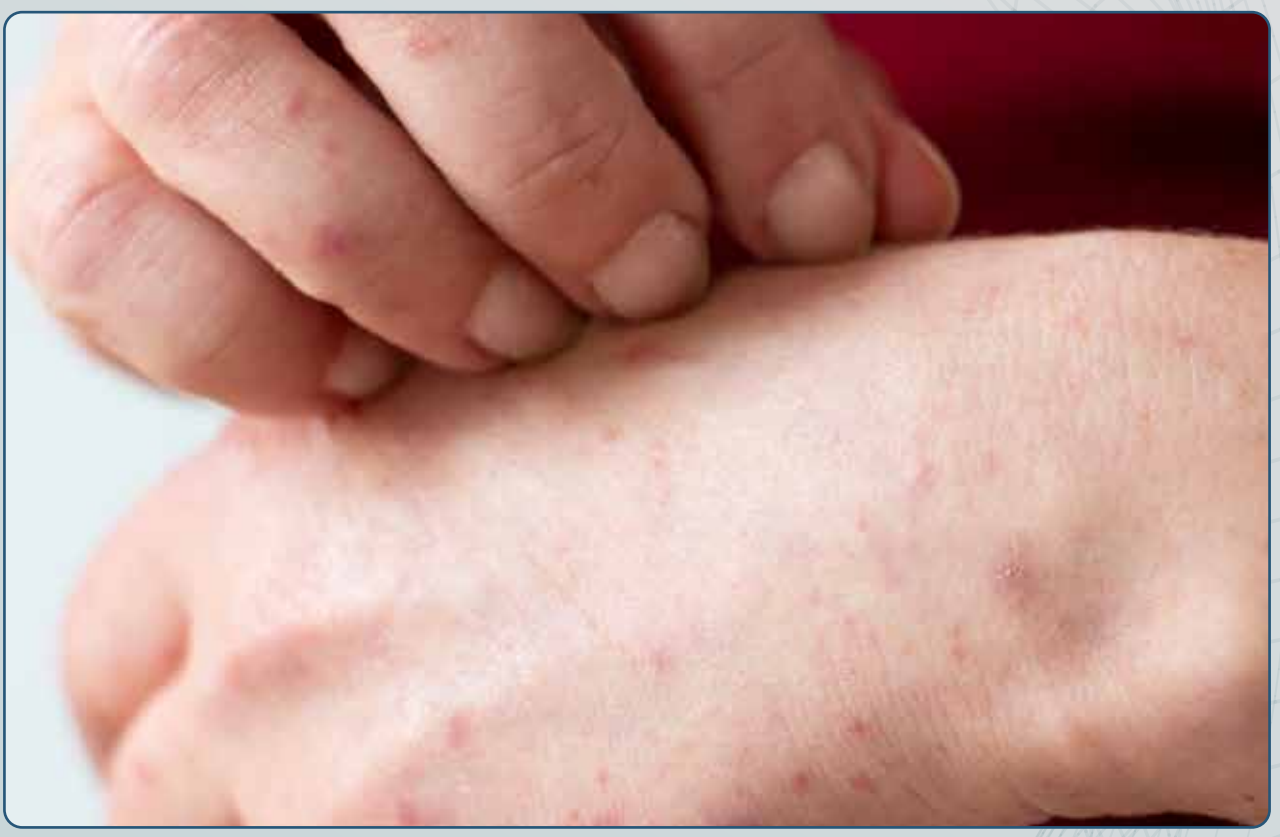
# IADVL



# SIG PRURITUS

## Co-ordinator

Dr Asit Mittal

## Convener

Maj Gen (Dr.) Rajesh Verma

## Members

Dr. Iffat Hassan, Dr. John Stephen,
Dr. Kapil Vyas, Dr. Praveen Kumar S,
Dr. Rajesh M Buddhadev, Dr. Rajesh Kumar,
Dr. Shagufta Parveen Rather, Dr. Sudip Das
Dr. Vikas Shankar

Dr. Asit Mittal

Maj Gen (Dr.) Rajesh Verma

## EDITORIAL

## Dr Asit Mittal, Maj Gen (Dr.) Rajesh Verma

Itch is seen as a central symptom across multiple disorders both dermatological as well as systemic. Originally considered a mild form of pain, the discovery of itch specific molecular and cellular pathways in last decade or so has led to a distinct field worthy of inquiry. Not only that the seminal new discoveries in itch biology are rapidly translating to new therapies. The aim of this news letter, which is second in this series is to keep our members updated with all the new exponential scientific information emerging in this field. The news letter contain “current literature” which is a collection of articles and reviews on various aspects of itch ,which we believe would be relevant to both the academician as well as an average clinician. A guest column by Dr Shawn Kwatra,a renowned itch researcher and Director John Hopkins itch center on” Neuroimmune based endotypes in chronic Pruritus”. A review on” psychotropic drugs in chronic Pruritus” and a short review on” scabies itch”. We sincerely hope that the readers will find this newsletter informative.

Happy reading

# NEUROIMMUNE-BIASED ENDOTYPES IN CHRONIC PRURITUS

**Shawn Kwatra, MD**
Associate Professor of Dermatology and Oncology
Director, Johns Hopkins Itch Centre
Johns Hopkins University School of Medicine

What a joy it is to share this guest column with esteemed members of the Special Interest Group (SIG) on Pruritus within the Indian Association of Dermatologists and Venereologists and Leprologists. I am writing from Baltimore, Maryland where I am the Director of the Johns Hopkins Itch Centre. In our centre I run a basic and translational research laboratory, conduct clinical trials, and care for patients for their intractable itch.

As compared to just a few years ago, we have come a long way in advancing our understanding of the various etiologies of chronic pruritus as well as uncovering novel therapeutic strategies. One of the biggest learnings of the past few years is that there are distinct endotypes or subtypes of chronic pruritus even within unique diseases. For example, chronic pruritus of unknown origin (or CPUO), which presents with intractable, generalized pruritus, can be biased towards either end of the neuroimmune spectrum. Indeed, our group found that subsets of patients with aging related changes to their immune system had dysregulation of Type 2 inflammation, often times manifesting on peripheral blood testing with increased blood eosinophils or IgE (1). These patients tend to have their itch improve with immunosuppressive or immunomodulating agents such as methotrexate, intramuscular or oral steroids, or dupilumab. Conversely, there are also CPUO patients that are more likely to have myelopathy or spinal disc disease and actually have generalized neuropathic pruritus that remains unresponsive to immunomodulating therapies.

The precision medicine movement is not limited to itch of unknown origin, recently our group uncovered that there are neuroimmune based endotypes of prurigo nodularis (PN) as well. PN patients with spinal disc disease or myelopathy were found to have decreased levels of circulating blood inflammatory cytokine levels as compared to those with immune biased endotypes of PN (2). Further, machine learning approaches have classified distinct clusters of PN patients with subgroups of patients that are highly atopic, and other patients that suffer from chronic comorbid diseases such as chronic kidney disease (3). This suggests that PN also may be amenable in the future to precision medicine-based approaches with a variety of agents recently approved or in late-stage clinical trials.

With the development of multiple immune-modulating agents, including monoclonal antibodies as well as small molecule inhibitors and Jak inhibitors, immune dysregulation that is responsible for chronic itch is now mostly manageable. The next great untapped frontier within chronic pruritus is a focus on neuropathic pruritus. These patients are suffering greatly and the minimal relief they experience is often times with sedating agents, like gabapentin or pregabalin, that increases the risk of falls and also psychological disturbance. Many of the breakthroughs in managing these patients will be guided by expert dermatologist working groups working together to harmonize guidelines and expert consensus.

I am looking forward to all of the great work the SIG in pruritus will accomplish working collectively. I look forward to in the near future visiting with many of you in India, and furthering global cooperation towards advancing the management of chronic pruritus.

References

1. Roh YS, Khanna R, Patel SP, Gopinath S, Williams KA, Khanna R, Pritchard T, Sutaria N, Choi J, Alphonse MP, Kwatra MM, Kwatra SG. Circulating blood eosinophils as a biomarker for variable clinical presentation and therapeutic response in patients with chronic pruritus of unknown origin. J Allergy Clin Immunol Pract. 2021 Jun;9(6):2513-2516.e2. doi: 10.1016/j.jaip.2021.01.034. Epub 2021 Feb 3. PMID: 33548514.

2. Sutaria N, Alphonse MP, Marani M, Parthasarathy V, Deng J, Wongvibulsin S, Williams K, Roh YS, Choi J, Bordeaux Z, Pritchard T, Dillen C, Semenov YR, Kwatra MM, Archer NK, Garza LA, Dong X, Kang S, Kwatra SG. Cluster Analysis of Circulating Plasma Biomarkers in Prurigo Nodularis Reveals a Distinct Systemic Inflammatory Signature in African Americans. J Invest Dermatol. 2022 May;142(5):1300-1308.e3. doi: 10.1016/j.jid.2021.10.011. Epub 2021 Oct 27. PMID: 34717952; PMCID: PMC9038640.

3. Wongvibulsin S, Parthasarathy V, Pahalyants V, Murphy W, Sutaria N, Roh YS, Bordeaux ZA, Deng J, Taylor MT, Semenov YR, Kwatra SG. Latent class analysis identification of prurigo nodularis comorbidity phenotypes. Br J Dermatol. 2022 May;186(5):903-905. doi: 10.1111/bjd.20957. Epub 2022 Mar 25. PMID: 34927720.

# CURRENT LITERATURE PRURITUS AND PRURIGO

Dr. Asit Mittal, Dr. Kapil Vyas

## CLINICAL DERMATOLOGY – PATHOPHYSIOLOGY AND THERAPY

*Rintaro Shibuya1, Riko Takimoto-Ito ,Naotomo Kambe1 and Kenji Kabashima.A New Era with the Development of Cytokine-Based Therapy for Pruritus Journal of Investigative Dermatology (2022) 142, 47e52; doi:10.1016/ j.jid.2021.09.023*

**Abstract**

Chronic pruritus is clinically defined as pruritus that lasts at least six weeks, although most patients suffer from pruritus for much longer, ranging from months to years .One study reported that 90% of patients with chronic inflamma- tory diseases experienced pruritus, and a relationship was noted between the intensity of pruritus and impaired sleep quality, work productivity, and mental health. Chronic pruritus is also closely linked to psychiatric conditions, as evidenced by a high prevalence of depression or suicidal ideation in patients with chronic pruritus .One study indicated the annual median total costs of chronic pruritus to be $1,067 per pa- tient , whereas another study on patients with chronic pruritus in North America calculated the life- time economic burden for individuals to be $274,921 and the societal burden to be approximately $88.81 billion. Antihistamines, occasionally used as first-line drugs for pruritus, do not suppress pruritus caused by other mediators.The researchers defined clini- cally meaningful improvement in pruritus as a 3- to 4-point improvement from baseline in the peak pruritus score on the numerical rating scale between days 2 and 15. By day 4, more patients who received dupilumab were more likely to have a 3-point improvement in their peak daily NRS score for pruritus than those who received placebo .IL-31 receptor is a heterodimeric complex composed of IL-31RA and OSMR. IL-31 receptors are expressed on various cells, including peripheral nerves, KCs, and immune cells .Multiple clinical trials have now demonstrated the antipruritic effect of nemolizumab, a humanized anti-human IL-31RA mAb, for patients with AD .The antipruritic efficacy of nemolizumab as a monotherapy in AD has also been demonstrated in phase 2 trials for 12 weeks , where patients were randomly assigned to nemolizumab or placebo every 4 weeks .Although comparison between two different clinical studies with nemolizumab and dupilumab cannot reach a conclusion, IL-31etargeting therapy seems to be specifically efficacious for pruritus, whereas IL-4/13etargeting therapy appears to show better clearance of skin inflammation alongside itch, suggesting the varying pathophysiologic roles of IL-4/13 and IL-31 in AD.Efficacy of an anti-TSLP mAb on AD was evaluated in phase 2 clinical trials, where mixed results for its efficacy on pruritus were found.A phase 2 trial, in which 113

patients were enrolled and received subcutaneous tezepelu- mab 280 mg or placebo every 2 weeks with topical corti- costeroid, showed that a higher, but not statistically significant, percentage of tezepelumab-treated patients ach- ieved an EASI 50 response at week 12 compared with the placebo group .Here, the proportion of patients who had a 4-point or greater improvement in peak pruritus NRS score from baseline was higher in the upadacitinib 15 mg/day and 30 mg/day groups than the placebo group at weeks 1, 4, and 16. . Bieber et al. (2021) have conducted a double-blind phase 3 trial of abrocitinib to compare with dupilumab and showed the superiority of the 200-mg dose, but not the 100-mg dose, of abrocitinib to dupilumab with respect to the improvement of 4 points in peak pruritus NRS score at week 2 .Nemolizumab has also demonstrated efficacy on severe pruritus in patients with moderate-to-severe prurigo nodularis in a recent randomized phase 2 clinical trial .Despite pruritus being a common complaint in the derma- tological field, many patients are refractory to available therapies. Currently, many drugs targeting itch-inducing cy- tokines are under development, and some of them are effective in controlling the signs and symptoms of pruritus. Therefore, new therapies focused on cytokine-mediated pruritus are expected to bring about dramatic changes in patient outcomes over the next few years

