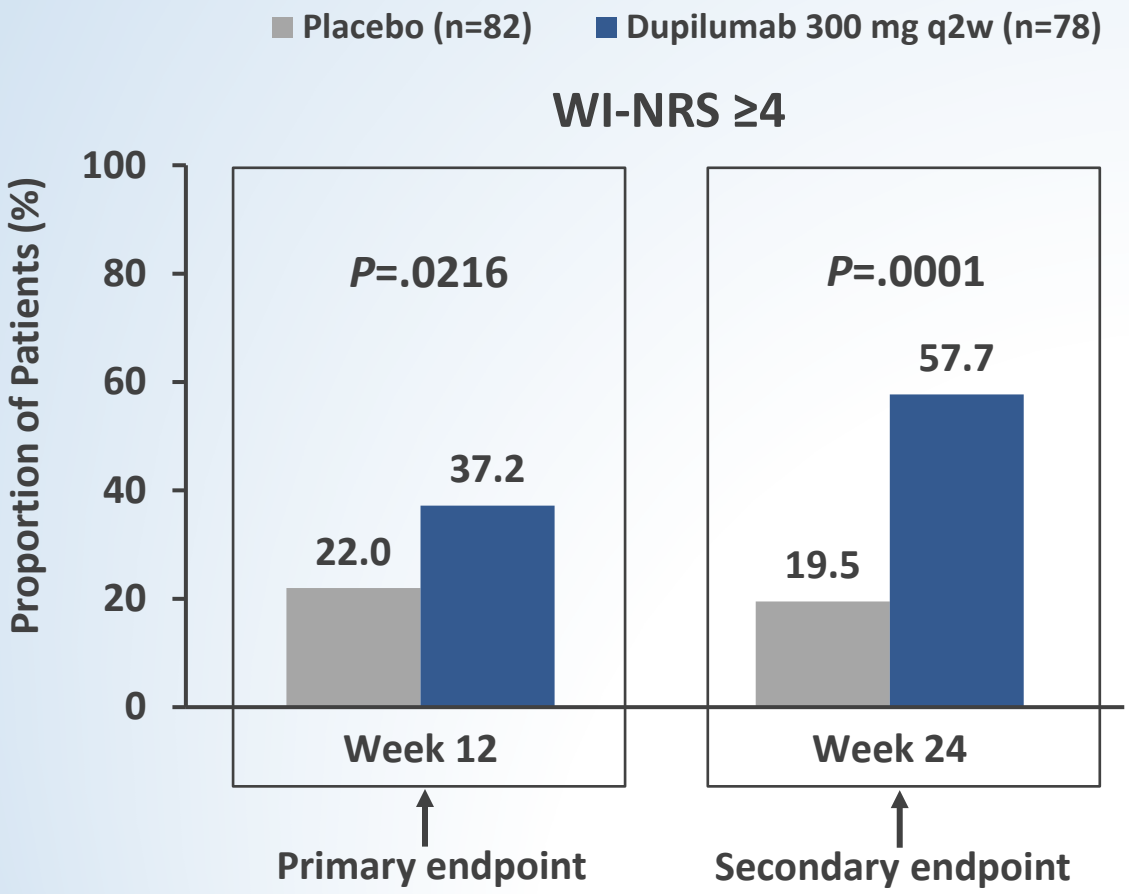
Drug Names	Mechanism of Action	Route	Trial Names Trial ID #	No. Pts.	Study Completion
Dupilumab	IL-4Rα inhibits IL-4 and IL-13	SC	LIBERTY-PN PRIME 2* NCT04202679	160	Nov 22, 2021
			LIBERTY-PN PRIME† NCT04183335	151	Feb 3, 2022

