ISSN 0001-5555

ActaDV

ACTA DERMATO-VENEREOLOGICA

Volume 100 2020 **Theme issue**

Advances in Dermatology and Venereology

A Non-profit International Journal for
Interdisciplinary Skin Research, Clinical and Experimental
Dermatology and Sexually Transmitted Diseases

Frontiers in Dermatology and Venereology

- A series of theme issues in relation to the 100-year anniversary of ActaDV

Official Journal of
- European Society for Dermatology and Psychiatry

Affiliated with
- The International Forum for the Study of Itch

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ACTA DERMATO-VENEREOLOGICA

The journal was founded in 1920 by Professor Johan Almkvist. Since 1969 ownership has been vested in the Society for Publication of Acta Dermato-Venereologica, a non-profit organization. Since 2006 the journal is published online, independently without a commercial publisher. (For further information please see the journal's website https://www.medicaljournals.se/acta)

ActaDV is a journal for clinical and experimental research in the field of dermatology and venereology and publishes high-quality papers in English dealing with new observations on basic dermatological and venereological research, as well as clinical investigations. Each volume also features a number of review articles in special areas, as well as Correspondence to the Editor to stimulate debate. New books are also reviewed. The journal has rapid publication times.

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Acta Dermato-Venereologica – 100 years

The celebrations comprice a symposium and a series of theme issues jointly called ”Frontiers in Dermatology and Venereology”

In 1920, *Acta Dermato-Venereologica* (*ActaDV*) was founded in Stockholm by the Chairman of Dermatology and Syphilidology at Karolinska Institutet, Professor Johan Almkvist. To begin with, it was a minor tri-lingual journal (German, French, English) with contributions mainly from Europe. Today, 100 years and 6 editors later, the journal is an online, open access and peer-reviewed publication, own by a non-profit society and produced entirely in-house without any dependency on a commercial publisher. For an historic review see *Vahlquist A. ActaDV 100 years – An incomplete history*[1]. Annually, ActaDV releases 250–300 papers submitted from all around the world. The acceptance rate is around 50% and the impact factor 3.4–4.2 in recent years, i.e. among top 10 in the field.

As part of the celebration of the journal's 100 years birthday, *ActaDV* will organize a symposium ”Frontiers in Dermatology and Venereology” with invited speakers from Europe and the USA (see full program below), and publish a series of connected theme issues with contributions from the speakers and other invited key-opinion-leaders around the world (see next page). It is hoped that these undertakings will help to spur the scientific interest in Dermatology and Venereology.

On behalf of the editorial board and as principal organizer of the centenary celebrations, I wish to sincerely thank all the authors who kindly accepted to contribute to the theme issues, the specially appointed theme editors, and the skilful work of the editorial office without which nothing of this had been possible.

Uppsala in December 2019

Anders Vahlquist

Former Editor-in-Chief and current Chairman of the Society for Publication of Acta Dermato-Venereologica

[1]Vahlquist A. ActaDV 100 years – An incomplete history. Forum for Nord Derm Venereol 2020; 24 (in press).

Acta Dermato-Venereologica will celebrate its 100-year anniversary with a symposium
Date: 15th May 2020. *Place*: Swedish Society of Medicine, Stockholm, Sweden

Frontiers in Dermatology and Venereology

Programme:

Chairperson: Olle Larkö

9.00–10.30 ”ActaDV 100 year; an historic perspective”, *Anders Vahlquist*
”Skin fragility and blistering diseases”, *Leena Bruckner-Tuderman*
”Is permanent cure for genodermatoses in sight?”, *Jouni Uitto*

10.50–12.00 ”Psoriasis: News in pathogenesis and therapy”, *Jonathan Barker*
”Where are we with prevention of atopic dermatitis?”, *Hywel Williams*

Chairperson: Anders Vahlquist

13.00–14.10 ”Melanoma: News in epidemiology and therapy”, *Julia Newton-Bishop*
”Itch; scratching the surface is not enough”, *Gil Yosipovitch*

14.30–16.00 ”Combatting skin infections: A priority not just in Africa”, *Roderick Hay*
”The changing spectrum of STI in Europe”, *Angelika Stary*
End of meeting ”The promising future of ActaDV”, *Olle Larkö*

The registration for this symposium is open. For more information (https://medicaljournals.se/acta/Acta100Year.pdf) and registration form (https://medicaljournals.se/actadv100/registration.php).

Frontiers in Dermatology and Venereology

Centenary theme issues in Volume 100 of *Acta Dermato-Venereologica*
An overview

Current issue

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Theme editors: Elke Weisshaar, Tasuku Akiyama and Jacek Szepietowski

- The Challenge of Basic Itch Research, *E. Carstens, T. Follansbee, M.I. Carstens*
- Mechanisms and Management of Itch in Dry Skin, *C. Sagita Moniaga, M. Tominaga, K. Takamori*
- Non-dermatological Challenges of Chronic Itch, *A.E. Kremer, T. Mettang, E. Weisshaar*
- Itch and Psyche: Bilateral Associations, *R. Reszke, J.C. Szepietowski*
- A New Generation of Treatments for Itch, *E. Fowler, G. Yosipovitch*
- Challenges in Clinical Research and Care in Pruritus, *M.P. Pereira, C. Zeidler, M. Storck, K. Agelopoulos, W.D. Philipp-Dormston, A.G.S. Zink, S. Ständer*

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- The Woronoff Ring in Psoriasis and the Mechanisms of Postinflammatory Hypopigmentation, *J. Prinz*
- Psoriasis and Treatment: Past, Present and Future Aspects *C. Reid, C.E.M. Griffiths*
- Psoriasis and Co-morbidity, *M. Amin, E.B. Lee, T-F. Tsai, J.J. Wu*
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Blistering skin disorders
Theme editor: Kaisa Tasanen

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- Drug Development in Pemphigoid Diseases, *K. Bieber, R.J. Ludwig*
- Bullous Drug Reactions, *M. Mockenhaupt*

Genodermatoses
Theme editors: Anette Bygum and Matthias Schmuth
Content details TBA

Skin malignancies
Theme editors: Veronique Bataille and Nicole Basset Seguin
Content details TBA

Atopic dermatitis
Theme editors: Magnus Lindberg and Carl-Fredrik Wahlgren
Content details TBA

Cutaneous and genital infections
Theme editors: Roderick Hay and Kristian Kofoed
Content details TBA

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ActaDV
Advances in dermatology and venereology

Itch and Pruritic Disorders

Theme Editors:

Elke Weisshaar, Tasuku Akiyama and Jacek Szepietowski

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REVIEW ARTICLE

The Challenge of Basic Itch Research

Earl CARSTENS, Taylor FOLLANSBEE and Mirela IODI CARSTENS
Department of Neurobiology, Physiology and Behavior, University of California, Davis, USA