*a. Sutaria N, Adawi W, Goldberg R, Roh YS, Choi J, Kwatra SG. Itch: Pathogenesis and treatment. J Am Acad Dermatol. 2022 Jan;86(1):17-34. doi: 10.1016/j.jaad.2021.07.078. Epub 2021 Oct 12. PMID: 34648873.*

Itch pathogenesis is broadly characterized into histaminergic and nonhistaminergic pathways and transmitted via 2 main receptor families: G protein-coupled receptors and transient receptor potential channels. In the skin, itch is primarily transmitted by unmyelinated type C and thinly myelinated type Aδ nerve fibers. Crosstalk between the immune and neural systems modulates itch transmission at the skin, spinal cord, and brain. Among the many known pruritogens, Th2 cytokines, such as interleukin-4, interleukin-13, interleukin-31, and thymic stromal lymphopoietin, are particularly important mediators that signal through shared Janus kinase pathways, representing novel targets for novel itch therapeutics. Emerging evidence has also revealed that the opioidergic system is a potent modulator of itch transmission, with increased μ-opioid activity and decreased κ-opioid activity contributing to itch pathogenesis. Optimal management of itch requires that treatment approaches be tailored to specific etiologic itch subtypes. When the etiology is unknown and patients are given a diagnosis of chronic pruritus of unknown origin, treatment should be guided by the presence of Th2 polarization, often reflected by increased blood eosinophils. In the second article of this 2-part series, we outline our current understanding of itch pathogenesis and discuss available and emerging treatments for itch.

*b. Müller S, Bieber T, Ständer S. Therapeutic potential of biologics in prurigo nodularis. Expert Opin Biol Ther. 2022 Jan;22(1):47-58. doi:10.1080/14712598.2021.1958777. Epub 2021 Aug 4. PMID: 34289753.*

Introduction: Prurigo nodularis (PN) or chronic prurigo of nodular type (CNPG) is a subtype of chronic prurigo with severe pruritus and neuroimmune underlying pathophysiology occurring in a plethora of dermatological, systemic, neurologic, and psychiatric conditions.Areas covered: We review the increasing repertoire of biologics in the treatment of CNPG focusing on those targeting interleukins 4, 13, 31, oncostatin M and IgE. Presented information is based on a database research on current clinical trials (clinicaltrials.gov, European Clinical Trials Database (EudraCT), US clinical trial registry ICH-GCP) and a PubMed search for latest publications conducted with the combinations of the terms 'chronic prurigo,' 'prurigo nodularis,' 'pathophysiology,' 'treatment,' 'therapy', and 'biologics.'Expert opinion: CNPG gets more and more attention as new therapeutic targets have been revealed in recent years, thus allowing the use of targeted approaches. The off-label advent of dupilumab offered advanced insight into the pathogenesis of CNPG and showed an impressive relief of pruritus in the vast majority of patients. New therapies including biologics (e.g. nemolizumab, tralokinumab, lebrikizumab), small molecules (e.g. neurokinin-1 receptor antagonists, janus kinase inhibitors) as well as mu-opioid receptor antagonists and nalbuphine, a μ-antagonist/κ-agonist, are in the pipeline and offer new hope for an improved future patient care.

*c. Wang F, Trier AM, Li F, Kim S, Chen Z, Chai JN, Mack MR, Morrison SA,Hamilton JD, Baek J, Yang TB, Ver Heul AM, Xu AZ, Xie Z, Dong X, Kubo M, Hu H,Hsieh CS, Dong X, Liu Q, Margolis DJ, Ardeleanu M, Miller MJ, Kim BS. A basophil-neuronal axis promotes itch. Cell. 2021 Jan 21;184(2):422-440.e17. doi:10.1016/j.cell.2020.12.033. Epub 2021 Jan 14. PMID: 33450207; PMCID: PMC7878015.*

Itch is an evolutionarily conserved sensation that facilitates expulsion of pathogens and noxious stimuli from the skin. However, in organ failure, cancer, and chronic inflammatory disorders such as atopic dermatitis (AD), itch becomes chronic, intractable, and debilitating. In addition to chronic itch, patients often experience intense acute itch exacerbations. Recent discoveries have unearthed the neuroimmune circuitry of itch, leading to the development of anti-itch treatments. However, mechanisms underlying acute itch exacerbations remain overlooked. Herein, we identify that a large proportion of patients with AD harbor allergen-specific immunoglobulin E (IgE) and exhibit a propensity for acute itch flares. In mice, while allergen-provoked acute itch is mediated by the mast cell-histamine axis in steady state, AD-associated inflammation renders this pathway dispensable. Instead, a previously unrecognized basophil-leukotriene (LT) axis emerges as critical for acute itch flares. By probing fundamental itch mechanisms, our study highlights a basophil-neuronal circuit that may underlie a variety of neuroimmune processes

1. *Alam M, Buddenkotte J, Ahmad F, Steinhoff M. Neurokinin 1 ReceptorAntagonists for Pruritus. Drugs. 2021 Apr;81(6):621-634. doi:10.1007/s40265-021-01478-1. Epub 2021 Mar 6. PMID: 33675531; PMCID: PMC8102458.*

a. Pruritus, commonly known as itch, is a very common symptom in numerous dermatological disorders and systemic diseases. It can manifest as acute, or when

lasting longer than 6 weeks, it is considered chronic and can lead to significant distress and reduced quality-of-life of those suffering. Current therapeutics are limited and are lacking in efficacy, and the development of more effective treatments is needed. The neurokinin 1 receptor (NK1R) antagonists are a novel class of drugs that possess several properties such as antidepressant, anxiolytic and antiemetic activities. Recently, several studies have described the antipruritic activity of NK1R antagonists for treating chronic pruritus. In this review we outline the pathogenesis of chronic pruritus, the mechanism by which the neuropeptide substance P (SP) and its receptor NK1R may be targeted to inhibit pruritic activity, and the efficacy and tolerability of NK1R antagonists, which have been, or are currently being investigated for treating conditions where chronic pruritus is a major symptom. Increasing evidence from ongoing and completed studies demonstrates the importance of SP and NK1R signalling in mediating pruritic activity. Several NK1R antagonists have shown significant antipruritic activity and thus targeting the SP-NK1R pathway may provide a therapeutic option for treating chronic pruritus of certain origin/s in the foreseeable future.

*2. Chen W, Li Y, Steinhoff M, Zhang W, Buddenkotte J, Buhl T, Zhu R, Yan X, Lu Z, Xiao S, Wang J, Meng J. The PLAUR signaling promotes chronic pruritus. FASEB J. 2022 Jun;36(6):e22368. doi: 10.1096/fj.202200079R. PMID: 35596683; PMCID:PMC9323474.*

a. Chronic itch is a complex sensation of the skin frequently associated with skin diseases, such as atopic dermatitis (AD) and psoriasis. Although Serpin E1 is implicated in chronic itch, its receptor and signaling pathways involved in itch are not known. In this study, the clinical relevance of a putative Serpin E1 receptor PLAUR to chronic itch, and the neuro-cutaneous Serpin E1-PLAUR signaling are explored. We found that PLAUR is overexpressed in skin specimens of human lesional AD and lesional psoriasis, and sensory neurons innervating MC903-induced AD-like murine skin. Murine PLAUR+ sensory neurons responded to Serpin E1, resulting in enrichment of numerous itch- and inflammation-related genes and their protein release. PLAUR resides in TLR2+ neurons and Serpin E1 stimulus led to transcriptional upregulation of TLR2 and its co-signaling proteins. Agonists of TLR2 propagated itch-related gene transcription including BNP, OSM, and PAR2. OSM induced acute itch in mice and promoted G-CSF and IL-8 release from human keratinocytes. Serpin E1 inhibitor reduced MC903-induced itch, epidermal hyperplasia, immunocyte infiltration, and resulted in lower transcription/expression levels of Serpin E1 and OSM. Taken together, the PLAUR-TLR2-OSM signaling promotes skin-nerve communication, cutaneous inflammation, and itch, all feeding into an aggravation of AD and exaggerated itch circuits.

*3. Tsoi LC, Hacini-Rachinel F, Fogel P, Rousseau F, Xing X, Patrick MT, Billi AC, Berthier CC, Kahlenberg JM, Lazzari A, Wiegmann H, Ständer S, Piketty C,Julia V, Krishnaswamy JK, Gudjonsson JE. Transcriptomic characterization of prurigo nodularis and the therapeutic response to nemolizumab. J Allergy Clin Immunol. 2022 Apr;149(4):1329-1339. doi: 10.1016/j.jaci.2021.10.004. Epub 2021 Nov 29. PMID:*

*34857395; PMCID: PMC8995330.*

a. Background Prurigo nodularis (PN) is a debilitating, difficult-to-treat, intensely pruritic, chronic inflammatory skin disease characterized by hyperkeratotic skin nodules. The pathogenesis of PN is not well understood but is believed to involve cross talk between sensory nerve fibers, immune cells, and the epidermis. It is centered around the neuroimmune cytokine IL-31, driving an intractable itch-scratch cycle.ObjectiveWe sought to provide a comprehensive view of the transcriptomic changes in PN skin and characterize the mechanism of action of the anti-IL-31 receptor inhibitor nemolizumab.MethodRNA sequencing of biopsy samples obtained from a cohort of patients treated with the anti-IL-31 receptor inhibitor nemolizumab and taken at baseline and week 12. Generation and integration of patient data with RNA-Seq data generated from reconstructed human epidermis stimulated with IL-31 and other proinflammatory cytokines.ResultsOur results demonstrate that nemolizumab effectively decreases IL-31 responses in PN skin, leading to effective suppression of downstream inflammatory responses including TH2/IL-13 and TH17/IL-17 responses. This is accompanied by decreased keratinocyte proliferation and normalization of epidermal differentiation and function. Furthermore, our results demonstrate how transcriptomic changes associated with nemolizumab treatment correlate with improvement in lesions, pruritus, stabilization of extracellular matrix remodeling, and processes associated with cutaneous nerve function.ConclusionThese data demonstrate a broad response to IL-31 receptor inhibition with nemolizumab and confirm the critical upstream role of IL-31 in PN pathogenesis.

*4. Lu PH, Chuo HE, Kuo KL, Liao JF, Lu PH. Clinical Efficacy and Safety of Sodium Thiosulfate in the Treatment of Uremic Pruritus: A Meta-Analysis of Randomized Controlled Trials. Toxins (Basel). 2021 Oct 30;13(11):769. doi: 10.3390/toxins13110769. PMID: 34822553; PMCID: PMC8624535.*

a. Uremic pruritus is a distressful complication of chronic kidney disease and results in impaired quality of life and higher mortality rates. Intravenous sodium thiosulfate has been reported to alleviate pruritus in hemodialysis patients. We performed a systematic review and meta-analysis to estimate the efficacy of intravenous sodium thiosulfate in patients with uremic pruritus. A systematic search of electronic databases up to June 2021 was conducted for randomized controlled trials that evaluated the clinical effects of sodium thiosulfate in the management of patients with uremic pruritus. Two reviewers selected eligible articles and evaluated the risk of bias; the results of pruritus assessment and uremic pruritus-related laboratory parameters in selected studies were analyzed. There are four trials published between 2018 and 2021, which include 222 participants. The sodium thiosulfate group displayed significant decrease in the pruritus score (standardized mean difference = −3.52, 95% confidence interval = −5.63 to −1.41, p = 0.001), without a significant increase in the adverse effects (risk ratio = 2.44, 95% confidence interval = 0.37 to 15.99, p = 0.35) compared to the control group. Administration of sodium thiosulfate is found to be a safe and efficacious complementary therapy in improving uremic pruritus in patients with chronic kidney disease.

