Chronic Itch Clinical Cases & Management

Gil Yosipovitch MD FAAD
Professor &
Director Miami Itch Center
Disclosures

- Advisory Boards: Trevi, Pfizer, Sanofi, Menlo, Galderma, Sienna
- Consultant: Opko LEO, J&J, Menlo, Novartis
- PI; Tioga, Roche, Pfizer, Allergen
- Funded: GSK, LEO Foundation, Pfizer, Sun Pharma
Outline

• Understanding itch of different types
• Pathophysiology of itch in PN and its treatment
• Atopic itch and its new management
• Itch without rash and its management
• Neuropathic itch
Chronic pruritus

- Primary skin lesions with or without chronically scratched lesions present
  - Dermatologic cause
    - Atopic eczema
    - Psoriasis
    - Xerosis
    - Scabies
    - Contact dermatitis
    - Insect bite
    - Lichen planus
  - Systemic cause
    - Chronic kidney disease
    - Cholestasis
    - Hodgkin’s lymphoma
    - Polycythemia vera
    - HIV infection
    - Hyperthyroidism
  - Neuropathic cause
    - Brachioradial pruritus
    - Notalgia paresthetica
    - Postherpetic itch
  - Psychogenic cause
    - Obsessive–compulsive disorder
    - Delusions of parasitosis
    - Substance abuse

- No primary skin lesions; chronically scratched lesions present or absent
  - Nondermatologic cause
Important Questions to Ask an Itchy Patient

- **Duration:** years/weeks/days
- **Severity**
- **Localization:** generalised/ localized/
- **Periodicity:** paroxysmal, continuous, occurring in short bouts, nocturnal
- **Affect on sleep**
- **History of itch in other personal contacts**
- **Factors that exacerbate itch:** heat, water, dryness
- **Factors that alleviate itch:** (drugs or cooling agents)
- **Drugs:** (opiates, aspirin, penicillin, antimalarials)
- **History of atopy**
- **Travel history**
PN in African Americans and AD
What Causes Itch

- Skin
- Immune System
- Nervous System

Pruritus
Population coding
Molecular specificity of receptor activation
TSLPR
NPRA
TSLP
NPPB
GRP
H1, H4
IL-31R
ST2
IL-31
IL-33
Mrgprs
Neutrophil
Eosinophil
Mast cell
Blood vessel
Histamine-triggered neurons
Nonhistaminergic neurons
Neuropeptides
Dermis
Spinal Cord
Dorsal ganglion
Contralateral spinothalamic tract ascends to the thalamus
Brain
Thalamus
Neurons
C fibers
Epidermis
Stratum granulosum
Epidermis and Dermal–Epidermal Junction
Itch triggers
Yosipovitch and Bernhard, NEJM. 2013 Apr 25; 368 (17):1625.
Prurigo Nodularis

Itch

Activation of retrograde signaling pathways

Neurogenic inflammation, attraction of inflammatory cells

‘Axiotomy’ of epidermal peripheral nerve endings

Scratching
Various Forms of Prurigo

The first three may develop subsequently

Zeidler et al. Acta Derm Venereol. 2018
Treat underlying disease, emollients, intralesional injection of triamcinolone (in single lesions); if necessary, treat the sleep disturbance, psychosomatic concomitant treatment.

Step 1:
- Topical corticosteroids*
- UV phototherapy (e.g. PUVA*)
- Topical drugs that target the nerves KAL

Step 2:
- Gabapentinoids

Step 3:
- Topical KAL, Capsaicin
- Antidepressants

Step 4:
- μ- and kappa opioid receptor antagonists
- Immunosuppressants
- Thalidomide
- NK-1 inhibitors

* Step 4: Treat underlying disease, emollients, intralesional injection of triamcinolone (in single lesions); if necessary, treat the sleep disturbance, psychosomatic concomitant treatment.
Targeting the peripheral neural system

- Topical ketamine 5-10% lidocaine 5% and amitryptiline 5% in lipoderm base (targeting ion channels)
- TRPV1 antagonists