Basic mechanisms and pathways of itch signaling are reviewed, with an emphasis on the progress to date as well as remaining challenges in translating current knowledge to the clinical treatment of chronic itch. Recent studies reveal 3 subsets of pruriceptive sensory neurons highly expressing itch-related genes. Their fibers project into the spinal cord to activate neurons expressing gastrin releasing peptide (GRP) and its receptor (GRPR), which connect to neurons that express the substance P (NK-1) receptor and project to the parabrachial nucleus and thalamus. Spinal inhibitory interneurons release GABA, glycine and dynorphin to modulate segmental itch transmission. However, nearly all pruriceptive neurons also respond to algogens such as capsaicin. Alternative theories of itch-pain discrimination, such as intensity or spatial contrast, are based on the observation that focal stimulation of nociceptive nerve endings elicits itch while more widespread stimulation elicits pain. These findings cloud the issue of a labeled line for itch- a long-debated but currently unresolved challenge. In higher primates there is a dichotomy of histaminergic and non-histaminergic itch-signaling pathways which is less demarcated in rodents, suggesting species differences. A cardinal symptom of chronic itch is alloknesis, i.e., mechanical or touch-evoked itch. Recent evidence indicates that low-threshold mechanosensory afferents can access the spinal itch pathway, but are normally kept in check by inhibitory interneurons expressing neuropeptide Y (NPY). In chronic itch, NPY-mediated inhibition is reduced, allowing touch to excite itch-signaling pathways. These recent advances provide novel targets for development of therapeutic strategies to relieve chronic itch.

Key words: itch; pain; labeled-line coding; gastrin releasing peptide; alloknesis.

Accepted Oct 15, 2019; Published Jan 9, 2020

Acta Derm Venereol 2020; 100: adv00023.

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SIGNIFICANCE

This paper reviews the basic mechanisms and pathways of itch signaling, emphasizing the progress to date as well as remaining challenges in translating current knowledge to the clinical treatment of chronic itch. Major questions that are addressed include: is itch signaled by a labeled-line pathway separate from that for pain; can alternative theories explain the ability to distinguish between itch and pain; are there specific markers of itch (such as gastrin releasing peptide and its receptor); are there histaminergic and non-histaminergic itch-signaling pathways? We also address challenges in understanding touch-evoked itch (alloknesis) as a symptom of chronic itch.

Like pain, acute itch provides a warning signal for the organism to scratch away insects or plant spicules from the skin surface or to dig out invasive parasites. However, chronic itch lasting >6 weeks does not serve a useful function but instead imposes suffering, high socioeconomic costs, and reduces the quality of life. It has been estimated that itchy skin conditions such as atopic dermatitis or psoriasis affect upwards of 10% or more of the general population with associated annual health care and economic costs in the billions of dollars (1–6). Most types of chronic itch are resistant to antihistamines, so there is a pressing need to develop novel drugs and other treatment strategies. This is one of the great challenges for translational itch research. Optimism is warranted based on recent research that has led to new effective treatments for chronic itch (7).

OVERVIEW OF ITCH PATHWAY

Huge strides have been made in the past decade in our understanding of how itch is transduced and transmitted from the periphery into the central nervous system. A schematic overview of itch processing is shown in **Fig. 1**. A wide variety of itch mediators interact with their cognate receptors that are expressed in the free nerve endings of pruriceptive afferents in the skin. Fig. 1 provides a partial list. Histamine is the most well-known itch mediator, acting at histamine H1 and H4 receptors linked to TRPV1, the heat- and capsaicin-sensitive ion channel (8, 9), which opens to depolarize the nerve ending and thereby activate voltage sensitive sodium channels (Nav 1.7, 1.8) to initiate action potentials in the afferent fiber. Many non-histaminergic itch mediators act via TRPA1 (10), and recent reports implicate TRPV4 in histamine, serotonin and chloroquine itch transduction (11–13). Single-cell RNA sequencing has been used recently to categorize 11 subpopulations of dorsal root ganglion