*5. Misery L. Pruriplastic Itch-A Novel Pathogenic Concept in Chronic Pruritus.Front Med (Lausanne). 2021 Jan 20;7:615118. doi: 10.3389/fmed.2020.615118. PMID:33553207; PMCID: PMC7854543.*

a. The International Association for the Study of Pain (IASP) defined three descriptors for pain: nociceptive pain is "pain that arises from actual or threatened damage to non neural tissue and is due to the activation of nociceptors"; neuropathic pain is "pain caused by a lesion or disease of the somatosensory nervous system"; and nociplastic pain is "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain." Based on clinical and pathophysiological arguments, a similar definition of "pruriplastic pruritus" should be made. Pruriplastic pruritus would include psychogenic pruritus, as well as some cases of pruritus ani, vulvar pruritus, sensitive skin or other poorly understood cases of pruritus. This new descriptor of itch could serve as systematic screening for altered pruriceptive function in patients who suffer from chronic itch and it may also help in defining better tailored treatment by identifying patients who are likely to respond better to centrally rather than to peripherally targeted therapies.

*6. Gael M, Adam T, Mariano-Bourin M, Bursztejn AC. Efficacy of dupilumab in chronic prurigo and chronic idiopathic pruritus: a systematic review of current evidence and analysis of response predictors. J Eur Acad Dermatol Venereol. 2022 Sep;36(9):1541-1551. doi: 10.1111/jdv.18221. Epub 2022 May 31. PMID: 35569006.*

a. Dupilumab has demonstrated a great reduction in chronic pruritus that is the hallmark of atopic dermatitis (AD). Underscoring relevant pathogenesis similarities emerging from AD, chronic idiopathic pruritus (CIP) and chronic prurigo (CP), several authors suggested the beneficial role of dupilumab in these conditions. The evidence on this subject is limited with no precise data available. In this study, we carried out a systematic literature review in order to evaluate the efficacy of dupilumab on both pruritus and skin manifestations in the two largest retrospective cohorts of patients with CP and CIP and tried to identify potential response predictors. Electronic searches were conducted on 4 databases. Our primary outcome was the improvement in pruritus measured by a reduction in the patient's reported numerical rating scale of itch (NRSI) by >4. Secondary outcomes included the proportion of patients with a complete response at the end of treatment, reduction in the number of lesions by the Investigator Global Assessment (IGA), improvement in numerical rating scale of sleep (NRSS), improvement in quality of life measured by the Dermatology Life Quality Index (DLQI), time until patient perceived any improvement (Time-First) and time until the patient-reported absence of pruritus (Time-Final). Descriptive statistics were calculated for each demographic and clinical variable. Univariate logistic regression analyses were conducted to explore the association between response to dupilumab and potential predictive factors. We included 25 articles in the analysis, counting a total of 153 patients. Based on CP patients' cohort (n = 132),

the mean NRSI at baseline was 8.79 ± 0.86 and the NRSI final was 2.32 ± 1.27. The mean time to first improvement was 5.18 ± 3.13 weeks, while the time to complete improvement of pruritus (Time-final) was 13.6 ± 12.0 weeks. Ninety patients out of 109 (83%) noticed an improvement in pruritus before 4 weeks of dupilumab therapy. At the end of treatment, 18 patients out of 126 (14%) had a complete remission of pruritus and 110 patients out of 123 (89%) had a reduction of NRSI >4. The reduction in NRSI was significantly greater in patients improving before 4 weeks of treatment (6.57 ± 1.71) compared with patients improving in more than 4 weeks (5.49 ± 1.39, P < 0.001). Patients with history of AD and those who have been previously treated with cyclosporine or methotrexate had a significantly lower reduction in NRSI (e.g. 6.05 ± 1.34 vs. 7.08 ± 1.90, P < 0.01 for nonassociated AD patients). Based on CIP patient's cohort (n = 21), the mean NRSI at baseline was 8.33 ± 0.80 and the NRSI final was 0.95 ± 0.59. The mean time to first improvement was 2 ± 0 weeks, while the time to complete improvement (Time-final) was 14.6 ± 10 weeks. At the end of treatment, 3 patients out of 21 (14%) had a complete remission of pruritus and 100% of patients had a reduction of NRSI >4. No serious treatment-emergent adverse events were reported. The most common adverse event was mild conjunctivitis (13 cases). We highlight the importance of one early sign of improvement as a predictor of the future response to dupilumab: the improvement before 4 weeks of treatment that leads significantly to a greater final reduction in NRSI. Furthermore, patients with the presence or history of atopy appear to be less responsive to dupilumab than nonatopic patients and develop more side effects, in particular conjunctivitis.

*7. Lin YL, Wang CL, Liu KL, Yeh CN, Chiang TI. Omega-3 Fatty Acids Improve Chronic Kidney Disease-Associated Pruritus and Inflammation. Medicina (Kaunas). 2022 Jun 13;58(6):796. doi: 10.3390/medicina58060796. PMID: 35744059; PMCID: PMC9229849.*

a. Background and Objectives: Chronic kidney disease-associated pruritus (CKD-aP) is a common symptom in hemodialysis patients. A frequent and intense itching sensation largely torments patients, impacts quality of life outcomes, and it has an independent association with mortality. The objective of this study is to investigate the effects of oral supplementation with omega-3 polyunsaturated fatty acid (omega-3 PUFA) on circulating interleukin-6 (IL-6), cardiometabolic parameters, skin moisturization, and the consequent symptoms of pruritus in hemodialysis patients. Materials and Methods: Volunteers on maintenance hemodialysis with very severe pruritus symptoms were enrolled in this prospective cohort study. Subjects were instructed to consume 1000 mg fish oil once daily for 3 months. Pruritus scoring, skin moisture, plasma IL-6, and cardiometabolic parameters were measured at baseline, and at the first, second, and third month post-supplementation with fish oil for assessment of the clinical significance. Results: A total of 27 patients who had a mean age of 67.33 ± 11.06 years and 3.98 ± 3.23 years on hemodialysis completed the study. Supplementation with omega-3 PUFA significantly decreased IL-6 levels (p < 0.001), but increased the levels of c-reactive protein (CRP) (p < 0.05). Evaluation of the cardiovascular risk showed

significant (all p < 0.001) decreases in the total cholesterol (CHO), low-density lipoprotein (LDL), and triglycerides (TG) levels, and an increase in the high-density lipoprotein (HDL) level. A significant decrease in plasma creatinine (CR) was observed (p < 0.001), but the decrease was limited. Supplementation with omega-3 PUFA significantly improved (all p < 0.001) skin hydration on both the face and arms, as well as disease-related symptoms of pruritus. Conclusion: Omega-3 PUFA supplementation improved inflammation, renal function, cardiovascular parameters, dry skin conditions, and the consequent symptoms of pruritus in hemodialysis patients.

*8. Yang H, Chen W, Zhu R, Wang J, Meng J. Critical Players and Therapeutic Targets in Chronic Itch. Int J Mol Sci. 2022 Sep 1;23(17):9935. doi:10.3390/ijms23179935. PMID: 36077340; PMCID: PMC9456029.*

a. Chronic itch is one of the most prominent clinical characteristics of diverse systematic diseases. It is a devastating sensation in pathological diseases. Despite its importance, there are no FDA-labelled drugs specifically geared toward chronic itch. The associated complex pathogenesis and diverse causes escalate chronic itch to being one of the top challenges in healthcare. Humanized antibodies against IL-13, IL-4, and IL-31 proved effective in treatment of itch-associated atopic dermatitis but remain to be validated in chronic itch. There are still no satisfactory anti-itch therapeutics available toward itch-related neuropeptides including GRP, BNP, SST, CGRP, and SP. The newly identified potential itch targets including OSM, NMB, glutamate, periostin, and Serpin E1 have opened new avenues for therapeutic development. Proof-of-principle studies have been successfully performed on antagonists against these proteins and their receptors in itch treatment in animal models. Their translational interventions in humans need to be evaluated. It is of great importance to summarize and compare the newly emerging knowledge on chronic itch and its pathways to promote the development of novel anti-itch therapeutics. The goal of this review is to analyze the different physiologies and pathophysiologies of itch mediators, whilst assessing their suitability as new targets and discussing future therapeutic development.

*9. Labib A, Ju T, Lipman ZM, Yosipovitch G. Evaluating the Effectiveness of Intranasal Butorphanol in Reducing Chronic Itch. Acta Derm Venereol. 2022 Jun 9;102:adv00729. doi: 10.2340/actadv.v102.2153. PMID: 35470402.*

a. Intractable itch is defined as a chronic itchy state in which the cause cannot be removed or otherwise treated through the general course of medical practice (1). Many of these conditions include dermatological aetiologies (2, 3), in addition to other systemicaetiologies. Quality of life, pertaining to sleep, depression, anxiety, and relationships, has been found to be significantly impaired in patients with severe itch (4). There is data to suggest that in chronic itch of multiple types there is an imbalance of mu opioid receptor over-activation and kappa opioid receptor

downregulation (5). Therefore, the use of butorphanol, a kappa-opioid receptor agonist and mu-opioid receptor antagonist to decrease itch. There are a few case series reporting on the use of intranasal butorphanol as treatment for intractable itch with results finding butorphanol to be highly effective at a rapid speed of onset, and well tolerated, for different itch-associated chronic etiologies (5, 6). However, the current literature lacks any larger scale study on the effectiveness of butorphanol over a longer period. MATERIALS AND METHODS Patients who were prescribed intranasal butorphanol for the treat-ment of chronic pruritus were identified and evaluated for this study using the following parameters: date of medication prescrip-tion from November 2017 to December 2021 at the University of Miami Hospital and satellite clinics, and patient age at prescription date ≥ 18 years. Patients were instructed to administer at least 1 puff of 1 mg equivalent, and up to 4 mg equivalent (4 puffs) interspaced as a divided dose throughout the day, of intranasal butorphanol 10 mg/ml. Patients used intranasal butorphanol every day between the first and second visit, unless otherwise indicated. Itch was quantified using a pruritus numerical rating score (NRS) at the initial visit prior to intranasal butorphanol initiation and at the subsequent visit(s). Pruritus NRS is a validated tool that is reliable and sensitive in assessing itch in patients with atopic dermatitis (AD) (7); it is embedded within the University of Miami electronic medical record system. Important information was extracted in a comprehensive chart review. Patient data were de-identified and statistically analysed using a paired t-test and a 2-tailed Wilcoxon signed-rank test. Statistical significance was assigned at $p < 0.05$. RESULTSA total of 33 adults were analysed in this retrospective chart review. Butorphanol was prescribed for a variety of pruritic diseases. The mean ± standard deviation (SD) length of itch history prior to butorphanol initiation was approximately 43 ± 63.8 months (Table I). Of the total 33 patients, 26 (79%) patients were re-evaluated following treatment, while 7 (21%) patients were lost to follow-up (3; 9%) or never began treatment (4; 12%). The remainder of the results will evaluate only the participants who were enrolled in this study, received butorphanol treatment, and were reassessed in a follow-up visit. Two participants were excluded from 24-h worst itch NRS statistical analyses due to lack of obtained data in either pre- or post-assessments. The average-itch NRS mean was 8.00±2.21 and the worst-itch NRS mean was 9.79 ± 0.51 for the 26 patients who were analysed within the last 5 years. Post-treatment, the average-itch NRS mean and the worst-itch NRS mean in this group were 5.08 ± 2.69 and 7.13±3.39, respectively, at the second patient visit (Fig. 1A). The average period between the first and second visits was approximately 2.6 ± 3.35 months; although, many patients reported that the efficacy of treatment occurred following the first few days. The results demonstrate significant reduction in average- and worst-itch NRS ($p < 0.002$). Fourteen (54%) patients experienced a 4-point or more decrease in average-itch NRS and 7 (29%) patients experienced a 4-point or more decrease in worst-itch NRS. Three (12%) patients, who otherwise did not demonstrate meaningful reduction in itch NRS, reported anecdotal improvement in itch. In patients who experienced either a quantifiable or quali-fiable improvement in pruritus, the antipruritic effect of the drug was noted to occur after 1 use in the majority of cases. Amongst these 26 participants, 20

(77%) patients continued treatment with intranasal butorphanol for the intended treatment period (until subsequent follow-up visit), while 6 (23%) patients discontinued treatment prior to the intended treatment period due to adverse effects and/or intolerance. Nine (35%) patients reported at least 1 side-effect. Five of the 7 patients discontinued treatment early due to ad-verse effects and 1 patient who experienced improved itch with butorphanol eventually stopped treatment because of intolerance to side-effects. The most common adverse effects include dizziness and/or nausea (3 patients; 12%), abnormal dreams (2 patients; 8%), feelings of intoxication or altered sense of consciousness (2 patients; 8%) and drowsiness (2 patients; 8%).