Stull et al. Exp opin pharma 2016
Gibson et al. Plos One 2015
Topical Ketamine

Ketamine is a N-methyl-D-aspartate (NMDA) antagonist used for general anesthesia that has been formulated and studied as a topical agent, mainly for the management of neuropathic pain.
Retrospective study of Topical use of ketamine 5-10% lidocaine 5% and amitryptiline 5%

- Study in 96 patients in an itch center
- The average NRS was 8.63 ± 1.62 before and 4.19 ± 2.9 after treatment with an average reduction of 4.61 ± 2.77
- Itch reduction duration from 30 mins- 7 hours

Lee et al. JAAD 2017
Adverse effect

- Serious:
  Recent report of encephalopathy after extensive use all over the body in an elderly patient
  Recommendation not to apply for whole body only severe itchy areas
- Common
  Burning

Other
Allergy to lidocaine

Cardis et al. JAMA Dermatol. , 2016. Lee et al, JAAD 2017
AD Clinical Features

- Follicular Eczema
  - Papules
- Discoid Eczema
- Xerosis (dry skin) + Lichenification
Infrauricle Fissure Stages
High Association of Infrauricle Fissure and VAS Itch Scores In Follow Up

Kwatra et al. J. Amer Acad Dermatol 2012
Atopic Dermatitis  
Pruritic Psoriasis  
Healthy

RNA sequencing  
Differentially-expressed Genes

Nattkemper et al. J Invest Dermatol 2018
Within this Itch transcriptome, we can narrow-down to a number of mediators that likely play an important role in Itch in AD

- IL4-IL13
- IL-31
- PAR2- Tryptase
- NK-1
How to Reduce Itch of AD

- Avoid alkaline bar soaps that aggravate itch
- Low pH moisturizers
- Topicals with Hypochloric acid
- Crisaborole
- Topical Immunomodulators

Mechanisms of Itch induction by $\uparrow$ pH in Atopic Eczema and Impaired Barrier

Th 1 → 2 Inflammation

↓ FLG  ↓ PCA  $\uparrow$ pH  $\uparrow$ SP  ↓ Barrier

IL-4, 13  ↓ ceramide  IL-$\alpha$/β  TSLP

$\uparrow$ pH  ↓ LB secretion

PAR2

Pruritus
Topical PDE4 Non Steroidal Inhibitor for Itch of AD

**FIGURE 1.** cAMP-activated intracellular signaling in normal healthy skin (A), untreated atopic dermatitis (B), and atopic dermatitis treated with the PDE4 inhibitor crisaborole (C). AMP, adenosine monophosphate; cAMP, cyclic adenosine monophosphate; PDE4, phosphodiesterase 4.
PDE 4 inhibitor Crisaborole

- Rapid reduction of itch in AD in first 2 days

Yosipovitch et al. Acta Derm 2018
Other Topical antipruritics in the market

- Pramoxine 1-2.5%
- Strontium 4%
- Menthol 1-2%

Yosipovitch & Patel Fitzpatrick 8th Edn 2012
Double Layer Wet Pajamas

- Effective for itch reduction
- Moisturizer with low potency steroid with silicone base on top a wet layer and dry layer on top
- Associated with the recovery of epidermal barrier.
- Induces clinical improvement by the release of restoration of intercellular lipid lamellar structure.

Block stratum corneum itch signaling

Poor barrier

↑Nerve fibers & receptors
Secretion of NGF
Pruritogenic cytokines

Capillary Network

Nerve plexus (Aδ- and C-fibres)

↑TEWL

Stratum Corneum

Epidermis
The end of the antihistamine era for AD

Usually not effective for chronic itch
Targeted Immuno Treatments
New Era in Itch Treatment of AD

• Dupilumab
• Nemolizumab
• JAK/Stat inhibitors
The humanized monoclonal antibody (mAb) dupilumab binds to the α-subunit of the IL-4 receptor, which is part of both the IL-4 and IL-13 receptor complex. Dupilumab modifies signalling of both the IL-4 and IL-13 pathways.
Dupilumab significantly improved pruritus

% Change in Average Weekly NRS Score

Study Week

Placebo (n=16)
150 mg (n=22)
75 mg (n=8)
300 mg (n=21)