doi: 10.2340/00015555-3343
Acta Derm Venereol 2020; 100: adv00023

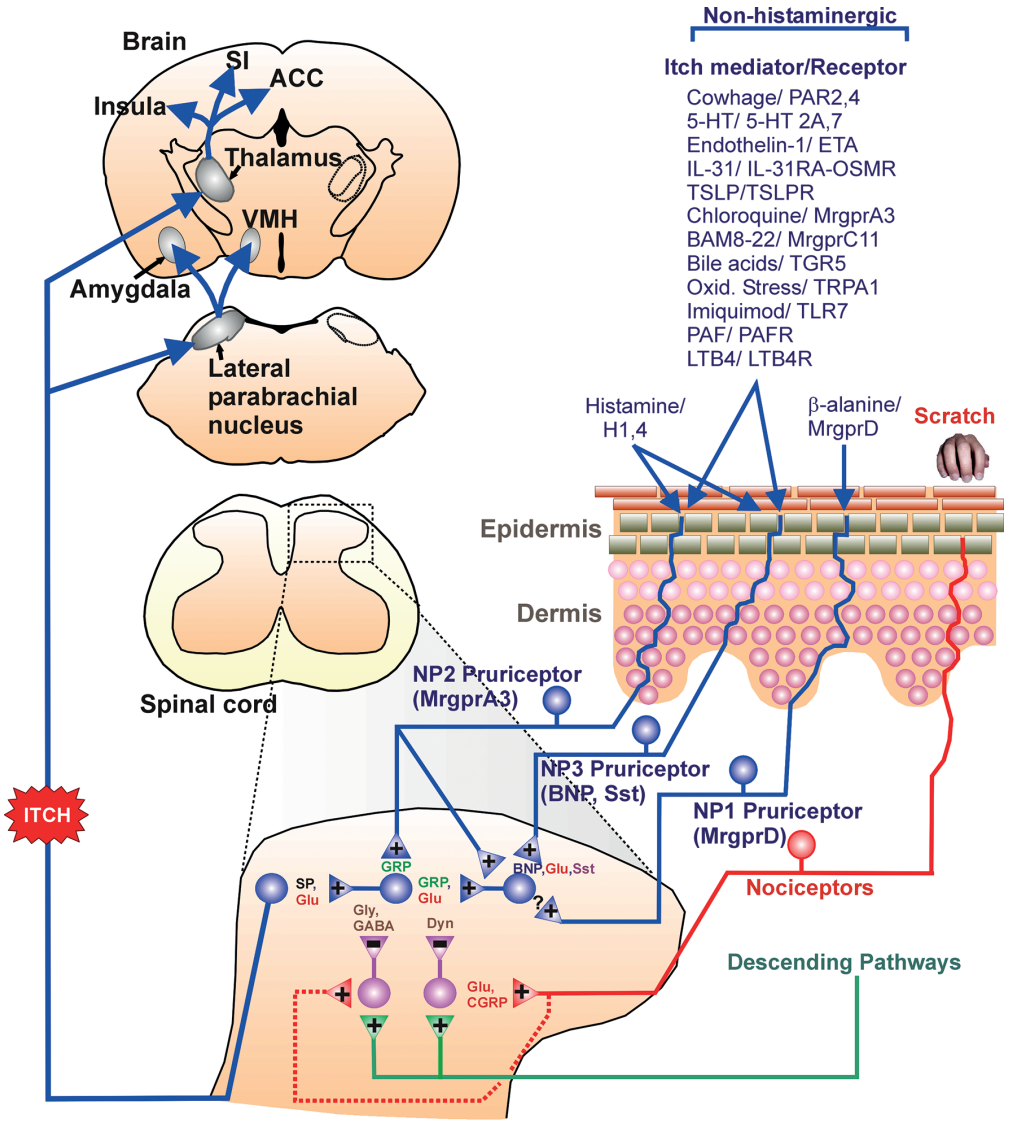

Fig. 1. Schematic of itch-signaling pathways. 5-HT: 5-hydroxytryptamine (serotonin); ACC: anterior cingulate cortex; BNP: brain natriuretic peptide; CGRP: calcitonin gene related peptide; Dyn: dynorphin; Glu: glutamate; Gly: glycine; GRP: gastrin releasing peptide; IL: interleukin; LTB4: leukotriene B4; Mrgpr: Mas-related G-protein coupled receptor; PAF: platelet activating factor; PAR: protease-activated receptor; SI: primary somatosensory cortex; SP: substance P; Sst: somatostatin; TLR: toll-like receptor; TLSP: thymic stromal lymphopoietin.

(DRG) cells, with 3 largely nonpeptidergic (NP) groups expressing genes associated with itch: NP1 (*MrgprD*), NP2 (*MrgprA3*), and NP3 (brain natriuretic peptide [BNP] and somatostatin) (14). *MrgprD*, *MrgprA3*, BNP and somatostatin have all been implicated in itch (15–18). In addition, neuroimmune interactions have been implicated in chronic itch. Recent studies have implicated IL-31 (19, 20), IL-4 and IL-13 (21) in itch and itch sensitization, leading to the development of biologics and antagonists that block activation of sensory neurons by cytokines (7). Clearly, improved understanding of the peripheral transduction of itch and immune function is already addressing the challenge of translating basic research into more effective treatments for chronic itch.

Pruriceptive afferent fibers transmit signals into the spinal cord dorsal horn, where they release neuropeptides including BNP (17), possibly gastrin releasing peptide (GRP) (22, 23), substance P (23), neuromedin B (24), and somatostatin (25) as well as the neurotransmitter glutamate (see below). The spinal circuitry includes excitatory interneurons that express GRP and substance P (26, 27), as well as itch-inhibitory interneurons expressing GABA, glycine and dynorphin (28–31) (Fig. 1). Projection neurons ultimately give rise to ascending itch-signaling pathways to the parabrachial nucleus and somatosensory thalamus. A high percentage of ascending projection neurons express the NK-1 receptor (32, 33). A majority of antidromically identified spinothalamic and spinoparabrachial projection neurons in rats respond to intradermal injection of pruritogens, with most also responding to the algogens capsaicin and mustard oil (34, 35). Using a double-label strategy, we observed similar

proportions of retrogradely labeled spinothalamic and spinoparabrachial neurons that co-express the activity marker, c-fos, following intradermal injection of histamine, chloroquine or capsaicin (36). Finally, the spinal itch-signaling circuitry is very likely under descending modulatory influences from the brainstem, although this has only begun to be experimentally addressed (37, 38).

IS THERE A LABELED LINE FOR ITCH?

On the one hand, there is evidence that spinal transmission involving the neuropeptide GRP provides a specific pathway for itch transmission (discussed further below). On the other hand, based on neural recordings from peripheral and second- or higher-order neurons in the spinal cord and brain, it is evident that neurons that respond to pruritogens invariably also respond to algogens such as capsaicin, mustard oil, and other noxious stimuli. Thus, there appear to be few if any itch-specific neurons, implying that itch must be distinguished from pain (and other dysesthetic sensory qualities) by some mechanism that can decode activity in non-selective neurons. A great challenge of basic itch research is to reconcile these seemingly disparate observations to understand how itch is conveyed to the brain and how it is discriminated from pain and other sensory qualities.

There is much evidence that activation of pruritogen-sensitive primary afferent fibers elicits a sensation of itch via a specific "labeled line" pathway. An older study using electrical stimulation at discrete sites on the skin surface reported that the intensity of the evoked itch increased as a function of increasing stimulus frequency but never transitioned to pain (39). A seminal observation was that mechanically insensitive C-fibers recorded by microneurography responded to cutaneous application of histamine, such that the action potential firing pattern closely paralleled the time course of concomitant itch sensation (40). More recent studies suggest that activation of specific primary afferents elicits itch, even though the afferents respond to algogenic as well as pruritogenic stimuli. For example, MrgprA3 is a Mas-related G-protein-coupled receptor expressed in sensory nerve endings that respond to the itchy antimalarial drug chloroquine (15). When TRPV1 (the capsaicin and heat-sensitive receptor) is genetically engineered into sensory neurons expressing MrgprA3 in otherwise TRPV1-null mice, capsaicin activation of these neurons elicits itch (scratching) rather than the pain behavior that is normally elicited by capsaicin (41). Moreover, MrgprA3-expressing sensory nerves responded not only to chloroquine but also capsaicin and other chemicals, indicating that they are not itch-specific (41). Optogenetic activation of MrgprA3-expressing peripheral afferents also elicited itch-related scratching behavior (27). These findings indicate that activation of MrgprA3-expressing nerve endings elicits itch, regardless of whether they are activated by pruritic, algogenic or artificial stimuli. This implies that although the MrgprA3-expressing afferents are not exclusively activated by itchy stimuli, they access circuits at higher levels of the nervous system that selectively signal itch but not pain.