*10. Chu L, Wang LK, Wu Y, Yang H, Wang W, Lu Q, Deng H. Plasma Steroids and Endocannabinoids Used as Biomarkers to Assess the Pruritus Severity of Patients With Prurigo Nodularis. Actas Dermosifiliogr. 2022 Mar;113(3):244-253. English,Spanish. doi: 10.1016/j.ad.2022.02.016. Epub 2022 Feb 8. PMID: 35282859.*

a. Background: Prurigo nodularis (PN) as an extremely pruritic and hyperplastic chronic dermatosis induces psychologically and physiologically stressful responses. PN-induced responses in the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-gonadal (HPG) axes and endocannabinoid system (ECS) are abnormal. Extant studies on the PN's pathogenesis mostly focused on the PN's psychological responses. To date, the PN's physiological responses remain not been fully uncovered yet.Objectives: To investigate the PN-induced physiological responses via the levels of five steroids and two endocannabinoids combined with their ratios in plasma and examine the association between the psychological and physiological responses.Materials and methods: Thirty-six patients with PN, 36 age- and gender-matched healthy controls were recruited. The PN's psychological symptoms including pruritus severity, pain and life quality were measured with the visual analog scale, the prurigo score index, numerical rating scale, verbal rating scale and dermatology life quality index. Their concentrations of steroids and endocannabinoids were determined with liquid chromatography-tandem mass spectrometry.Results: Compared to controls, the PN patients showed lower plasma levels in cortisol, cortisone, N-arachidonoyl-ethanolamine (AEA), and the ratio of DHEA to 1-arachydonoyl glycerol (1-AG), which negatively moderately and over correlated with PN's symptoms, especially with the pruritus severity. Additionally, the PN patients exhibited higher levels in the ratios of testosterone and 1-AG to cortisol, which positively moderately and over correlated with pruritus severity. Thus, the seven biomarkers would be sensitive and reliable biomarkers for assessing the pruritus severity of PN because they met the screening criteria that the biomarkers show intergroup differences and showed moderate or over correlation with the pruritus severity of PN.Conclusions: To the best of our knowledge, this is the first study exploring PN-induced physiological responses. The findings suggest that alterations in these three endocrine systems may lead to new insights to psychological mechanisms and responses to prurigo nodularis.

*11. Weisshaar E, Szepietowski JC, Bernhard JD, Hait H, Legat FJ, Nattkemper L,Reich*

*A, Sadoghi B, Sciascia TR, Zeidler C, Yosipovitch G, Ständer S. Efficacy and safety of oral nalbuphine extended release in prurigo nodularis: results of a phase 2 randomized controlled trial with an open-label extension phase. J Eur Acad Dermatol Venereol. 2022 Mar;36(3):453-461. doi: 10.1111/jdv.17816. Epub 2021 Dec 1. PMID: 34780095.*

a. Background: Treatment of prurigo nodularis (PN) is challenging and new treatment options are needed.Objective: To evaluate the efficacy and safety of two oral doses of the kappa opioid agonist and mu opioid antagonist nalbuphine extended release (NAL-ER) tablets in a phase 2, multicentre, randomized, double-blind, placebo-controlled trial with an open-label, 50-week extension phase.Methods: Subjects with moderate-to-severe PN were randomized to NAL-ER 81 mg (NAL-ER81) or 162 mg (NAL-ER162) tablets twice-daily or placebo for 8 weeks of stable dosing following a 2-week titration period. Subjects completing Week 10 with a Worst Itch Numerical Rating Scale (WI-NRS) score ≥5 at the time of rollover (or during the observation period) were eligible for open-label treatment.Results: Of 63 randomized subjects, 62 were treated and comprised the modified intent-to-treat population (MITT), 50 completed 10 weeks of treatment. In the MITT analysis, 8 subjects (44.4%) treated with NAL-ER162 (P = 0.32) and 6 (27.3%) treated with NAL-ER81 (P = 0.78) achieved ≥30% reduction from baseline in 7-day WI-NRS at Week 10 (primary efficacy endpoint) vs. 8 (36.4%) in the placebo group. Itch reduction was significant among 8/12 (66.7%) subjects completing Week 10 treated with NAL-ER162 vs. placebo (8/20, 40.0%; P = 0.03). Additionally, 6 subjects (33.3%) treated with NAL-ER162 and 3 (13.6%) treated with NAL-ER81 achieved ≥50% reduction from baseline in 7-day WI-NRS at Week 10 (coprimary endpoint). Extended open-label treatment was associated with further improvements in itch reduction and favourable changes in PN lesion activity as assessed by Prurigo Activity Score. Adverse events occurred predominantly during dose titration and were of mild-to-moderate severity. The safety profile did not change with extended open-label treatment.Conclusion: In adult subjects with PN, oral treatment with NAL-ER 162 mg twice daily provided measurable anti-pruritic efficacy in subjects completing ≥10 weeks of treatment and was well tolerated

*12. Yoshitani H, Ito J, Kozono H. Post-Marketing Surveillance Study of the Safety and Efficacy of Nalfurafine (Capsules 2.5 μg, Oral Dispersing Tablets 2.5μg) in 1186 Patients with Chronic Liver Disease and Intractable Pruritus. Hepat Med. 2022 May 2;14:37-66. doi: 10.2147/HMER.S352775. PMID: 35530746; PMCID: PMC9075016.*

a. Background :Nalfurafine (Remitch®, Toray Industries, Inc.) is a selective κ-receptor agonist approved in Japan for the improvement of pruritus in patients with chronic liver diseases (only when existing treatments bring insufficient efficacy) in May 2015.MethodsA post-marketing Specific Drug Use Survey was conducted in Japan (March 1, 2016 to June 30, 2020) of the safety and efficacy of nalfurafine for the improvement of pruritus in patients with chronic liver disease.ResultsAmong 1186 cases analyzed for safety, the incidence of adverse drug reactions was 9.4% (112/1186 cases), lower than 61.4% reported in

pre-marketing surveillance (297/484 cases). No specific safety issues were found and no cases of concern for drug dependence identified. Efficacy (itch improvement) was demonstrated in 73.16% (815/1114 cases; 12-week analysis set) and in 85.67% (520/607; general assessment of itch improvement at 1-year analysis set). A significant difference was found in 4 items of itch improvement at 12 weeks and 8 items of itch improvement at 1 year. No noteworthy issues were identified. Mean Visual Analog Scale (VAS) values after 12 weeks and 1 year after the first dose were significantly lower than the baseline ($p < 0.0001$ for both treatment durations). Mean severity scores (Kawashima's classification scheme) were significantly lower than the pretreatment score at 12 weeks and 1 year after the first dose (both $p < 0.0001$). No concerns were identified in the efficacy and safety of nalfurafine in patients with specific background, ie, the elderly (aged ≥ 65 years), those with renal impairment, and those on long-term treatment (≥ 365 days) compared with patients without corresponding background.ConclusionNo new safety issues of concern or cases of insufficient efficacy were identified in this Specific Drug Use Survey of the safety and efficacy of nalfurafine for the improvement of pruritus in patients with chronic liver diseases.

*13.Todurga Seven ZG, Çakır Gündoğdu A, Ozyurt R, Özyazgan S. The Effects ofCannabinoid Agonist, Heat Shock Protein 90 and Nitric Oxide Synthase Inhibitors on Increasing IL-13 and IL-31 Levels in Chronic Pruritus. Immunol Invest. 2022 Oct;51(7):1938-1949. doi: 10.1080/08820139.2022.2083973. Epub 2022 Jun 8. PMID:35675220.*

Background: Heat shock protein 90 (Hsp90) inhibitor and cannabinoid agonists ameliorate dry skin-induced chronic itch. We have recently reported that cannabinoids, hsp90 and nitric oxide (NO) are involved in dry skin-induced itch. Here, we investigated the contribution of the Th2 cell signaling pathway to the antipruritic effect of the hsp90 inhibitor 17-Alilamino-17-demethoxygeldanamycin (17-AAG), nitric oxide synthase (NOS) inhibitor Nω-Nitro-L-arginine methyl ester hydrochloride (L-NAME) and cannabinoid agonist WIN 55,212-2 on a dry skin-induced scratch.Methods: Dry skin-induced chronic itching was created by topical application of AEW (acetone/diethyl ether/water). WIN 55,212-2 (1 mg/kg, i.p.), L-NAME (1 mg/kg, i.p.) and increasing doses of 17-AAG (1, 3 and 5 mg/kg,i.p.) were administered to Balb/c mice (for each group, n = 6). After these applications, skin tissues were taken from the nape region of all of the mice. Gene and protein expressions of IL-13 and IL-31 were evaluated in skin tissues by RT-PCR and immunohistochemistry, respectively.Results: IL-13 and IL-31 mRNA expressions and immune positive cell counts were increased in the AEW applied groups. WIN 55,212-2 reduced both of the increased cytokines levels, while L-NAME decreased only the IL-13. 17-AAG dose-dependently reduced the increased cytokine levels. IL-13 and IL-31 levels significantly decreased following the co-administration of these agents.Conclusion: These results show that increased levels of IL-13 and IL-31 are associated with pruritus. Hsp90 inhibition and cannabinoid system activation may induce antipruritic effects through down-regulation of these cytokines

*14.Brand M, Kremer AE. Systemic pruritus: what is new in diagnosis and treatment?].Dermatologie (Heidelb). 2022 Aug;73(8):600-608. German. doi:10.1007/s00105-022-05027-z. Epub 2022 Jun 30. PMID: 35925235; PMCID: PMC9358966.*

a. Background: Chronic pruritus is a common symptom of various systemic diseases. In particular, patients with chronic renal failure, hepatobiliary diseases, and myeloproliferative neoplasms are affected.Objectives: The purpose of this review is to provide an overview of laboratory chemistry and imaging diagnostics as well as current and novel therapeutic approaches to pruritus of systemic diseases.Materials and methods: An extensive PubMed search was performed.Results: To clarify the cause of chronic pruritus, a step-by-step diagnosis is recommended, which is based on the frequency of pruritus-associated diseases. A basic diagnosis enables a cost-effective and targeted clarification at the level of a general practitioner. Current topical and drug therapy recommendations of pruritus in chronic renal failure, hepatobiliary diseases, myeloproliferative neoplasms, and rarer causes are summarized. In addition, novel therapeutic approaches such as the κ opioid receptor agonist difelikefalin, bezafibrate, inhibitors of the ileal bile acid transporter (IBAT), and the JAK-STAT pathway are highlighted.Conclusions: Chronic pruritus in systemic diseases can be a diagnostic challenge. A staged diagnostic approach facilitates identification of the underlying disease. Improved pathophysiological understanding has led to the first approved therapeutic options for chronic kidney disease-associated and hepatic pruritus.