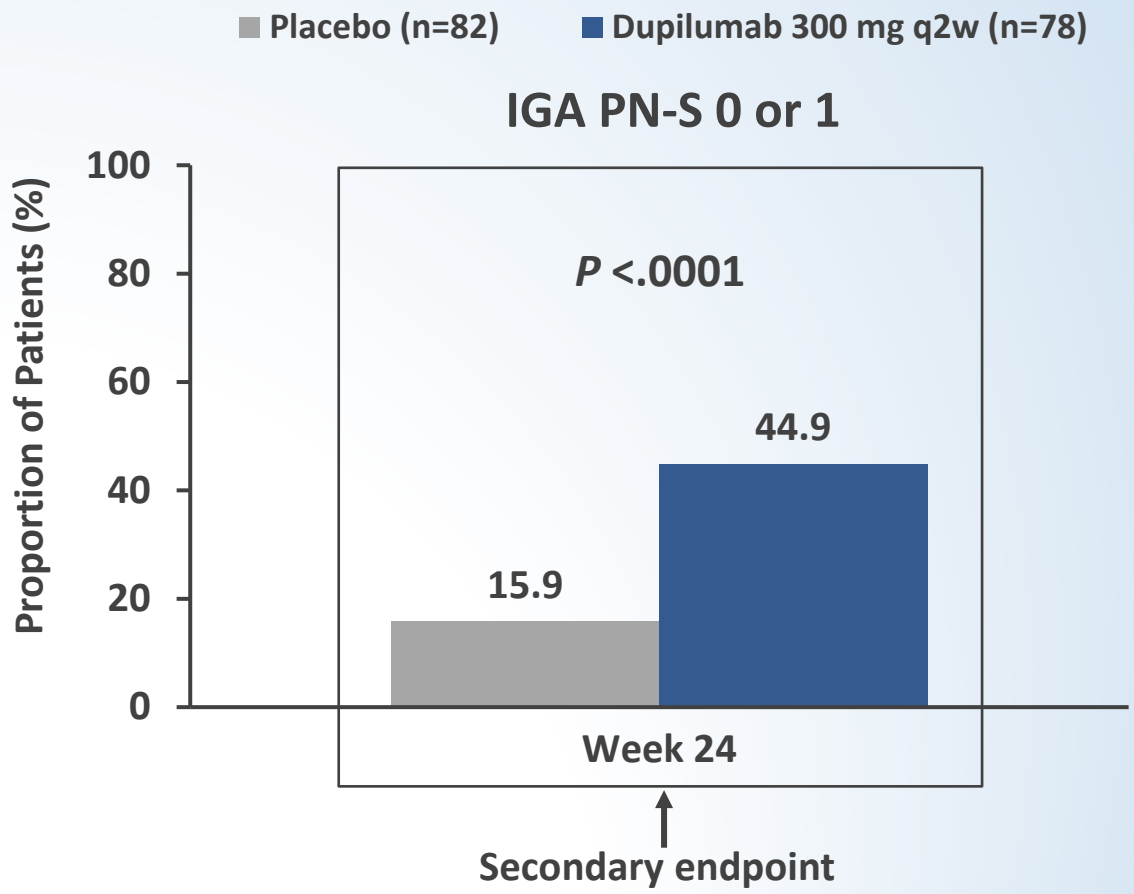
Rα, receptor alpha; SC, subcutaneous.

Source: ClinicalTrials.gov, August 16, 2022, using filters for prurigo nodularis, recruiting, active not recruiting, completed, and phase 3.

Dupilumab Efficacy: Phase 3 PRIME 2 Trial

Proportion of patients with ≥4-point improvement in WI-NRS and IGA PN-S 0 or 1





IGA PN-S, Investigator's Global Assessment PN-Stage; WI-NRS, Worst Itch-Numeric Rating Scale.

Yosipovitch G, et al. Presented at 2022 AAD Annual Meeting. LBA S026.

Dupilumab Safety: PRIME 2 Trial

Percentage of patients with ≥1 TEAE from baseline to week 24

Patients, n (%)	Placebo (n=82)	Dupilumab 300 mg Q2W (n=77)
Any TEAE*	42 (51.2)	44 (57.1)
Any death	0	0
TEAEs reported in ≥5% of patients in any treatment group		
Headache	5 (6.1)	4 (5.2)
TEAE groups of interest		
Herpes viral infections	0	5 (6.5)
Skin infections	7 (8.5)	4 (5.2)
Conjunctivitis	0	3 (3.9)

*None of the TEAEs were severe and al patients recovered while continuing dupilumab.
TEAE, treatment-emergent adverse event.