This concept is also reflected in a "population coding" theory, which is similar to the selectivity theory (**Fig. 2**A). Using calcium imaging of DRG sensory neurons, we found that most if not all neurons that responded to itch mediators additionally responded to capsaicin and mustard oil (42, 43). The same was true for superficial dorsal horn neurons (44). Similarly, high percentages of neurons in the ventral posterior medial and posterior triangular thalamic nuclei responded to pruritogens as well as capsaicin (45). We postulated that pruritogen- and algogen-sensitive DRG and spinal dorsal horn neurons signal itch, whereby these non-selective spinal neurons access itch-specific central mechanisms (Fig. 2A). In contrast, pruritogen-insensitive but algogen-sensitive neurons signal pain. Note that this idea still embodies

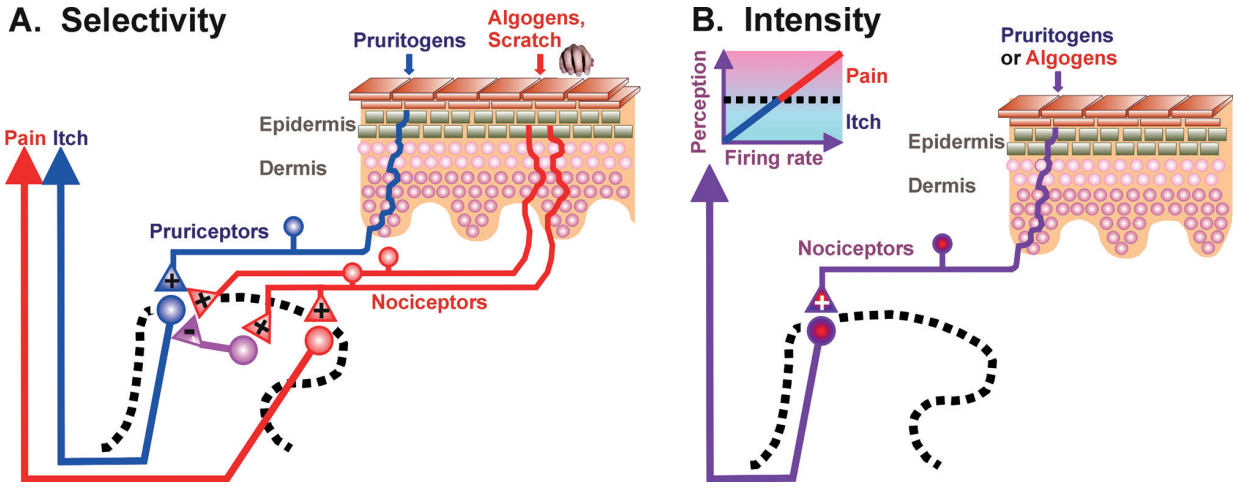

Fig. 2. Itch theories. A: selectivity (similar to population coding). B: intensity theory. See text for explanation. +: excitatory synapse; –: inhibitory synapse.

separate, central labeled line mechanisms for itch and pain. Pain-evoking stimuli would activate both populations of neurons, implying that itch and pain are elicited simultaneously. In this case, pain sensation dominates due to the ability of nociceptive spinal input to activate itch-inhibitory interneurons (Fig. 2A) (46), consistent with the selectivity theory of itch. Itch perception may also be masked by stronger pain.

IS GASTRIN RELEASING PEPTIDE AN ITCH-SPECIFIC MARKER?

A role for GRP in itch was first demonstrated by a significant reduction in pruritogen-evoked scratching, but not pain behavior, in transgenic mice lacking the GRP receptor (GRPR) (22). Neurotoxic destruction of GRPR-expressing spinal neurons also significantly attenuated pruritogen-evoked scratching but not pain behavior (47). These findings were recently corroborated by the report that chemogenetic activation of GRP-expressing dorsal horn neurons elicited behavioral signs of itch but not pain (48). These data strongly support GRP and GRPR expressed in spinal neurons as itch-specific markers.

However, another recent study reported that selective activation of GRP-expressing spinal neurons elicited behavioral signs of both itch and pain (27). The authors genetically engineered TRPV1 into GRP-expressing spinal neurons in otherwise TRPV1-null mice. Intrathecal administration of capsaicin dose-dependently elicited behavioral signs of itch (scratching) as well as pain (licking). At higher doses of capsaicin (1–20 μg), pain (but not itch) responses decreased and were rescued by administration of the μ-opioid antagonist naloxone. The authors suggested that high-dose capsaicin triggered an opioid mechanism that reduced pain but not itch, and that a common population of GRP-expressing spinal neurons signals both itch and pain. This is consistent with the intensity theory of itch (Fig. 2B), which postulates that itch is signaled by a lower firing rate and pain by a higher firing rate in a common population of spinal neurons. Indeed, capsaicin elicited much higher firing rates in GRP-expressing spinal neurons compared to those elicited by the pruritogens SLIGRL, chloroquine or histamine (27). In general, capsaicin and mustard oil elicited consistently higher firing rates compared to pruritogens in spinal dorsal horn neurons, including spinothalamic projection neurons (49). Thus, there is conflicting evidence as to whether GRP- and GRPR-expressing spinal neurons are itch-specific or signal both itch and pain, a challenge to theories of itch-pain discrimination that requires future studies to resolve.

Besides GRP, neuromedin B (24), brain natriuretic peptide (BNP) (17), glutamate (50) and substance P (51) have also been implicated in the spinal transmission of itch. We found that individual intrathecal delivery of receptor antagonists of GRP (RC-3095), substance P (L-733060) or the AMPA glutamate receptor (CNQX), partially reduced scratching behavior and spinal neuronal responses to chloroquine, while a combination of all 3 antagonists completely inhibited these responses (52). This is supported by another study reporting that of dorsal horn neurons responsive to intradermal histamine or chloroquine, some responded to intrathecal delivery of BNP or GRP, but less commonly to both (53). These findings suggest that there may be parallel spinal pathways for itch, each utilizing these neurotransmitters/neuropeptides to different extents. CNQX almost completely abolished scratching and neuronal responses to histamine, implicating glutamate as the primary spinal neurotransmitter in histaminergic itch (52). These studies provide points of intervention in the spinal cord to block the transmission of itch signals.

SPATIAL CONTRAST THEORY OF ITCH

A further complication to our understanding of itch mechanisms is the finding that a dominant sensation of itch, together with sub-dominant nociceptive sensations (burning, stinging, pricking), were elicited by insertion of either a single histamine-loaded, or capsaicin-loaded, or native cowhage spicule into the skin (54). This implies that highly localized activation of a minimal number of nociceptive nerve endings in the skin by either pruritogenic or algogenic chemicals is sufficient to elicit a dominant sensation of itch. This supports the "spatial contrast" theory of itch, which holds that limited activation of nociceptive nerve endings is itchy, while activation of a greater number of nerve endings over a broader area (e.g., by intradermal injection of capsaicin) is painful, possibly due to disruption of a specific pattern for itch via the activation of many nociceptors. This concept was suggested as a possible mechanism of neuropathic itch following nerve injury that results in degeneration of most but not all C-fibers, such that activation of the few spared fibers elicits a sensation of itch (55). The challenge remains to explain how either itch or pain results from localized patterns of activation of nociceptive C-fibers.

HISTAMINERGIC VS. NON-HISTAMINERGIC ITCH: SPECIES DIFFERENCES?