*15.Ingrasci G, Tornes L, Brown A, Delgado S, Hernandez J, Yap QV, Yosipovitch G. Chronic pruritus in multiple sclerosis and clinical correlates. J Eur Acad Dermatol Venereol. 2022 Aug 26. doi: 10.1111/jdv.18561. Epub ahead of print. PMID: 36017740.*

Background: To date, little is known about the prevalence of itch in multiple sclerosis (MS) and its characteristics.Objectives: In this cross-sectional study, we assessed the prevalence, intensity and characteristics of chronic pruritus in MS patients and its effect on quality-of-life and association with MS symptoms, clinical signs, comorbidities and MRI findings.Methods: MS patients presenting to an outpatient neurology clinic were asked about their current symptoms. Those who experienced chronic pruritus were administered the Standardized Itch Questionnaire and Itch Quality of Life forms. All patients' medical records were reviewed. Patients with any medical conditions associated with chronic itch were excluded.Results: Seventy-seven total MS patients were included, and 27 (35%) reported pruritus. The average itch NRS severity was 5.42 (range 0-10). The most affected body parts were the extremities, face or scalp, and trunk. Itch was characterized as acute (74%), paroxysmal (59%) and tingling (55%). Heat (52%) was the most common aggravating factor, while cold temperatures had no effect. Compared with MS patients without itch, itch patients reported more fatigue (77% vs 44%, p = 0.004), heat sensitivity (48% vs 20%, p = 0.0177), cognitive impairment (62% vs 26%, p = 0.0029) and depression or anxiety (48% vs 16%, p = 0.0063). Additionally, itch patients had more T2 hyperintensities in the posterior cervical

cord and anterior pons/ventromedial medulla (74.1% vs 46.0%, p = 0.018 and 29.6% vs 8.0%, p = 0.020, respectively). Finally, T2 hyperintensities in the anterior pons/ventromedial medulla were strongly associated with itch localized to the face or scalp (OR 11.3, 95% CI 1.6–78.6, p = 0.025).Conclusion: MS patients experience paroxysmal neuropathic pruritus that is most frequently localized to the extremities, face or scalp. Patients with itch were more likely to have MS-related comorbidities and demyelinating lesions in the spinal cord or brainstem.

*16. Lipman ZM, Yosipovitch G. Substance use disorders and chronic itch. J AmAcad Dermatol. 2021 Jan;84(1):148–155. doi: 10.1016/j.jaad.2020.08.117. Epub 2020 Sep 3. PMID: 32891774.*

a. Chronic pruritus is one dermatologic manifestation of an underlying substance use disorder. Recent literature has uncovered similarities between the general neurologic mechanisms of addiction and chronic itch, largely involving activation of the dopaminergic reward circuits within the brain and imbalances between mu and kappa opioid receptor activation. It is likely that the use of specific drugs, like central nervous system stimulants and opioids, results in further activation and imbalances within these pathways, perpetuating both addiction and pruritus simultaneously. Opioid users often present to dermatology clinics with a generalized pruritus, whereas individuals using central nervous system stimulants like cocaine and methylenedioxymethamphetamine (MDMA), as well as legally prescribed drugs like treatments for attention deficit hyperactivity disorder, frequently complain of crawling, delusional infestation-like sensations underneath the skin. Because of these overlapping mechanisms and similar clinical presentations to many other chronically itchy conditions, it is necessary for dermatologists to consider and investigate an underlying substance use disorder to effectively treat these patients.

*17. Pereira MP, Schmelz M, Ständer S. Mechanisms and therapeutic targets for neuropathic itch. Curr Opin Neurobiol. 2022 Aug;75:102573. doi: 10.1016/j.conb.2022.102573. Epub 2022 Jun 8. PMID: 35689909.*

Neuropathic pruritus conditions arise from structural and/or functional damage of the peripheral or central nervous system. Novel findings of pruritus specific mediators and pathways strengthen the specificity theory of pruritus transmission, however electrophysiological studies suggest that focal activation of nociceptors and distinct discharge patterns of primary afferents also contribute to the development of the sensation of pruritus. A complex interplay between excitatory and inhibitory interneurons at spinal level, non-neuronal cells and descending modulation from upper centers contributes to neuronal sensitization and clinically to the chronicity of pruritus, as well as accompanying phenomena such as alloknesis and hyperknesis. Several topical, systemic and non-pharmacological therapeutic approaches directed at distinct targets are currently available.

## EPIDEMIOLOGY

*1. Roh YS, Choi J, Sutaria N, Kwatra SG. Itch: Epidemiology, clinical presentation, and diagnostic workup. J Am Acad Dermatol. 2022 Jan;86(1):1-14.doi: 10.1016/j.jaad.2021.07.076. Epub 2021 Aug 21. PMID: 34428534; PMCID:PMC8678917.*

Itch, or pruritus, is the uncomfortable sensation underlying the desire to scratch. Itch is a very common complaint in the general population that can result from dermatologic, systemic (eg, renal, hepatobiliary, endocrine), paraneoplastic, neuropathic, and psychogenic etiologies. Chronic itch is associated with significant sleep disturbances and profoundly reduces overall quality of life. Certain populations, including elderly and African Americans, are at increased risk of experiencing heightened burden of itch. Because of the variable clinical presentation and wide-ranging etiologies, itch presents a challenge for clinicians. The initial evaluation should include a complete blood count, with differential, hepatic, renal, and thyroid function testing along with diabetes screening. Further testing should be guided by history and physical examination findings. There should be a heightened concern for underlying malignancy in individuals older than 60 years of age who have a history of liver disease and diffuse itch less than 12 months of duration. For individuals with chronic pruritus of unknown origin, increased blood eosinophils may serve as a biomarker of T helper cell type 2 polarization and response to immunomodulator therapies. In this first part of a 2-part continuing medical education series, we describe the broader epidemiology and specific conditions associated with itch and the clinical presentation and diagnostic workup for patients with itch.

*2. Lee J, Suh H, Jung H, Park M, Ahn J. Association between chronic pruritus, depression, and insomnia: A cross-sectional study. JAAD Int. 2021 Mar 21;3:54-60. doi: 10.1016/j.jdin.2021.02.004. PMID: 34409371; PMCID: PMC8361905.*

Background: Skin diseases that cause chronic pruritus can have negative effects on a patient's quality of life.Objective: We evaluated the associations between chronic pruritus and psychological conditions including insomnia and depression.Methods: This study included responses from 91 participants with chronic pruritus (response rate: 74.6%). A survey including questionnaires regarding data on demographic characteristics, intensity of pruritus using the visual analog scale (VAS) and the 4-item itch questionnaire, and the degrees of insomnia and depression measured by the Insomnia Severity Index and Beck Depression Inventory, respectively.Results: Patients with symptoms of insomnia or depression had significantly more intense pruritus than patients without psychological symptoms (insomnia, VAS median [interquartile range]: 7.0 [5.0-8.25] vs. 5.0 [3.0-7.5]; depression, VAS median [interquartile range]: 7.5 [5.0-8.25] vs. 5.0 [3.0-7.0]). Multivariable analyses revealed that patients with moderate to severe pruritus were more likely to have depression than those with mild

pruritus (odds ratio: 10.95; 95% confidence interval: 2.24-53.06). There were no differences in the severity of insomnia and depression among skin diseases.Limitations: This study had a cross-sectional design and limited generalizability.Conclusion: Chronic pruritus is significantly associated with insomnia and depression, regardless of the etiology.

*3. Pereira MP, Farcas A, Zeidler C, Ständer S. Chronic Pruritus of Unknown Origin: Clinical Profile and Disease-Related Burden. Acta Derm Venereol. 2021Sep 17;101(9):adv00550. doi: 10.2340/00015555-3892. PMID: 34405244.*

Chronic pruritus of unknown origin is established when no underlying origin for pruritus can be determined. This retrospective cohort study aimed to determine the clinical profile and disease-related burden of chronic pruritus of unknown origin. A total of 263 patients (female/male: 154/109, median age 55 years) were included. Moderate to severe itch intensities were recorded (median average itch: 5.5/10, n = 200; median worst itch: 7.5/10, n = 199). In most cases pruritus lasted longer than 1 year (77.6%), occurred daily (68.2%), occurred in attacks (72.8%), and was often accompanied by dysaesthesias, such as burning, tingling and stinging. Quality of life was moderately impaired, while 22.2% and 12.4% of patients showed pathological anxiety and depression scores. Scratch lesions were associated with higher intensities of itch and greater impairment of quality of life, while women were more burdened by the disease than men. Chronic pruritus of unknown origin may occur at any age and the majority of patients endure severe itch with substantial disease-related burden.

*24.Zeidler C, Pereira MP, Dugas M, Augustin M, Storck M, Weyer-Elberich V,Schneider G, Ständer S. The burden in chronic prurigo: patients with chronic prurigo suffer more than patients with chronic pruritus on non-lesional skin: A comparative, retrospective, explorative statistical analysis of 4,484 patients in a real-world cohort. J Eur Acad Dermatol Venereol. 2021 Mar;35(3):738-743. doi: 10.1111/jdv.16929. Epub 2020 Nov 6. PMID: 32924186.*

Background: Chronic prurigo (CPG) is known as a high burdensome disease characterized by severe pruritus and multiple pruriginous lesions. Interestingly, the disease-specific burden is not well established and there are no data which compare the impact of CPG with chronic pruritus (CP) on non-lesional skin (CP-NL). Objectives: To address this issue, we analysed datasets from 4484 patients with either CPG or CP-NL.Methods: Demographic medical data and additional information collected by validated patient reported outcome tools were analysed. The visual analogue scale and numerical rating scale (NRS) were used for assessing the pruritus intensity, the ItchyQoL for patients' quality of life, the Hospital Anxiety and Depression Scale and the Patient Needs Questionnaire' as a part of Patient Benefit Index for Pruritus for

measuring the importance of 27 patient needs in terms of treatment goals. The Neuroderm questionnaire was used to assess the history of pruritus characteristics and the impact on sleep.Results: Patients with CPG suffered longer and with a higher intensity from pruritus [NRS worst the last 24 h, CPG 6.0 (4.0;8.0) vs. CP-NL 3.0 (5.0;7.0), P < 0.001]. In them, pruritus occurred more often and the whole day and night which led to more loss in sleeping hours [CPG 3.0 h (2.0;4.0) vs. CP-NL 2.0 h (1.0;4.0), P < 0.001]. Patients with CPG showed higher scores for depression [HADS-D, CPG 6.0 (3.0;10.0) vs. CP-NL 5.0 (2.0;8.0), P < 0.001], more impaired quality of life [ItchyQol; CPG: 72.6 (61.6;83.6) vs. CP-NL 59.4 (48.4;70.4), P < 0.001] and higher weighted needs in the predefined treatment goals.Discussion: Not only the presence of severe pruritus and pruriginous lesions but also sleep disorders and other mental symptoms may contribute to a higher burden in patients with CPG when compared with patients with CP-NL.

## EXPERIMENTAL DERMATOLOGY

*25.Tseng PY, Hoon MA. Oncostatin M can sensitize sensory neurons in inflammatory pruritus. Sci Transl Med. 2021 Nov 10;13(619):eabe3037. doi: 10.1126/scitranslmed.abe3037. Epub 2021 Nov 10. PMID: 34757808.*

Chronic itch is a major symptom of many inflammatory skin diseases. This type of pruritus is thought to be facilitated by cytokines that activate cutaneous nerve fibers; however, the molecular components and mechanisms involved are poorly understood. We found that the cytokine oncostatin M (OSM) is highly up-regulated in psoriasis, atopic dermatitis, and cutaneous T cell lymphoma, diseases associated with chronic itch. OSM receptor (OSMR) is expressed by itch-selective natriuretic polypeptide B (Nppb) neurons, and single-cell sequencing showed that OSM is mainly produced by dermal T cells and monocytes. Unlike canonical pruritogens, OSM does not activate sensory neurons. Instead, it sensitizes neurons by potentiating neural responses to pruritogens and by enhancing neural excitability. Knockout of OSMR in sensory neurons attenuated OSM-sensitized itch and inflammatory itch in mice, and pharmacological antagonism of the OSMR complex effectively alleviated pruritus in experimental inflammatory dermatitis in a rodent model. Together, our results uncover OSM as an itch neuromodulator and reveal OSM signal transduction as a potential target for antipruritic therapy.