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Yosipovitch G, et al. Presented at 2022 AAD Annual Meeting. LBA S026.

Dupilumab Efficacy and Safety: Phase 3 PRIME Trial

Findings	Placebo Q2W (n=76)	Dupilumab 300 mg Q2W (n=75)
Primary endpoint: Itch relief at 24 weeks (≥4-point reduction in WI-NRS)	18%	60% (*P* <.0001)
Secondary endpoint: Lesion healing (clear or almost clear skin) at 24 weeks (IGA PN-S)	18%	48% (*P* <.0004)
TEAEs Nasopharyngitis Headache	63% 4% 5%	71% 5% 5%
Treatment discontinued due to TEAEs	4%	0%

Yosipovitch G, et al. Presented at 2022 EADV Annual Meeting. Abstract 3583.

Findings From Phase 3 Trial of Nemolizumab

- FDA granted breakthrough therapy designation for PN in 2019
- Preliminary topline findings from phase 3 OLYMPIA 2 trial (NCT04501679) released June 22, 2022
  - 16-week trial with 274 PN patients
- Primary endpoints
  - 56% of patients in nemolizumab cohort achieved ≥4-point reduction in itch as measured by PP-NRS vs 21% in placebo group (*P* <.0001)
  - 38% patients taking nemolizumab reached clearance or almost clearance of skin lesions by IGA score vs 11% taking placebo (*P* <.0001)
- FDA granted breakthrough therapy designation for PN in 2019

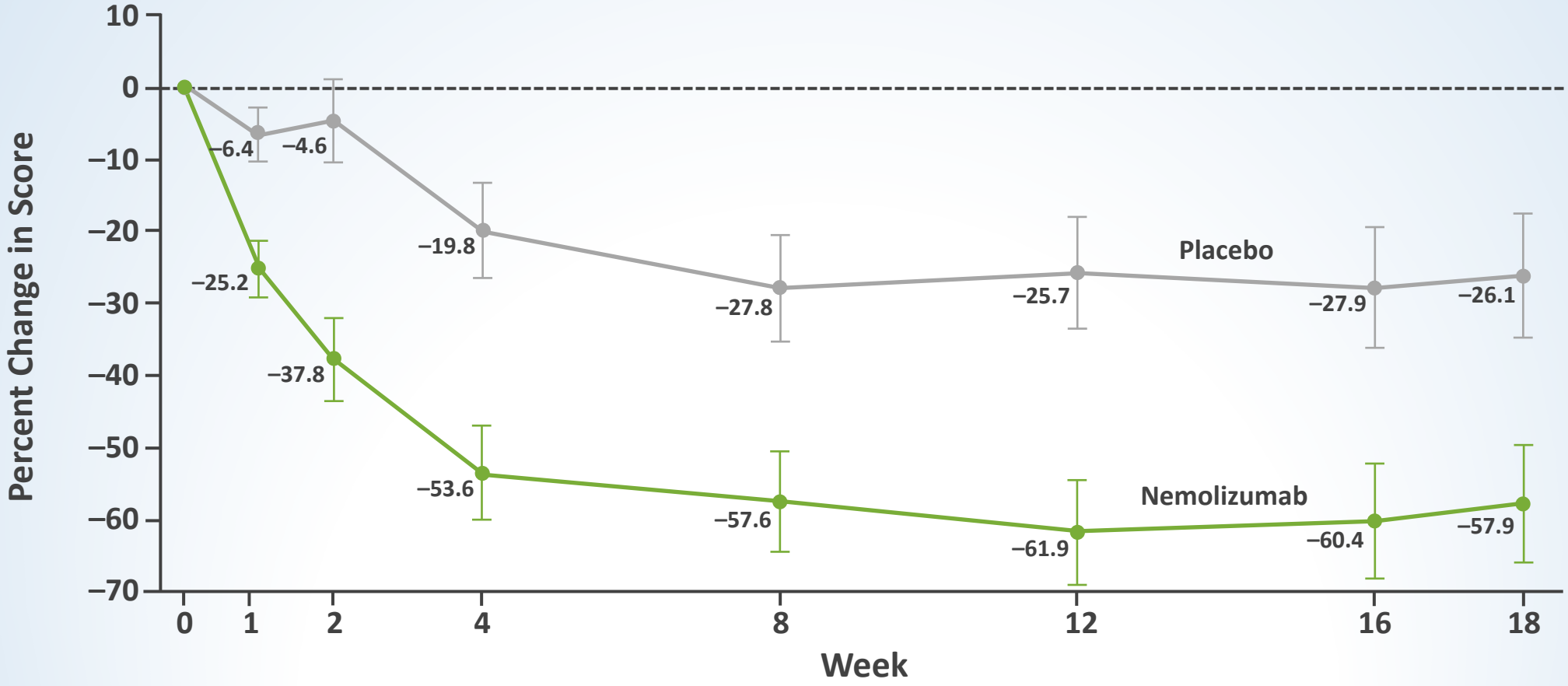
Full publication of results expected soon