It is a dogma that there are two types of itch, histaminergic and non-histaminergic. In humans, histaminergic itch is mediated by the histamine-sensitive, mechanically insensitive C-fiber afferents mentioned above (40, 56). In contrast, non-histaminergic itch can be elicited by spicules of cowhage, which contain proteases (57, 58). Cowhage excites mechanically sensitive polymodal nociceptors (56, 59). The duality of histamine- and cowhage-sensitivity applies to non-human primates as well, since intradermal injections of histamine or placement of cowhage spicules activated largely separate po-

pulations of spinothalamic tract neurons (60). However, in rodents there appears to be greater overlap in primary and secondary sensory neurons responsive to histamine and non-histaminergic itch mediators. Using calcium imaging of mouse DRG and trigeminal ganglion (TG) cells, it was variously reported that 100% (15), 50% (61) or 17–23% (62) of chloroquine-responsive cells also responded to histamine. Using *in vivo* recording from identified MrgprA3-expressing DRG cells in mice, 78% (7/9) responded to both histamine and chloroquine (41). Recordings from mouse spinal dorsal horn neurons revealed that 47–71% of chloroquine-responsive neurons also responded to histamine (63). In rat somatosensory thalamus, all 7 chloroquine-responsive neurons that were additionally tested with histamine responded, although it is noted that a large number of histamine-responsive thalamic neurons did not respond to chloroquine (45). These data imply that histaminergic and non-histaminergic pathways may be more segregated in humans and non-human primates compared to rodents. A challenge for the field is to understand the limitations of rodent models for translation to human itch.

THE CHALLENGE OF CHRONIC ITCH AND ALLOKNESIS

Cardinal symptoms of chronic itch are ongoing ("spontaneous") itch, alloknesis (mechanical or touch-evoked itch), and hyperknesis (increased itch to a normally itchy or punctate mechanical stimulus). In healthy normal mice, lightly touching the skin does not elicit any behavioral signs of itch. However, following intradermal injection of histamine and other pruritogens, light touch elicits immediate scratch bouts – a model of alloknesis (64). Chemogenetic silencing of spinal neuropeptide Y (NPY) – expressing neurons led to increased touch-evoked scratching (65), and intrathecal delivery of NPY-1 receptor agonists reduced touch-evoked scratching (66), implying that the NPY-expressing neurons normally inhibit itch elicited by low-threshold mechanoreceptors. Scratching elicited by intradermal chloroquine, but not mechanical stimulation, was attenuated by antagonizing or ablating GRPR-expressing neurons, implying that mechanical itch is independent of, or converges downstream of GRP-GRPR signaling in the spinal itch circuit (**Fig. 3**). A reduction in the number of cutaneous Merkel cells and reduced expression of the mechanotransduction channel piezo2, as occurred in aged mice or under dry skin conditions, was associated with increased alloknesis, while chemogenetic activation of Merkel cells prevented alloknesis in dry skin (67). This suggests that Merkel cells connected to slowly adapting type I (SAI) afferents excite NPY-expressing interneurons to inhibit spinal itch transmission. It was very recently reported that activation of neurons expressing the NPY-1 receptor promotes mechanical itch (68). Mechanical itch was not affected following ablation of spinal neurons expressing the NK-1 receptor, implying that mechanical itch is transmitted via a pathway independent of that for chemical itch (Fig. 3). NPY-mediated inhibition can be overcome by mechanoreceptor activation of NPY-1 receptor-expressing neurons to drive the mechanical itch-signaling pathway under conditions in which Merkel cell-SAI input is reduced (Fig. 3).

A number of animal models have been developed to mimic various types of chronic itch and alloknesis, including atopic dermatitis, psoriasis and others (69, 70). Repeated topical application of ovalbumin induced an atopic dermatitis-like condition in mice, characterized by skin hyperplasia and lesions, increased IgG and Th2 cytokines, and importantly, increased spontaneous scratching behavior, alloknesis and hyperknesis (32). Alloknesis, but not hyperknesis or spontaneous scratching, was nearly abolished in OVA-treated mice that received intrathecal injection of substance P-saporin but not bombesin-saporin. This implies that the effect of low-threshold

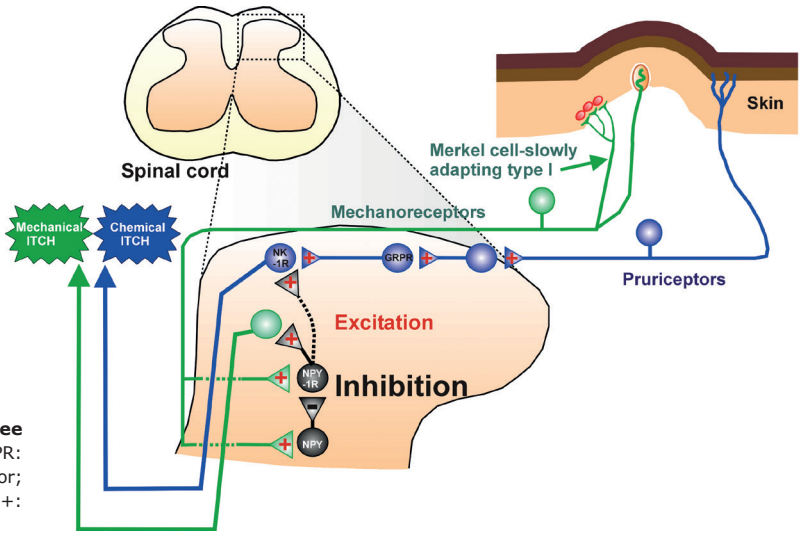

Fig. 3. Schematic of mechanical itch (alloknesis). See text for explanation. GRP: gastrin releasing peptide; GRPR: gastrin releasing peptide receptor; NK-1R: neurokinin-1 receptor; NPY: neuropeptide Y; NPY-1R: neuropeptide Y-1 receptor; +: excitatory synapse; –: inhibitory synapse.

mechanoreceptor input to inhibit itch signaling neurons occurred downstream of GRPR-expressing neurons but requires NK-1 receptor-expressing neurons, supporting the idea that mechanoreceptive input converges onto the chemical itch-signaling pathway (Fig. 3; dashed line connecting NPY-1R to NK-1R). Consistent with this, intrathecal NPY agonists suppressed both chemically- and mechanically-evoked itch behavior (66).

Given that alloknesis is quite bothersome to patients suffering from many types of chronic itch, a challenge to the field is to better understand how low-threshold mechanosensory input interacts with spinal itch-signaling pathways and potential anti-alloknesis interventions targeting spinal NPY1 receptors.

CONCLUSIONS

The preceding text has identified a number of challenges arising from basic itch research to explain how itch can be discriminated from pain, and to translate our increasing knowledge of itch signaling into clinical treatment. Given the remarkable progress of the past decade and the current strong interest in itch research, several novel approaches to the treatment of chronic itch are already being used and more can be expected in the near future. Nevertheless, it has been debated for more than 100 years whether itch and pain are signaled by separate labeled-line pathways or by a common population of non-specific neurons. This debate continues unresolved up to the present, with arguments favoring both concepts.

ACKNOWLEDGMENTS

The author's work has been supported by a grant from the National Institute of Arthritis, Musculoskeletal and Skin Diseases, National Institutes of Health (AR057194).