*26.Scuron MD, Fay BL, Connell AJ, Peel MT, Smith PA. Ruxolitinib Cream Has Dual Efficacy on Pruritus and Inflammation in Experimental Dermatitis. Front Immunol. 2021 Feb 15;11:620098. doi: 10.3389/fimmu.2020.620098. PMID: 33658996; PMCID: PMC7917252.*

The goal of this study was to elucidate the anti-pruritic and anti-inflammatory

efficacy of ruxolitinib cream in experimentally-induced dermatitis. Atopic dermatitis (AD), the most common chronic relapsing inflammatory skin disease, significantly impairs patients' quality of life, with pruritus being a common complaint. The sensation of itch results from the interplay between epidermal barrier dysfunction, upregulated immune signaling and the activation of the central nervous system. The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway plays a central role in pro-inflammatory cytokine signaling in AD. Ruxolitinib cream is a potent and selective JAK1/2 inhibitor currently undergoing clinical evaluation in adults with mild-to-moderate AD (NCT03745638, NCT03920852 and NCT03745651). The efficacy of ruxolitinib cream was tested in murine models of acute and chronic dermatitis and was also characterized in an ex vivo human skin dermatitis model. Ruxolitinib cream was highly effective at ameliorating disease symptoms in multiple murine dermatitis models through downregulation of T helper (Th)2-driven inflammation, resulting in reduced skin thickening and decreased itch. Pathway analysis of mouse ear tissue and human skin explants underscored the role for ruxolitinib in ameliorating inflammation and reducing itch via modulation of the JAK-STAT pathway. Together, the data offer a strong rationale for the use of ruxolitinib cream as a potent therapeutic agent for the clinical management of atopic dermatitis.

.

*27.Nelson TS, Taylor BK. Targeting spinal neuropeptide Y1 receptor-expressing interneurons to alleviate chronic pain and itch. Prog Neurobiol. 2021 Jan;196:101894. doi: 10.1016/j.pneurobio.2020.101894. Epub 2020 Aug 7. PMID: 32777329; PMCID: PMC8088728.*

An accelerating basic science literature is providing key insights into the mechanisms by which spinal neuropeptide Y (NPY) inhibits chronic pain. A key target of pain inhibition is the Gi-coupled neuropeptide Y1 receptor (Y1). Y1 is located in key sites of pain transmission, including the peptidergic subpopulation of primary afferent neurons and a dense subpopulation of small, excitatory, glutamatergic/somatostatinergic interneurons (Y1-INs) that are densely expressed in the dorsal horn, particularly in superficial lamina I-II. Selective ablation of spinal Y1-INs with an NPY-conjugated saporin neurotoxin attenuates the development of peripheral nerve injury-induced mechanical and cold hypersensitivity. Conversely, conditional knockdown of NPY expression or intrathecal administration of Y1 antagonists reinstates hypersensitivity in models of chronic latent pain sensitization. These and other results indicate that spinal NPY release and the consequent inhibition of pain facilitatory Y1-INs represent an important mechanism of endogenous analgesia. This mechanism can be mimicked with exogenous pharmacological approaches (e.g. intrathecal administration of Y1 agonists) to inhibit mechanical and thermal hypersensitivity and spinal neuron activity in rodent models of neuropathic, inflammatory, and postoperative pain. Pharmacological activation of Y1 also inhibits

mechanical- and histamine-induced itch. These immunohistochemical, pharmacological, and cell type-directed lesioning data, in combination with recent transcriptomic findings, point to Y1-INs as a promising therapeutic target for the development of spinally directed NPY-Y1 agonists to treat both chronic pain and itch.

*28.Hashimoto T, Mishra SK, Olivry T, Yosipovitch G. Periostin, an Emerging Player in Itch Sensation. J Invest Dermatol. 2021 Oct;141(10):2338-2343. doi: 10.1016/j.jid.2021.03.009. Epub 2021 May 20. PMID: 34023128.*

Periostin, an extracellular matrix and matricellular protein, binds to several types of integrins that transduce its signals. Its function in allergic inflammation is the establishment of sustained chronic inflammation through an amplification of T helper type 2 immune responses. In addition, recent studies have shown a significant role of periostin in itch sensation through direct integrin-mediated stimulation of nerve fibers and interaction with immune and nonimmune cells (e.g., macrophages, eosinophils, basophils, and keratinocytes). The objective of this review is to describe the role of periostin in itch induction in human and animal models and its expression in human pruritic conditions.

*29.Zhang Q, Henry G, Chen Y. Emerging Role of Transient Receptor Potential Vanilloid 4 (TRPV4) Ion Channel in Acute and Chronic Itch. Int J Mol Sci. 2021 Jul 15;22(14):7591. doi: 10.3390/ijms22147591. PMID: 34299208; PMCID:*

Itch is a clinical problem that leaves many sufferers insufficiently treated, with over 20 million cases in the United States. This is due to incomplete understanding of its molecular, cellular, and cell-to-cell signaling mechanisms. Transient receptor potential (TRP) ion channels are involved in several sensory modalities including pain, vision, taste, olfaction, hearing, touch, and thermosensation, as well as itch. Relative to the extensive studies on TRPV1 and TRPA1 ion channels in itch modulation, TRPV4 has received relatively little research attention and its mechanisms have remained poorly understood until recently. TRPV4 is expressed in ganglion sensory neurons and a variety of skin cells. Growing evidence in the past few years strongly suggests that TRPV4 in these cells contributes to acute and chronic disease-associated itch. This review focuses on the current experimental evidence involving TRPV4 in itch under pathophysiological conditions and discusses its possible cellular and molecular mechanisms.

*30.Badwy M, Baart SJ, Thio HB, Huygen FJPM, de Vos CC. Electrical neurostimulation for the treatment of chronic pruritus: A systematic review. Exp Dermatol. 2022 Mar;31(3):280-289. doi: 10.1111/exd.14468. Epub 2021 Dec 7. PMID:34637585; PMCID: PMC9299998.*

Approximately one fifth of the world population experiences continuous itch for 6

weeks or more during their life, that is chronic itch. It is diverse in its aetiologies, and it is notoriously hard to treat. Because itch and pain have largely overlapping pathophysiology and the demonstrated efficacy of neurostimulation in treatment of selected chronic pain conditions, we conducted a systematic review to investigate whether neurostimulation could be an effective treatment for chronic itch. We identified two randomized controlled trials and 17 open label studies or case reports investigating various neurostimulation modalities for the treatment of refractory itch of various aetiologies. Transcutaneous electrical nerve stimulation (TENS) was the most investigated modality (n = 17), and in the largest number of conditions. Other modalities were cutaneous field stimulation (n = 2), painscrambler (n = 1), transcranial direct current stimulation (n = 1) and peripheral nerve field stimulation (n = 1). Atopic dermatitis was the most studied condition (n = 5). Despite the large heterogeneity in used stimulation paradigms and outcome parameters, all studies reported a positive effect of at least one neurostimulation modality. Our review indicates that electrical neurostimulation could be considered for the treatment of refractory chronic itch of selected aetiologies, such as atopic dermatitis or burn pruritus. However, better understanding of the mechanisms of action of the neurostimulation modalities and regimens in various pruritic conditions is necessary.

*31.Kim BS, Inan S, Ständer S, Sciascia T, Szepietowski JC, Yosipovitch G. Role of kappa-opioid and mu-opioid receptors in pruritus: Peripheral and central itch circuits. Exp Dermatol. 2022 Aug 30. doi: 10.1111/exd.14669. Epub ahead ofprint. PMID: 36054458*

Modern genetic approaches in animal models have unveiled novel itch-specific neural pathways, emboldening a paradigm in which drugs can be developed to selectively and potently target itch in a variety of chronic pruritic conditions. In recent years, kappa-opioid receptors (KORs) and mu-opioid receptors (MORs) have been implicated in both the suppression and promotion of itch, respectively, by acting on both the peripheral and central nervous systems. The precise mechanisms by which agents that modulate these pathways alleviate itch remains an active area of investigation. Notwithstanding this, a number of agents have demonstrated efficacy in clinical trials that influence both KOR and MOR signalling. Herein, we summarize a number of opioid receptor modulators in development and their promising efficacy across a number of chronic pruritic conditions, such as atopic dermatitis, uremic pruritus and beyond.

## PRURITUS ASSESSMENT TOOLS

35. Storck M, Sandmann S, Bruland P, Pereira MP, Steinke S, Riepe C, Soto-Rey I, Garcovich S, Augustin M, Blome C, Bobko S, Legat FJ, Potekaev N, Lvov A, Misery L, Weger W, Reich A, Şavk E, Streit M, Serra-Baldrich E, Szepietowski JC, Dugas M, Ständer S, Zeidler C. Pruritus Intensity Scales across Europe: a

prospective validation study. J Eur Acad Dermatol Venereol. 2021 May;35(5):1176-1185. doi: 10.1111/jdv.17111. Epub 2021 Feb 3. PMID: 33411947.

Background: Chronic pruritus (CP) is a subjective symptom, and it is necessary to assess its intensity with validated patient-reported outcome tools in order to allow determination of the treatment course.
Objectives: So far, the itch intensity scales were validated in small cohorts and in single languages. Here, we report the validation of the numerical rating scale, the verbal rating scale and the visual analogue scale for the worst and average pruritus intensity in the last 24h in several languages across Europe and across different pruritic dermatoses.
Methods: After professional translation, the intensity scales were digitized for use as a tablet computer application. Validation was performed in clinics for Dermatology in Austria, France, Germany, Italy, Poland, Russia, Spain, Switzerland and Turkey.
Results: A total of 547 patients with contact dermatitis, chronic nodular prurigo, psoriasis vulgaris, lichen planus or cutaneous T-cell lymphoma were included. The intensity scales showed a high level of reproducibility and inter-correlations with each other. The correlation with the Dermatology Life Quality Index was weak to strong in nearly all countries and dermatoses with the exception of France and patients with chronic nodular prurigo, for which no statistically significant correlations were found.
Conclusions: The numerical rating scale, the verbal rating scale und the visual analogue scales are valid instruments with good reproducibility and internal consistency in German (Germany, Austria, Switzerland), French, Italian, Polish, Russian, Spanish and Turkish for different pruritic dermatoses. VAS worst was the best reproducible and consistent measuring instrument in all countries.

*37.Tuchinda P, Kulthanan K, Chularojanamontri L, Rujitharanawong C, Subchookul C, Trakanwittayarak S. The validity and reliability of the Thai-version of 5-D itch scale. Asian Pac J Allergy Immunol. 2022 Sep;40(3):254-262. doi: 10.12932/AP-100120-0738. PMID: 32247306.*

Background: Pruritus is commonly associated with skin disorders. The 5-D itch scale was developed as a specific questionnaire for pruritus. Objective: This study aimed to evaluate the validity, reliability, and sensitivity to change of the Thai 5-D itch scale in Thai patients.

Methods: The Thai Dermatology Life Quality Index (DLQI), patient's global assessment of disease severity (PatGA-VAS), Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL), and seven-day urticaria activity score (UAS7) were evaluated as correlation with Thai 5-D itch scale. Seventy-five stable patients (42 chronic urticaria patients and 33 eczema patients), who had no change in disease severity after 4-weeks were assessed for test-retest reliability.

Results: Of 130 pruritus patients who were treated at Department of Dermatology, Siriraj Hospital, 65 patients were diagnosed with chronic urticaria. The others were diagnosed with eczema. The validity of Thai 5-D itch scale correlated strongly with Thai DLQI total score ($r = 0.76$, $p < 0.0001$) and PatGA-VAS ($r = 0.79$, $p < 0.0001$). The strong reliability of Thai 5-D itch scale was demonstrated as intraclass correlation coefficient of 0.90. The changes in Thai 5-D itch scale was correlated with the changes in PatGA-VAS and UAS7 which indicated that the Thai 5-D itch scale had good sensitivity to change ($r = 0.66$) and ($r = 0.67$), respectively.

Conclusions: The Thai 5-D itch scale is a questionnaire with good validity, reliability and sensitivity to change to evaluate pruritus in Thai patients. This will support the use of 5-D itch scale in practice, in other languages.