PP-NRS, Peak-Pruritus Numerical Rating Scale.

Galderma press release. December 9, 2019. https://www.galderma.com/news/galderma-investigational-therapy-nemolizumab-granted-fda-breakthrough-therapy-designation; Galderma press release. June 22, 2022. https://www.galderma.com/news/galderma-announces-positive-data-phase-iii-trial-demonstrating-efficacy-and-safety-nemolizumab

Nemolizumab Efficacy: Improvement in Peak Pruritus Score

Change from baseline in weekly peak pruritus score
Phase 2 trial of patients with moderate-to-severe PN (N=70)

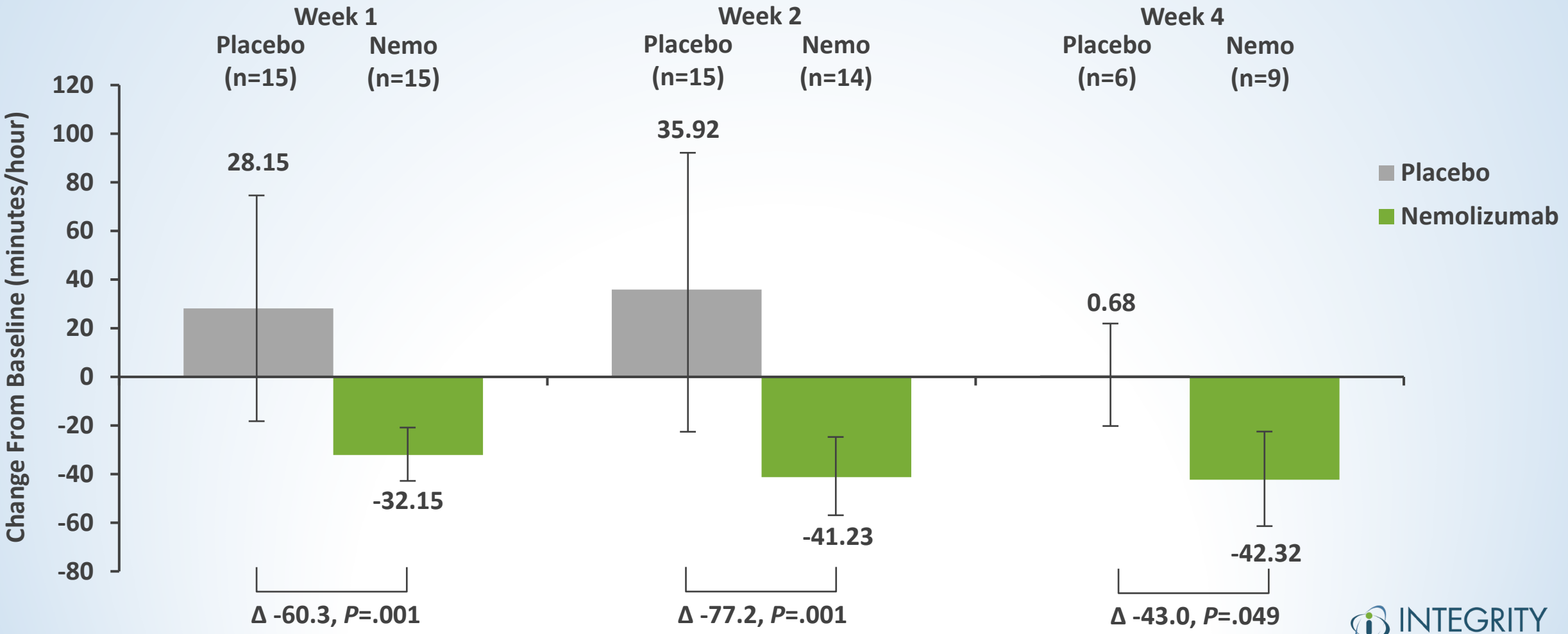


INTEGRITY CONTINUING EDUCATION

Ständer S, et al. *N Engl J Med*. 2020;382:706-716.

Nemolizumab Efficacy: Improvement in Itch/Sleep Ratio

Change from baseline in scratch duration/sleep duration ratio
Phase 2 trial of patients with moderate-to-severe PN (N=70)



INTEGRITY CONTINUING EDUCATION

Ständer S, et al. *J Eur Acad Dermatol Venereol.* 2022 Jun 29. [Online ahead of print]

Nemolizumab Safety

Phase 2 trial incidence of adverse events (≥5%), all causes

TEAEs by SOC (>5%), call causes, n (%)	Placebo (n=36)	Nemolizumab 0.5 mg/kg (n=34)
Infections and infestation	12 (33.3)	10 (29.4)
Skin and subcutaneous tissue disorders	12 (33.3)	10 (29.4)
Gastrointestinal disorders	5 (13.9)	7 (20.6)
Musculoskeletal and connective tissue disorders	5 (13.9)	6 (17.6)
General disorders and administration site conditions	4 (11.1)	5 (14.7)
Injury, poisoning and procedural complications	2 (5.6)	4 (11.8)
Renal and urinary disorders	2 (5.6)	2 (5.9)
Nervous system disorders	1 (2.8)	2 (5.9)
Respiratory, thoracic and mediastinal disorders	3 (8.3)	0