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Centenary theme section: ITCH AND PRURITIC DISORDERS

REVIEW ARTICLE

Mechanisms and Management of Itch in Dry Skin

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Chronic itch is a burdensome clinical problem that often accompanies pathological dry skin-based conditions, such as atopic dermatitis, and systemic disorders, such as kidney diseases, with an unclear pathomechanism and treatments. One of the basic mouse models to investigate mechanisms of itch associated with dry skin is a mixture of acetone and ether followed by water. Animal studies using the acetone and ether followed by water model have revealed that many mediators and receptors, e.g. mas-related G protein-coupled receptor family, transient receptor potential, and chemokines, are responsible for itch and its hypersensitivity, supporting the hypothesis that dry skin-induced itch is a histamine-independent pathway. New insights have been acquired into the interplay between neurones and non-neuronal cells in the initiation, modulation, and sensitization of itch. Several therapeutic options for itching have thus been developed. This review summarizes the updated pathogenesis and therapeutic strategies for itch in dry skin conditions.

Key words: dry skin; hypersensitivity; itch; sensory neuron; mouse model.

Accepted Oct 15, 2019; Published Jan 9, 2020

Acta Derm Venereol 2020; 100: adv00024.

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SIGNIFICANCE

Itch is an unpleasant sensation that may disturb quality of life, and for which the pathomechanism and appropriate treatments are unclear. Chronic itch, which lasts more than 6 weeks, often accompanies pathological dry skin-based conditions, such as xerosis, atopic dermatitis, liver and kidney diseases. A decline in skin barrier function is thought to be the primary cause of itch induced by dry skin. Many kinds of mediators, receptors, and channels are involved in itch signalling among the skin nervous system, skin cells, and central nervous system. Several therapeutic options for itching have thus been developed, such as phototherapy, phospholipids, antioxidants, and emollients.

Skin, the body's largest organ, serves as a first physiological barrier against the external environment. The barrier function of the skin is exerted by the epidermis, the most superficial layer of the skin, of which the stratum corneum (SC) is largely responsible for the barrier function. There are 2 elements important for the maintenance of SC humidity: intercellular lipids, which form the main barrier against diffusion of water across the SC, and natural moisturizing factor, which has a key role in the absorption of water in the SC. Impaired skin barrier integrity causes excessive water loss and leads to skin dryness (1, 2).

DRY SKIN

Dry skin is characterized by a scaly, rough, cracked, and fissured surface, and is closely associated with the somatosensory sensation of itch, especially chronic itch (3). Dry skin with chronic itch is the most common clinical manifestation of dermatoses, such as xerosis, atopic dermatitis (AD), and psoriasis, and is a common cutaneous manifestation in pruritic systemic diseases, such as chronic kidney disease (CKD), chronic liver diseases (CLD), and diabetes mellitus (DM) (4).

Histamine is a well-known substance that induces itch; however, antihistamines (histamine H_1-receptor blockers) are not fully effective in many dermatological and systemic diseases characterized by dry skin, suggesting that dry skin is an important feature of antihistamine-resistant (histamine-independent) itch (2). The underlying condition of dry skin is impaired function of the skin barrier, which can be caused by environmental factors, such as sun exposure, temperature, humidity, and genetic factors, such as filaggrin mutations (1, 5, 6). To assess skin barrier function, transepidermal water loss (TEWL), SC hydration, and pH are commonly used (1). The signs and clinical manifestations of dry skin are not only physically uncomfortable, but also affect patients psychologically (7).

Disease-related dry skin

Aged skin. Xerosis is one of the most prevalent dry skin conditions in the aged population worldwide (8), affecting over 50% of individuals aged ≥65 years (9). Multiple skin changes in the elderly are related to xerosis: (*i*) alterations in the barrier function of SC, including cellular and intercellular lipid matrix changes; (*ii*) pH variations; (*iii*) alterations in SC proteases; (*iv*) reduced activity of sebaceous and sweat glands; and (*v*) decreased oestrogen levels. All of these factors may lead to itch induction (10).

Inflammatory skin diseases. Dry skin itch is a common symptom in dermatoses characterized by dysfunction of the skin barrier, such as AD and psoriasis. In these diseases, pruritogens, such as cytokines and chemical mediators, are released from the affected area (5, 11). Pruritogens induce itch mainly by acting on the sensory nerves, and the affected area is scratched, then further aggravates dermatitis (12). This vicious cycle is called the "itch-scratch cycle". Skin hyperesthesia (a skin condition that involves an abnormal increase in sensitivity to stimuli) occurs in inflammation, such as AD (5). Elongation of the sensory nerve in the epidermis to immediately underneath the SC, due to drying and inflammation, is considered to be a cause of skin hyperesthesia. Nerve growth factor (NGF), amphiregulin (AR), and artemin (ARTN), which are nerve elongation factors (NEFs), and semaphorin 3A (Sema3A, a nerve repulsion factor (NRF)), are related to this aberrant nerve elongation and sprouting in AD (13).

More recently, Pogatzki-Zahn et al. (14) reported skin hyperesthesia in patients with chronic pruritus, such as AD, but it was not related to hyperinnervation in the epidermis, observed as a decreased number of cutaneous nerves crossing the basement membrane. The authors speculated that, although the nerves crossing the basement membrane were reduced, increased intraepidermal sprouting of nerves is possible. Another possibility is that the density, structure, and functional properties of intraepidermal nerves fluctuate in different skin disease states, especially in acute and chronic phases.

Systemic diseases. Dry skin is also a common cutaneous manifestation in pruritic internal diseases, such as CKD, CLD, and DM (4). Skin dryness may appear at different stages of CKD, but it is more frequently diagnosed in dialysis subjects (45%) (15). The functional abnormalities of eccrine sweat glands may account, at least in part, for dry skin in uraemic patients (16). It has been suggested that dry skin can cause itch in CKD; however, objective measurements of the barrier function of the skin, such as the degree of hydration of the skin, lipid bilayer abnormalities, and dryness of the skin, do not always correlate with pruritus (17).

The pathogenesis of pruritus in CLD is poorly understood and often refractory to treatment, with a prevalence of 40.3% (18). Several potential itch-causing substances may be involved, including bile salts, endogenous opioids, histamine, serotonin, and steroids (19). We reported recently that the plasma dynorphin A level of endogenous opioids correlates with the severity of pruritus and may reflect its degree in patients with CLD (20).

Skin disorders are common complications and comprise a broad spectrum of disorders in both type 1 and type 2 DM, e.g. cutaneous infection, dry skin, and pruritus (21). Clinical observations are supported by a reduced hydration of the SC and reduced sebaceous gland activity in patients with DM. Even in the absence of clinically apparent dry skin, patients with diabetes have an impaired desquamation process (22). Pruritus is more common in patients with diabetes who have dry skin or diabetic neuropathy (21). Higher postprandial glucose levels were reported to result in a higher probability of having generalized pruritus (23).