*38.Zeidler C, Pereira MP, Augustin M, Spellman M, Ständer S. Investigator's Global Assessment of Chronic Prurigo: A New Instrument for Use in Clinical Trials. Acta Derm Venereol. 2021 Feb 17;101(2):adv00401. doi: 10.2340/00015555-3701. PMID: 33236125.*

Chronic prurigo is a pruritic disease characterized by the development of pruriginous lesions due to scratching. The number of lesions is representative of the stage of the disease, while the presence of excoriations reflects the scratching activity. Aim of this study was to validate a new developed tool for the objective assessment of chronic prurigo. Investigator's Global Assessment scales for stage and activity were completed for 187 patients with chronic prurigo, who also reported patient-reported outcomes for itch intensity and quality of life. To assess the reliability and objectivity of the Investigator's Global Assessment, 5 independent raters completed the Investigator's Global Assessment scales for 8 patients twice. The scores increased with increased intensity of pruritus. The Investigator's Global Assessment stage scales correlated strongly with each other (Kendall's-tau-b 0.62) and moderately with the Investigator's Global Assessment activity scale (Kendall's-tau-b 0.47). Intra-rater test-retest reliability was excellent for all items, while the congruence among raters was very good for Investigator's Global Assessment - chronic prurigo activity (Kendall's W 0.84) and good for Investigator's Global Assessment stage scales (Kendall's W 0.747). Investigator's Global Assessment - chronic prurigo stage and activity are thus the best Investigator's Global Assessment instruments for use in assessing chronic prurigo.

*39.Kong HE, Francois S, Smith S, Lee G, Bradley B, Chen KH, Lawley LP, Spraker M, Roberts JS, Chen SC. Tools to study the severity of itch in 8- to 17-year-old children: Validation of TweenItchyQoL and ItchyQuant. Pediatr Dermatol. 2021 Sep;38(5):1118-1126. doi: 10.1111/pde.14662. Epub 2021 Aug 2. PMID: 34339533.*

Background/objectives: Validated pruritus-specific quality of life and self-reported

severity instruments exist primarily for adults. Clinical trials to develop therapeutics for children with chronic pruritus are hampered by the paucity of appropriate outcome measures. To address this gap, we aimed to develop validated instruments to measure itch-specific quality of life and self-reported severity in children.

Methods: We conducted in-depth, open-ended interviews of itchy children and generated concepts to develop TweenItchyQoL. We administered TweenItchyQoL, ItchyQuant, a cartoon-annotated self-reported pruritus severity numeric rating scale (NRS), and a non-cartoon NRS to 175 itchy children aged 8-17 years. We analyzed the data for feasibility, preference, reliability, construct validity, and responsiveness.

Results: Average completion time was 4.8 minutes for TweenItchyQoL and 33 seconds for ItchyQuant. The majority of patients either preferred ItchyQuant or found no difference between ItchyQuant and the NRS. Cronbach's alpha for TweenItchyQoL total and subscales ranged from 0.84 to 0.95. Test-retest reliability coefficients were ≥0.7 for TweenItchyQoL and 0.4 for ItchyQuant. A 3-dimensional bifactor model was most appropriate (RMSEA = 0.048) on the confirmatory factor analyses. As a function of those reporting worsening, improvement, or no change at their final visit, TweenItchyQoL and ItchyQuant scores in those cohorts changed as expected.

Conclusions: This new set of validated and feasible instruments shows promise to quantify itch severity and QoL impact in older children.

*40.Theunis J, Nordon C, Falissard B, Orri M, Mengeaud V, Misery L. Development and preliminary validation of the patient-reported Chronic Itch Burden Scale assessing health-related quality of life in chronic pruritus. Br J Dermatol. 2022 Jan;186(1):86-95. doi: 10.1111/bjd.20582. Epub 2021 Sep 1. PMID: 34128535.*

Background: Chronic pruritus (CP) significantly affects patients' health-related quality of life (HRQoL). Very few self-reported HRQoL questionnaires exploring CP have been developed according to international guidelines, thus limiting their use in preauthorization trials.

Objectives: To develop a self-reported HRQoL questionnaire in patients with CP owing to psoriasis, atopic dermatitis, seborrhoeic dermatitis of the scalp or idiopathic dermatitis, and to explore the preliminary psychometric properties of the questionnaire.

Methods: The study was performed in France. A conceptual framework was developed based on a structured literature review and expert insight, and was improved using three focus groups involving 19 participants. A 50-item questionnaire was created and tested with 21 participants using cognitive debriefings; 11 items were removed. A cross-sectional study including 251 participants was performed to explore the preliminary psychometric properties of the 39-item questionnaire. Dimensionality was explored using principal component analysis. Cronbach's alpha and correlation

*32.Stefaniak AA, Pereira MP, Zeidler C, Ständer S. Pruritus in Pregnancy. Am J Clin Dermatol. 2022 Mar;23(2):231-246. doi: 10.1007/s40257-021-00668-7. Epub 2022 Feb 21. PMID: 35191007; PMCID: PMC8860374.*

Pruritus in pregnancy is a common and burdensome symptom that may be a first sign of a pregnancy-specific pruritic disease (atopic eruption of pregnancy, polymorphic eruption of pregnancy, pemphigoid gestationis, and intrahepatic cholestasis in pregnancy) or a dermatosis coinciding with pregnancy by chance. Despite its high prevalence, pruritus is often underrated by physicians, and data regarding the safety profiles of drugs for pruritus are very limited. In this review, we illustrate the epidemiology, possible pathophysiology, clinical characteristics, and diagnostic workup of various pregnancy-related diseases and discuss antipruritic treatments. The prevalence of pruritus in pregnancy demonstrates the importance of symptom recognition and the need for an holistic approach, taking into account both the potential benefits for the patient and the potential risks to the fetus.

*33.Parvizi MM, Salami MH, Moini Jazani A, Javaheri R, Jaladat AM, Handjani F. Complementary and integrative remedies in the treatment of chronic pruritus: A review of clinical trials. J Cosmet Dermatol. 2022 May 17. doi: 10.1111/jocd.15094. Epub ahead of print. PMID: 35579366.*

Background: Chronic pruritus is one of the most common conditions in dermatology and a common manifestation in many systemic diseases. Since the etiology of chronic pruritus remains somewhat unknown, hence, conventional medications may not always show a good therapeutic response. This finding has led both investigators and patients to use herbal and complementary remedies for its treatment. The aim of this study was to review clinical trials in which herbal and complementary medicine was used in the control and treatment of chronic pruritus.

Materials and methods: In this study, we reviewed related articles in this domain, from 2000 to 2020. The search involved electronic databases including PubMed, Scopus, Web of Science, Cochrane, Google Scholar, and SID databases using the keywords "pruritus," "itch," "herb," "complementary medicine," "traditional medicine," "integrative medicine," and their related MeSH terms. Finally, we extracted the pertinent information from these articles and summarized the results.

Results: The findings of this study showed that 17 clinical trials have been conducted till date in order to evaluate the efficacy of herbal remedies and complementary medicines in the treatment of chronic pruritus. Herbal remedies including turmeric, Fumaria parviflora, Avena sativa, capsaicin, sweet almond oil, peppermint oil, violet oil, vinegar, as well as manual therapies including aromatherapy, auricular acupressure, and acupuncture, were significantly effective in the treatment of chronic pruritus.
Conclusion: There are only a few studies published on the therapeutic efficacy of herbal remedies and complementary medicine in the treatment of chronic pruritus.

coefficients (interitem, item-total score and item-dimension score) were measured. The number of items was reduced through expert consensus.

Results: In the 39-item version, three main dimensions were identified (Cronbach's alpha = 0·94) and all correlation coefficients were > 0·34. Upon review, 13 items were deleted owing to poor quality and six items were deleted by the team, generating a 20-item version. The questionnaire's factorial structure was best reflected with a two-dimension solution, i.e. (i) social and emotional repercussions and (ii) relation to others, fear of judgement.

Conclusions: The Chronic Itch Burden Scale patient-reported questionnaire explores broad aspects of HRQoL that are relevant for patients with various skin diseases. Its good cross-sectional validity makes it useful for trials and practitioners.

Some have shown promising results. Therefore, more evidence-based studies are needed in order to determine if herbal remedies and complementary medicine could be an effective alternative or adjuvant treatment modality in chronic pruritus.

*34.Elmariah S, Chisolm S, Sciascia T, Kwatra SG. Modulation of the kappa and mu opioid axis for the treatment of chronic pruritus: A review of basic science and clinical implications. JAAD Int. 2022 Apr 20;7:156-163. doi: 10.1016/j.jdin.2022.03.007. PMID: 35497636; PMCID: PMC9046882.*

Introduction-Treating chronic pruritus is challenging for dermatologists due to the lack of therapeutic options. We review the effects of κ-opioid receptor (KOR) and μ-opioid receptor (MOR) in the modulation of itch, summarize evidence supporting the efficacy and safety of opioid receptor–targeting agents in chronic pruritus, and address clinical considerations.

Results-Preclinical studies have found neural pathways underlying detection, transmission, and modulation of itch signaling and spotlighted the importance of neuronal KOR and MOR in itch perception. Clinical reports suggest that opioid axis modulation may be the basis for the successful treatment of chronic itch. Several agents (MOR antagonist naltrexone; KOR agonists nalfurafine and difelikefalin; dual-acting KOR agonists/MOR antagonists butorphanol and nalbuphine) have been evaluated for treating chronic pruritus in case series, small studies, and clinical trials; nalbuphine has progressed through preliminary (phase II/III) studies in uremic pruritus and prurigo nodularis. The antipruritic efficacy of these agents has been observed across multiple disorders with disparate etiologies, suggesting the potential utility of this class to provide a unified approach to chronic pruritus treatment.

Conclusions-The relative safety of these agents, including a reduced potential for dependence versus MOR-agonist analgesics, should help overcome resistance to the use of opioid receptor–targeting agents in chronic pruritus treatment.

*35. Reszke R, Kiliś-Pstrusińska K, Szepietowski JC. Chronic Kidney Disease-Associated Itch (CKD-aI) in Children-A Narrative Review. Toxins (Basel). 2021 Jun 29;13(7):450. doi: 10.3390/toxins13070450. PMID: 34209560; PMCID: PMC8309841.*

Chronic kidney disease (CKD) is a condition of widespread epidemiology and serious consequences affecting all organs of the organism and associated with significant mortality. The knowledge on CKD is rapidly evolving, especially concerning adults. Recently, more data is also appearing regarding CKD in children. Chronic itch (CI) is a common symptom appearing due to various underlying dermatological and systemic conditions. CI may also appear in association with CKD and is termed chronic kidney disease-associated itch (CKD-aI). CKD-aI is relatively well-described in the literature concerning adults, yet it also affects children. Unfortunately, the data on paediatric CKD-aI is particularly scarce. This narrative review aims to describe various aspects of CKD-aI with an emphasis on children, based on the available data in this population and the data extrapolated from adults. Its pathogenesis is described in details, focusing on the growing role of uraemic toxins (UTs), as well as immune

dysfunction, altered opioid transmission, infectious agents, xerosis, neuropathy and dialysis-associated aspects. Moreover, epidemiological and clinical aspects are reviewed based on the few data on CKD-aI in children, whereas treatment recommendations are proposed as well, based on the literature on CKD-aI in adults and own experience in managing CI in children.