* p<0.05; † p<0.01

Beck NEJM 2013
Anti–Interleukin-31 Receptor A Antibody Nemolizumab for Atopic Dermatitis

A Percentage Change from Baseline in Pruritus Score at 12 Wk

B Weekly Percentage Change in Pruritus Score

N Engl J Med 2017; 376:826-835
March 2, 2017
JAK/STAT Drugs on the Horizon
Alloknesis Itchy Sensitive Skin Common Clinical Phenomena in Chronic itch

Itch evoked by a stimulus that is normally not itchy
Peripheral and central itch sensitization

Results: sensitivity to chemical itch provocations

Patients with AD exhibit **increased intra- and extralesional sensitivity** to non-histaminergic itch only  Andersen et al. PAIN 2017
CNS targets for reducing neural sensitization itch

- GABA: gabapentin, pregabalin doses up to 2400mg Gaba/day and Pregab 300mg/day
- Other neurotransmitters: mirtazapine 15 mg
- Combo: mirtazapine and gabapentin/pregabalin

Stull & Yosipovitch Exp Opin Pharmacotherapy 2016
Tey & Yosipovitch Br J Derm 2011
Opioids in chronic itch: an imbalance between $\mu$- and $\kappa$-receptor activity?

- Nalfurafine (Japan)
- Butorphanol
- Nalbuphine
- Asimodoline

Tominga & Takamori J Invest Derm 2007
Butorphanol A kappa Agonist and Mu Antagonist

- Inhaler approved by FDA for migraine headaches
- 1-4 mg
- Side effects drowsiness, nausea
- Controlled substance
- Indications intractable chronic itch of different types

Targeting NK1 Receptor Sites
Receptors for Substance P
in the Itch Signaling Pathway

Serlopitant
Tradipitant
Aprepitant
Serlopitant Disrupts the NK₁R Mediated Itch Signaling Pathway in Pruritus

Serlopitant 1 mg and 5 mg Were Superior to Placebo for Reducing Pruritus, as Assessed by VAS Pruritus Score

At week 6, 43%, 38%, and 53% of patients in the serlopitant 0.25, 1, and 5 mg dose groups, respectively, reported a 4-point decrease in average VAS pruritus score, compared with only 26% of patients in the placebo group.

Yosipovitch et al. JAAD Feb 2018
Treatment of Atopic Itch

Figure 1: Recommended therapeutic ladder for patients with AD associated pruritus. Patients categorized based on severity of itch, impact on sleep and presence or relative absence of eczematous rash. All patients receive patient education and moisturizers. Based on patient severity, treatment should progress up the ladder. Patients with pruritus with minimal eczematous rash may require a distinct treatment strategy.

Pavlis & Yosipovitch Amer J Clin Derm 2017
Case of Chronic Itch without rash

- 55 year old patient with severe generalized itch for 2 years VAS 7-10
- Lichenified plaques on ankles and excoriations on back
- Work up negative for underlying systemic diseases
**PUO**

Pruritus of Undetermined Origin & Treatment Regimen

- Anti depressants
- NaSSA
- Kappa opioids (Butorphanol)
- Combo NaSSA & Anti Epileptics
- Gabapentin or Pregabalin
- Anti depressants
- NaSSA
- Topical anti pruritics
- NKI inhibitors
Severe Itch in a Motor-cyclist

- 45 year old patient NRS 10 out of 10.
- Mainly on his bilateral arms and shoulder girdle
- Patient is on large dose of opioids post back trauma.
- Patient is an avid cyclist and itch is aggravated after cycling
- Denies vehemently substance abuse
- Referred by Pain specialist for suspected opioid induced itch
- Course of naltrexone was not helpful
- Cervical Stenosis C5-C6
- Positive Ice pack sign +
• monosymptomatic
• dermatomal localization
• 80%: relevant cervical spine lesions*
• Neoplasms rare
• Cutaneous innervation: functional dysbalance of epidermal / dermal nerves

• monosymptomatic
• dermatomal localization
• Conflicting results: spinal cord related nerve fiber compression* vs.
• damage of peripheral nerves
• Epidermal nerves reduced
BRP-triggered generalized pruritus A New Entity?