Dry skin mouse models

Acetone-treated model (acute dry skin model with no itch). One mouse model to induce dry skin uses acetone application. The hair of mice is shaved over the rostral part of the back at least 3 days before acetone treatment. The shaved area was treated with acetone-soaked cotton balls for 5 min. In the control group, the shaved area was treated with sterile water (3, 24).

Analyses of experimental animals treated with acetone demonstrated that intraepidermal innervation-related factors, such as *NGF* and *ARTN* gene expression, were increased in the epidermis, and the artificial restoration of the barrier immediately following barrier disruption by acetone treatment inhibited the increase in these mRNA levels (3, 24). Others observed the release of histamine from mast cells in the skin of acetone-treated mice (25). We found that acetone-treated mice displayed a rapid increase in TEWL and a decrease in SC hydration during the first hour after treatment, which returned to normal by 48 h after the treatment. Thus, the acetone-treated mice manifest the characteristics of dry skin and have altered cutaneous barrier permeability. No scratching behaviours or epidermal hyperplasia were observed in the acetone-treated mice, although there was an increase in nerve fibre density in the epidermis (**Fig. 1**A). Of note, we found that the expression of epidermal NGF and AR (which promote nerve growth) was increased (3), but Sema3A (which inhibits nerve growth) expression was decreased (Tominaga et al., unpublished data) before the penetration of nerve fibres into the epidermis (Fig. 1B and C). The increase in intraepidermal nerve fibres may be an important factor for the regulation of itch in dry skin (3).

Acetone/ether/water (AEW)-treated model (chronic dry skin model with itch). The AEW-treated mouse model is one of the most well-known mouse models for the study of dry skin-induced itch (26). The hair of mice was shaved over the rostral part of the back at least 3 days before the start of the experiment. To disrupt the cutaneous barrier, cotton (2 × 2 cm) soaked in a mixture of acetone and ether (1:1) was placed on the shaved area for 15 s. Immediately after AE treatment, cotton soaked with distilled water was placed on the same area for 30 s. Treatments were performed twice daily under ether anaesthesia for 5–7 consecutive days. TEWL and scratching behaviour were increased, and SC hydration was decreased, under this treatment. The histopathological analysis showed that the AEW-treated mice had marked epidermal hyperplasia, parakeratosis, and infiltration of nerve fibres into the epidermis, but no infiltration of inflammatory cells in the dermis (26, 27). Overall, the AEW treatment produces

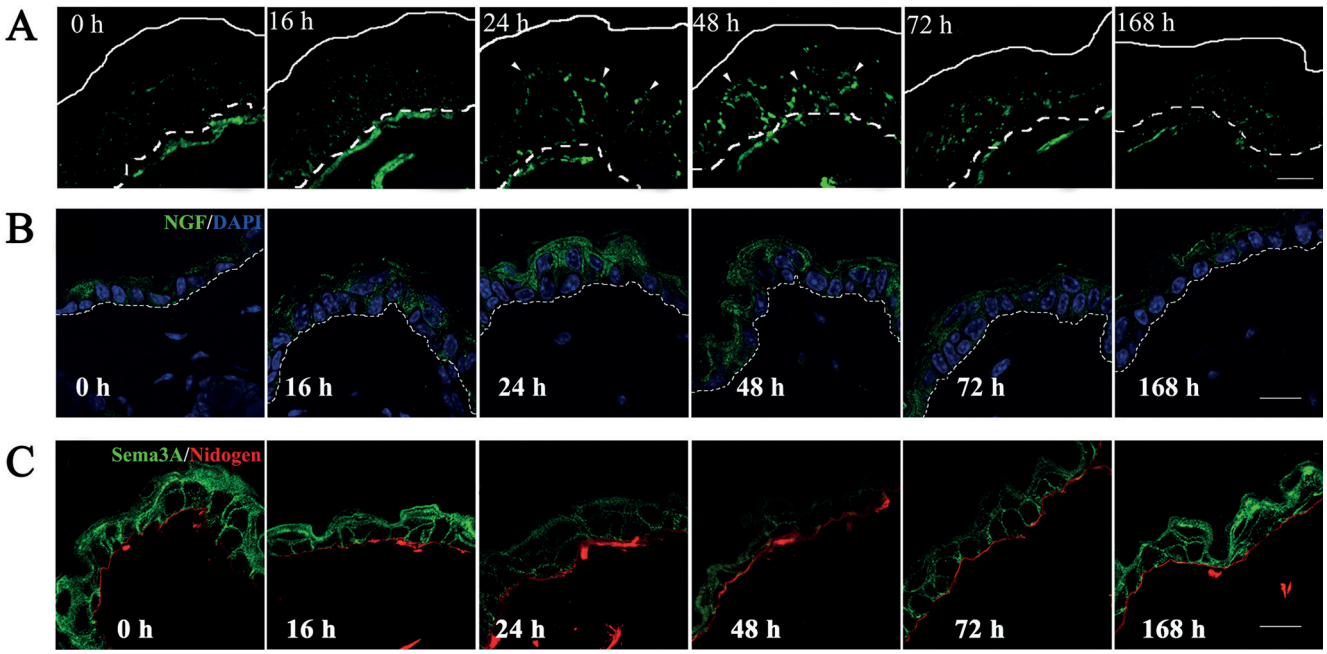

Fig. 1. Alterations in nerve fibre distribution, and nerve growth factor (NGF) and Sema3A expression in the epidermis of acetone-treated dry skin model mice. (A) Sequential alteration of intraepidermal nerve growth in acetone-treated mice was examined by immunohistochemistry using an anti-PGP9.5 antibody. (B, C) Maximum expression of NGF (*green*) was noted 16–24 h after the treatment (B). In contrast, the expression level of Sema3A (*green*) was decreased 24 h after acetone treatment (C). These expression levels gradually returned to normal by 168 h after the treatment. Nuclei are counterstained by DAPI (*blue*). The *broken lines* in panel A indicate the border between the epidermis and dermis (basement membrane). The basement membrane in panel B was stained with an anti-nidogen antibody (*red*). *White* and *broken lines* indicate the skin surface and the border epidermis and dermis (basement membrane), respectively. *Arrowheads* indicate epidermal nerve fibres (green). Scale bars: 15 μm.

marked skin barrier dysfunction, robust scratching, and changes in gene expression in sensory nerves and the skin (26), which recapitulate the dry skin symptoms present in many chronic itchy conditions in humans (28). There was no apparent difference in AEW-induced spontaneous scratching between mast cell-deficient mice (WBB6F1-W/W^{v}) and normal litter-mates (WBB6F1-$^{+/+}$) (26).