Review articles on various aspects of itch in special issue of journal of investigative dermatology " spotlight on itch"

The Sensation of Itch: From Biological Discovery to Medical Treatment Tornike Mamuladze1 and Brian S. KimJournal of Investigative Dermatology (2022) 142, 21–22; doi:10.1016/j.jid.2021.10.023

Peripheral Mechanisms of Itch Changxiong J. Guo1, Nathaniel S. Grabinski1 and Qin Liu Journal of Investigative Dermatology (2022) 142, 31–41; doi:10.1016/j.jid.2021.10.024

Itch: A Paradigm of Neuroimmune Crosstalk Fang Wang and Brian S. Kim1 https://doi.org/10.1016/j.immuni.2020.04.008

Interactions of the Neuro Immune StromalTriad in Itch Pang-Yen Tseng1 and Mark A. Hoon1 Journal of Investigative Dermatology (2022) 142,42–46; doi:10.1016/j.jid.2021.08.443

Circuit Mechanisms of Itch in the Brain Di Mu1 and Yan-Gang Sun2,3 Journal of Investigative Dermatology (2022) 142, 23–30; doi:10.1016/j.jid.2021.09.022

A New Era with the Development of Cytokine-Based Therapy for Pruritus Rintaro Shibuya1, Riko Takimoto-Ito1, Naotomo Kambe1 and Kenji Kabashima Journal of Investigative Dermatology (2022) 142, 47–52; doi:10.1016/j.jid.2021.09.023

# Psychotropic drugs in chronic pruritus

*Maj Gen (Dr.) Rajesh Verma, Col Biju Vasudevan, Prachi Verma*

Psychotropic drugs are the molecules that affects behaviour, mood, thoughts, or erception. There are various situations in which knowledge of psychotropic agents would be helpful to the dermatologist. These includes management of dermatological symptoms associated with psychiatric disorders, psychiatric symptoms associated with dermatological conditions and management of adverse effects associated with the use of psychotropic drugs. (1) Pruritus is a common symptom in dermatology and chronicity of this symptoms can be disabling for the patients to an extent of influencing their mood and behaviour. Off late , psychotropic drugs are found to be useful in chronic pruritus of different aetiologies. These drugs are not one of the prescription friendly class amongst dermatologists due to fear of adverse effects ,lack of awareness and experience This review will address several practice gaps regarding the use of psychotropic drugs in chronic pruritus. There are several classes of psychotropics agents with different mechanism of action. (2) These may either interrupt itch scratch cycle by modifying the behaviour to itch or altering the threshold by acting on different neurotransmitters.

| | |
|---|---|
| Antidepressants | Selective Serotonin reuptake inhibitors<br>Serotonin and Norepinephrine reuptake inhibitors<br>Tricyclic antidepressants |
| Antipsychotics | Typical antipsychotics (First generation)<br>Atypical antipsychotics (Second Generation) |
| Anxiolytics | Benzodiazepines<br>Nonbenzodiazepines |
| Mood Stabilizers | Lithium<br>Antiepileptic Drugs<br>Pregabalin and Gabapentin |

**Antidepressants:**

They are essentially used in the management of depressive disorders , anxiety disorders, social phobia and obsessive compulsive disorders. They are also sometimes useful in management of recalcitrant pruritic conditions .(3–5)

It is recommended to start the antidepressants with low doses and gradually increase at least every 14 days. They reach their therapeutic potential by four to six weeks. They are usually continued for a duration of 6 months and then gradually tapered off.

| | |
|---|---|
| SSRIs | Fluoxetine, Paroxetine, Citalopram, Escitalopram, Sertraline |
| TCAs | Amitriptyline, Nortriptyline, Doxepine, Imipramine, Chlorpramine |
| SNRIs | Venlafexine, Duloxetine, Mirtazipine |

## Selective Serotonin Reuptake Inhibitors:

SSRIs are the most widely prescribed class of antidepressants. SSRIs selectively inhibit serotonin reuptake increasing its availability which is then responsible for influencing mood, cognition, sleep, appetite, and sexual behaviour. They are safer and better tolerable as compared to TCAs. They are also safe in pregnant women.(4,6,7) Selective serotonin reuptake inhibitors (SSRIs) increase the threshold of itch generation and found to be useful in chronic pruritus associated with hepatobiliary diseases, chronic kidney disease and paraneoplastic itch. SSRI may also help in cases of chronic pruritus of undetermined origin.
Several RCTs revealed the efficacy of sertraline in hepatic pruritus in a daily dose of 75–100 mg.Sertraline is considered the fourth-line treatment option in the management of cholestatic pruritus. Paroxetine 20 mg daily is preferred SSRI in chronic pruritus associated with haematological malignancy. Most common side effects include gastrointestinal side effects like nausea, vomiting, diarrhoea, sexual dysfunction. Discontinuation symptoms like giddiness, agitation, anxiety, sensory disturbances may develop on stopping the treatment.(7)

| **SSRIs** | **Dosage** |
|---|---|
| Citalopram | 10-40 mg /day |
| Escitalopram | 5-20 mg/day |
| Fluoxetine | 20-60 mg/day |
| Paroxetine | 10-60 mg/day |
| Sertraline | 50-200 mg/day |

## SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS:

They are the newer agents acting both on serotonin and norepinephrine and thus increasing their levels leading to mood elevation. These are mostly used in neuropathic pruritus .They are less well tolerated than SSRIs but better tolerated than TCAs. Several reports suggest Mirtazapine to be useful in patients of chronic pruritus in hemodialysis patients and paraneoplstic pruritus. Mirtazipine is also useful in nocturnal Pruritus

| SNRIs | Dosage |
|---|---|
| Duloxetine | 30 - 120 mg/day |
| Venlafexine | 37.5 - 225 mg/day |
| Mirtazapine | 15 - 45 mg/day |

## TRICYCLIC ANTIDEPRESSANTS:

TCAs are the oldest class of antidepressants. Their mechanism of action is similar to SSRIs, increasing serotonin and norepinephrine in the synaptic cleft. Over the years they have been replaced by SSRIs due to increased sedation caused by TCAs and greater side effect profile. Currently, they are being increasingly used as antihistamines and for management of chronic recalcitrant pruritic conditions. TCAs like amitriptyline and nortriptyline should be used with caution in elderly and cardiac patients due to their anticholinergic effects.(8,9)

| TCAs | Dosage |
|---|---|
| Doxepine | 25-75 mg/day |
| Nortriptyline | 10- 150 mg/day |
| Amitriptyline | 10 – 200 mg/day |
| Clomipramine | 10 – 250 mg/day |
| Imipramine | 75 – 300 mg/day |

## DOXEPIN

One of the most extensively used TCAs due to its antihistaminic and sedative properties. It is a selective histamine H1 receptor blocker. It is used to break through the itch scratch cycle and to regularize sleep in severely pruritic recalcitrant conditions like prurigo nodularis, lichen simplex chronicus, atopic dermatitis, chronic urticaria etc. The initial dose is 25 mg/day which can be increased weekly by 10-25 mg, reaching a maximum of 100 mg/day.The most common side effect is sedation which can be minimized by taking the drug one hour before the bed. Others are dry mouth, blurring of vision, conductive defects, orthostatic hypotension.(10,11)

## ANTIPSYCHOTICS:

Antipsychotics are dopamine receptor antagonists, acting mainly by blocking D2 subtype receptors. Antipsychotics in dermatology are primarily used for delusional disorders, such as parasitic delirium and dermatitis artefacta, body focussed repetitive behaviours and chronic pruritus associated with psychogenic cause or substance abuse. Medications, such as chlorpromazine, risperidone, and olanzapine, are often used to augment treatment with an antidepressant or anxiolytic regimen. Olanzapine monotherapy has successfully treated itching related to self mutilation in patients who have failed other pharmacotherapies.Second-generation antipsychotics are the preffered agents because of a better side effect profile and compliance. The main side-effects of these agents are sedation and weight gain. Cutaneous side effects like pigmentation and photosensitivity are also reported.(3,4,12,13)

| First Generation (Typical) | Second Generation (Atypical) |
|---|---|
| Pimozide (1-6 mg/day) | Risperidone (0.5 - 5 mg/day) |
| Chlorpromazine | Olanzapine (5-15 mg/day) |
| Haloperidol (0.5-15 mg/day) | Aripiprazole (10-30 mg/day) |
| | Quetiapine (50-750 mg/day) |

# SCABIES ITCH – PATHOPHYSIOLOGY AND PROPOSED NOVEL TARGETS

Dr Sudip Das

## Pathophysiology of itch in scabies

There are no specific data available aiming to describe the pathophysiology of itch in scabies. And the molecular pathways linking scabies and itch are poorly understood. Despite therapy nightmare continues in a subset of patients in scabies.(1) .The itch is primarily non histaminergic so anti histamines have little or no role to play in management of scabies itch except the sedative antihistamines.

Table on Next Page

# PROPOSED PATHOPHYSIOLOGY OF ITCH

| | | |
|---|---|---|
| Direct scabies mite action | Scabies proteases | Activates PAR2 and MRGPRX2 on mast cells and sensory neurons |
| | Scabies psudoproteases | Activates TLRson sensory neuron,activate complement system and mast cell activation by HDM antigens |
| Secondary bacterial infection | S aureus delta toxin | Activates mast cells via MRGPRX2 |
| | S. aureus protease<br><br>S. aurueus and s.pyogens | Activates keratinocytes via PAR2<br><br>Sensory neurons get stimulated by n formylated peptides of Saureus and streptolysin S from S pyogens |
| Host immune responsesagainst scabies | Eosinophil infiltrates | Expression of neurotrophins, cutaneous nerve spouting and myelinization of nerves |
| | macrophage | Anginase 1and CD 163 M2 MACROPHAGES PRODUCE il31-INCRESED responsiveness of on sensory neurons though IL31R |
| | Mast cell activation<br><br>(histamine, alpha Tryptase) | Activation of histamine $H_1$ and $H_4$ prurireceptor.<br><br>Activation of protease- activated prurireceptor by tryptase. |
| Persistent infestation in absence of treatment | | Peripheral sensitization of prurireceptor : decreased threshold for activation, increased responsiveness and presence of ongoing activity.. |

## NOVEL THERAPEUTIC TARGETS OF ITCH IN SCABIES :

| Novel targets | Treatment options |
|---|---|
| PAR-2 | • Methylbenzyl methylcenzmidazole piperidinyl methanone (MMP) containing cream.<br>• Pepducin.<br>• Doxycycline and minocycline.<br>• Polidocanol.<br>• Emollient containing aquaphilus dolomae (ADE-G1) extrac. |
| MRGPRX2 | • Novel MRGPRX2 targeting antagonists.<br>• Natural polyphenolic compounds(i.e genistein).<br>• Shikonin.<br>• A tripeptide NK-1R antagonists(i.e OSF) with dual activity on MRGPRX2. |
| Th2 cytokines | • Biologics (i.e anti IL- 33 monoclonal antibody (mAb),anti-IL4 mAb, anti IL-13mAb, anti IL-31 mAb and anti IgE mAb.<br>• New generation small molecule ( Janus kinase /JAK ) inhibitors. |
| TRP channels | TRP channel modulators (eg topical capsaicin, topical calcineurin inhibitors, topical camphor, topical strontium hydrogel formulation and botulinum toxin. |

Refrences

1.Besner MorinC,Misery L .Emerging treatments and novel pathways in pruritus .J cut med surgery 2019; 23: 528-536.

2.Shin K ,Jin H ,You H -S et al .Clinical characteristics of pruritus in scabies.Indian J of Dermatol Venerol Leprol 2017;83:492-493

3.H S Kim,T Hashimoto,K Fischer,et al Scabies itch- an update on neuroimmune interactions and novel targets.JEADV,2021; 35:1765-76.

# IADVL ACADEMY 2022

CHAIRPERSON (2022-2023) - **Dr. Lalit Gupta**

CONVENOR (2022 - 2023) - **Dr. Rashmi Jindal**

## Ex - Offico Members

Dr Rashmi Sarkar (President)

Dr Jayadev Betkerur (Imm. Past President)

Dr Vijay Zawar (President Elect)

Dr Deepika Pandhi (Imm. Past Academy Chairperson)

Dr Dipankar De (Imm. Past Academy Convener)

Dr Dinesh Devaraj (Honorary Secretary General)

Dr Savitha S (Honorary Treasurer)

Dr Feroz K (Imm. Past Hon. Secretary General)

Dr Rakesh SV (Imm. Past Honorary Treasurer)

Dr Saumya Panda (Editor, IJDVL)

Dr Seetharam KA (Editor, IDOJ)

## Members

Dr. Abhishek Bhardwaj

Dr. Bhabani singh

Dr. Chander Grover

Dr. Devi K

Dr. Joyeeta Chowdhury

Dr. Malathi Munisamy

Dr. Nirupama Bhagya Laxmi Tatavarthi

Dr. Pooja Arora Mrig

Dr. Rahul kumar sharma

Dr. Ranugha PSS

Dr. Shekhar Nana Pradhan

Dr. Vinay K

# IADVL EC

PRESIDENT

**Dr. Rashmi Sarkar**

IMMEDIATE PAST PRESIDENT

**Dr. Jayadev Betkerur**

PRESIDENT ELECT

**Dr. Vijay Zawar**

VICE PRESIDENT

**Dr. Nirmaladevi Palanivel**

VICE PRESIDENT

**Dr. Vineet Relhan**

HONORARY SECRETARY GENERAL

**Dr. Dinesh Kumar Devaraj**

HONORARY TREASURER

**Dr. Savitha S**

HON. JOINT SECRETARIES

**Dr. Indrani Dey**

**Dr. Athota Kavitha**