Update on Chronic Itch and Its Management

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

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- Advisory Boards: Cosmoderm, Creabilis, Trevi, Celgene, Velocity, Eli Lilly, Pfizer
- Consultant: LEO, GSK/Stiefel
- Funded: GSK, LEO Foundation, Trevi, Allergen
Outline

• Mechanisms of Chronic itch
• Management of Chronic itch
Chronic Itch – Clinical Definitions

- IFSI definition: is itch that lasts 6 weeks or longer.
- Adversely affects quality of life as chronic pain
- Affects 16% of population & increases with age

Stander et al. Dermatology 2010
Kini et al. Arch Dermatol 2011
New Paradigm

• Chronic Itch is a disease state in its own right!!
• When itch patients receive adequate treatment for chronic itch – improvement in quality of life
• Anti-histamines in most cases do not work for chronic itch

Yosipovitch Clin & Exper Dermatol Res 2011
Yosipovitch & Bernhard NEJM April 25 2013
Keratinocytes talk to nerves in itch via GPCR and TRP

GPCR: Protease-activated receptor, Histamine receptor 1 & 4, Mrgpr, Opioids

E Lerner MGH
Topical Anti Pruritics
Target Skin Nerves: My Cook Book

1. Topical Pramoxine: facial and genital itch, uremic itch
4. Topical ketamine 2.5% -10% with amitryptilne 5% with lidocaine 5% with lipoderm bases
3. Strontium Gel 4% for neuropathic itch
4. Topical Capsaicin 0.1% with or without EMLA
5. Menthol 1-2%
6. Topical gabapentin 12%
7. Topical aspirin 3%

Yosipovitch & Patel Fitzpatrick 8th Edn 2012
Poterucha et al. JAAD 2013
Capsaicin Targeting TRPV1 & Menthol Targeting TRMP8

- Capsaicin, the active ingredient of chili peppers is used topically for local pain or itch for Centuries.
- Indications localized itch:
  1. Prurigo nodularis
  2. Uremic Itch
- Menthol 1% used for centuries to reduce itch and pain
  1. Works only on a subset of patients who respond also to cooling 30%
Combination Therapy with Local Anesthetic & Capsaicin

• Combo EMLA or Lidocaine ½ hr improves efficacy of Capsaicin

*Yosipovitch et al. Acta Derm Venereol. 1999*

*Papoui & Yosipovitch Exp Opinion Pharm 2011*
Itchy Cytokines
Targets for Pruritus of Inflammatory Skin disease & lymphoma Itch

Interleukin 31 an important mediator of itch in AD and CTCL

Interleukin 4 and 13 in atopic eczema: Dupilumab

Singer et al. JID 2013
Yosipovitch Abst JID 2013
IL-31 an Itchy Cytokine in CTCL

Marked pruritus vs Decreasing/Absent pruritus

Singer et al. JID 2013

P < 0.01
Peripheral & Central Sensitization in Chronic Itch

• Sensory stimuli is altered in chronic itch
• Central and peripheral sensitization
• Drugs such as SSRIs and anti epileptics can reduce central sensitization for pain

Ikoma et al. Nat Rev Neurosci 2006
CNS- Targets for Itch Treatment

- Reduction of Central sensitization of itch in brain
- Anti-depression drugs; SNRI group: mirtazapine 15 mg qhs

1. Drugs that decrease the release of several neurotransmitters, gabapentin, pregabalin
Doses up to 3200mg for gabapentin and pregabalin 300mg
- Combination of Gabapentin or Pregabalin with Mirtazapine low dose

J Amer Acad Dermatol 2004
J Amer Acad Dermatol 2007
Dermatol Therap 2008
The Role of Opioids in Chronic Itch an Imbalance between μ- and κ-Receptor-Activity?

Tominga & Takamori J Invest Derm 2007
A Kappa Agonist & Mu Antagonist For Intractable Chronic Itch

- Butorphanol is an analgesic inhaler FDA approved for acute pain.
- Effective in treating chronic intractable itch
- Doses 1mg = 1 puff; doses: 1mg up to 4 mg per day
- Disease indications: Chronic Pruritus, Atopic eczema, Lymphoma, Uremic

- *Dawn & Yosipovitch J Amer Acad Dermatol 2006*
Aprepitant A Neurokinin 1 inhibitor
New Antipruritic

- Aprepitant antiemetic agent in chemotherapy-induced nausea and vomiting
- Substance P inhibitor
- 80mg/d 40mg bid
- Extremely expensive 160$ per pill
- Effective for
  1. Prurigo & Atopic eczema
  2. CTCL
  3. EGFR induced itch

_Duval et al. NEJM 2009_
_Stander PLoS One. 2010_
Not All Itch`s Arise from The Skin

- Neuropathic itch can coincide with pain.
- Examples: Brachioradial itch, Notalgia Parasthetica
- Vulvar and scrotal itch
- Neuropathic itch from PHN

Yosipovitch & Samuel Dermatol Therap 2009
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
Hypothalamic stimulation → TSH → Inhibition

Drugs
- Neuroactives: Gabergic SNRI, opioids

CATECHOLAMINS
- epinephrine, norepinephrine

SYMPATHETIC FIBERS

ACTH

HYPOPHYSIS

Stimulation → Dopamine → Neurogenic

Optic Chiasma

Posterior lobe

Anterior lobe

MELANIN Synthesis

CELL MEDIATED IMMUNITY (Th-1) DEPRESSED

CORTICOSTEROIDS

Adrenal Gland

Stimulation → Autonomous Nerve System

TRAN ET AL. ACTA DERMATOLOGICA VENEREOLOGICA 2010

PADGETT DA, GLASSER R. HOW STRESS INFLUENCES THE IMMUNE RESPONSE. TRENDS IN IMMUNOLOGY. 2003

KIM & YOSIPOVITCH EXP DERMATOLOGY 2013
Cognitive Approach for Treatment of Itch

- Patients’ cognitive capability to control the itch-scratch can be enhanced with education, support, and cognitive and behavioral therapies

- Education:
  1. Teaching itch relieving interventions
  2. Use of medications.

- Support: individual and group counseling, enrolling in support groups, providing education resources.

- Cognitive and behavioral therapies
  1. Awareness training and habit reversal,
  2. Stress management education
  3. Guided imagery

*Tey et al. Clin Dermatol in press 2012*
Conclusion

• In addition to the dermatologic and somatosensory aspects of pruritus, the cognitive and emotional components must be evaluated and addressed to effectively manage chronic pruritus.

Tey et al. Clin Derm 2012