- 57/F
- Pruritus started on both arms
- MRT: spondylolisthesis in C3-5 due to a herniated vertebral disk at C4/5, osteochondrosis in C5-7, and spondylarthrosis in all cervical segments
- generalized after several months to neck, legs, abdomen, and back

Kwatra et al. JAAD 2013
CNS targets for itch treatment

• Higher doses seem to work better for neuropathic itch: GABA: gabapentin, pregabalin doses up to 3600mg Gaba/day and Pregab 300-600mg/day
• Combo: mirtazapine and gabapentin/pregabalin

Stull & Yosipovitch Exp Opin Pharmacotherapy 2016
Tey & Yosipovitch Br J Derm 2011
BOTOX AS AN ANTIPRURITIC

Botox reduced histamine-induced itch intensity in healthy men.

Reported to treat itch associated with:
- Lichen simplex chronicus
- Inverse psoriasis
- Notalgia paresthetica
- Post burn

The itch intensity AUC for the Botox treatment was significantly reduced from baseline for all follow up periods (p<0.01) and was significantly lower than the Saline treatment (p<0.05).
Treatment of Neuropathic itch

MILD ITCH
Topical:
Pramoxine
Lidocaine
Ketamine
Ke-Am-Li
Capsaicin cream

MODERATE ITCH
Topical:
Ke-Am-Li
Oral:
Gabapentin
Pregabalin
Mirtazapine

SEVERE ITCH
Topical:
8% Capsaicin patch
Oral:
Gabapentin or
Pregabalin with
Mirtazapine
Carbamazepine
Invasive:
Botulin Toxin A
Nerve Block
IV Ketamine

SEVERITY OF NEUROPATHIC PRURITUS
Chronic Itch and Sleep

Patients with chronic itch report a higher level of sleep-related problems compared to the general population:

- Majority of patients state itch intensity increases at night
- Trouble getting to sleep, trouble staying asleep, daytime fatigue
- Significant impact on quality of life

Patel & Yosipovitch Acta Derm 2007
Lavery Stull & Yosipovitch Int J Mol Sci 2016
Lavery et al. Acta Derm Venreol 2017
Treatments for Nocturnal itch

• Mirtazapine 15mg improves nocturnal itch
  Higher doses do not seem to work better
• Gabaergic drugs have also a sedating effect
• Sedating anti histamines H1 some pts respond well
• Sleeping pills do not seem to work for the itch
Stress Exacerbates Itch

• Patients with chronic itch—from dermatological\(^1\), neuropathic\(^2\), systemic\(^3\), and psychogenic\(^4\) causes—often report that stress exacerbates their itch
• Stress can predispose someone with an underlying disease to an outbreak of itch\(^5\)
• Chronic stress, especially in combination with genetic or environmental predisposition, typically worsens itch in mouse models\(^6\)

The Itch- Stress Anxiety Cycle

Figure by Hjalte H. Andersen
Treating chronic pruritus: beyond pills

- In the brain, pruritus and psyche are intertwined in a complex manner and the effect of one affects the other.
- In addition to the somatosensory aspects of pruritus, the cognitive and emotional components must be evaluated and addressed to effectively manage chronic pruritus.

*Tey et al. Clinics in Derm 2012*
Progressive Muscle Relaxation (PMR) for Itch Reduction

- Developed by Edmund Jacobson in 1932
- Involves tension and relaxation of muscle groups
- Positive effects in patients with chronic itch

![Graphs showing changes in Itch, Anxiety, and Depression](image)

Holistic Approach for Treatment of Itch
Acupuncture

1. Acupuncture of L11 in the elbow has been shown to reduce itch in Atopic dermatitis

Tey et al. Clin Dermatol 2013
Pafb Dermatol Therap 2013
Teaching coping mechanisms for itch; The Miami eczema school

• Education for parents and patients with atopic dermatitis on coping mechanisms
Conclusions

• No quick fix for all types of itch
• Managing the complexities, challenges, and costs of chronic itch requires a comprehensive approach that includes topical, oral, and non-pharmacological approaches