Blood and lymphatic system disorders	2 (5.6)	0
Metabolism and nutrition disorders	0	2 (5.9)
Psychiatric disorders	2 (5.6)	0
Vascular disorders	2 (5.6)	0

INTEGRITY CONTINUING EDUCATION

Ständer S, et al. Presented at 2022 AAD Annual Meeting. Poster 33307.

Case Study Returns

Case Study: Ashley, 39-Year-Old Female*

Patient Complaint and Return Presentation	• Ashley returns 4 weeks later with itching unabated • Patient was placed on high-dose topical corticosteroid at initial visit • Frequent emollients have also been used • Itching responded partially to a short course of oral corticosteroid • Sleep still frequently disrupted through the night because of itching • Now feeling anxious, depressed, and socially isolated
Inflammatory Mediators	• Partial response to oral corticosteroid shows presumed presence of T2-high inflammatory mediators such as IL-4/IL-13 and IL-31 • Blood tests did not show presence of parasites
Definitive Diagnosis	• Nodular PN

*This is a standardized case study; not a real patient.

What Would You Prescribe for Ashley?

Summary

- PN is a rare cutaneous disorder that carries a heavy disease burden
  - Incessant pruritus and sleep disturbance
  - Psychosocial difficulties and depression/anxiety
- Four different phenotypes (most commonly, nodular)
- Pathogenesis involves Th2-high inflammation involving neuroimmune mechanisms
- Emerging therapies target both neural and immunologic pathways
  - Dupilumab (FDA approved)
  - Nemolizumab (4 phase 3 trials)
  - Nalbuphine (1 phase 3 trial)
  - Vixarelimab (1 phase 2 trial)
- Treatment goals: control itch, heal skin lesions, improve sleep

Question & Answer

Thank You!