This dry skin model also exhibits alloknesis (scratching behaviour evoked by a stimulus that is normally non-pruriceptive) and hyperknesis (the abnormal pruriceptive state, in which a normally pruritic stimulus elicits a greater than normal duration and/or magnitude of itch) (27, 29), as described later in this review.

Special diet food model. HR-1 hairless mice fed a special diet (HR-AD) is one of the dry skin-based experimental mouse models. Mice were fed HR-AD for 48 days. These mice exhibited severe dry skin symptoms accompanied by a decrease in skin water-holding capacity, increase in TEWL, and prolonged scratching bout duration. Marked epidermal hyperplasia, and increase in circulating T cells and serum IgE are observed (30). Lipid composition analysis revealed that HR-AD is an essential fatty acid (EFA)-deficient diet. Feeding HR-AD with EFA inhibits the symptoms of dry skin (31). EFA deficiency was reported to depress skin barrier function due to structural changes in ceramides, and reduced elaboration and deposition of epidermal intercellular lipids (32). Therefore, HR-AD causes deterioration of the skin barrier function due to EFA deficiency.

MECHANISMS OF ITCH IN DRY SKIN

The sensation of itch is generated by the binding of itch-inducing substances to their cognate receptors on peripheral sensory afferents, e.g. unmyelinated C-fibre afferents and thinly myelinated Aδ-fibre afferents. The evoked action potential is transmitted through the ascending sensory pathway to the somatosensory cortex, resulting in the perception of itch (**Fig. 2**).

Sensory neurones

Nerve elongation and repulsion factors. In healthy skin, most cutaneous nerve fibres terminate under dermoepidermal junctions. An increased intraepidermal nerve density has been observed in the skin of patients with pruritic dermatological diseases, such as senile xerosis and AD (13), as well as in dry skin mice models (3, 33). The controlling mechanism of cutaneous nerve density is regulated by the balance of NEFs, such as NGF, ARTN and AR, and NRFs, such as Sema3A, produced by keratinocytes (5, 13). These axonal guidance molecules may also act on keratinocytes, immune cells, and vascular endothelial cells, and may be indirectly involved in the regulation of itching (34).

Matrix metalloproteinase (MMP)-2 and MMP-8. The process of cutaneous nerve growth in dry skin requires several MMPs for growth cones to penetrate the 3-dimensional extracellular matrix (ECM) barriers (Fig. 2). Using *in vitro* models of ECM, we found that MMP-2

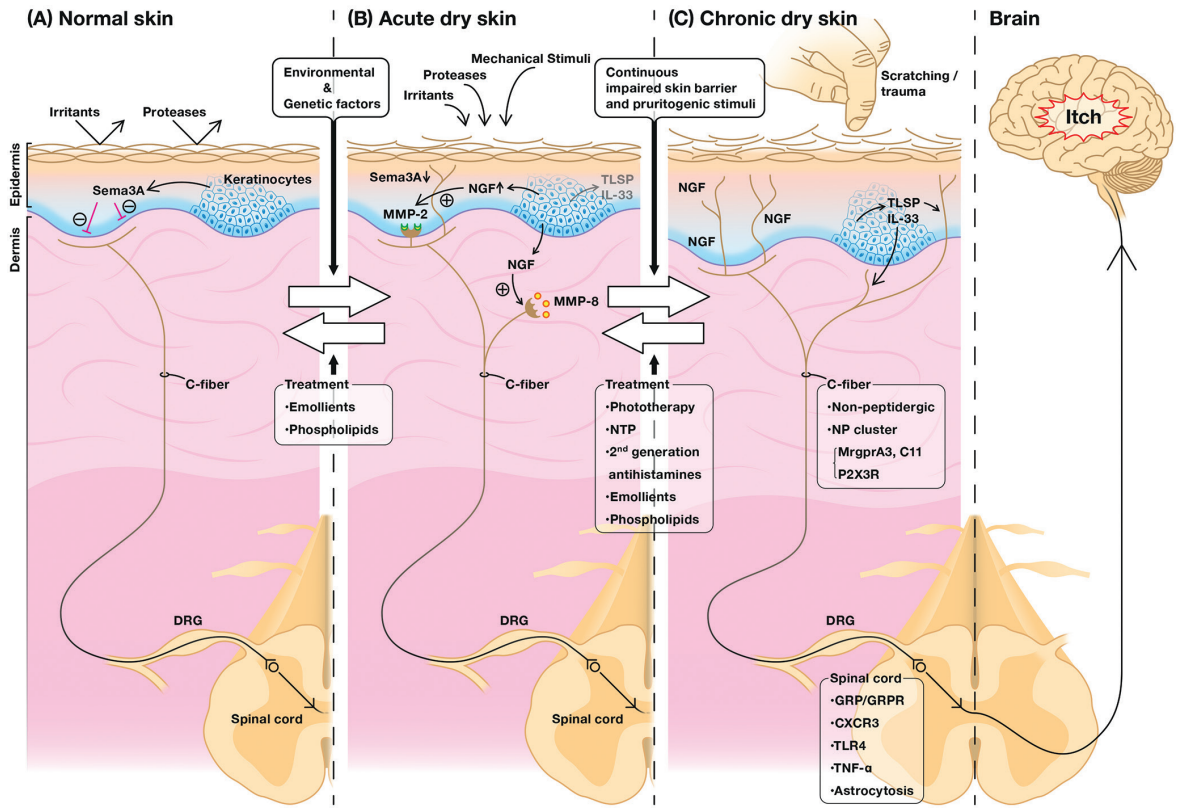

Fig. 2. Mechanisms and management of dry skin-induced itch. The perception of itch starts when endogenous and exogenous itch mediators activate their respective receptors/channels expressed in peripheral sensory afferents. Electric signals generated in the peripheral nerve endings are transmitted to the somatosensory cortex in the brain through the spinal cord, resulting in the recognition of itch. (A) In healthy skin, Sema3A, a nerve repulsion factor (NRF) produced mainly by keratinocytes (KCs), is dominant. It maintains the cutaneous nerve fibres under the dermo-epidermal junction. (B) During environmental stimuli in acute dry skin conditions, nerve growth factor (NGF), an epidermal nerve elongation factor (NEF) produced by KCs, is prominent and induces the elongation of cutaneous nerve fibres into the epidermis. This elongation may also be affected by thymic stromal lymphopoietin (TSLP) and interleukin (IL)-33 released from KCs. NGF also promotes matrix metalloproteinase (MMP)-2 and MMP-8 production in sensory nerve fibres, which leads to the penetration of nerve fibres into the basement membrane and their growth. Emollients and phospholipids are effective at alleviating the symptoms in this phase. (C) In chronic dry skin accompanying the itch-scratch cycle, such as in systemic or inflammatory skin diseases, more sensory nerve fibres penetrate the epidermis. In addition to substances released from KCs, the non-peptidergic C-fibres (NP cluster) are also involved in itch signalling, along with astrocytosis in the spinal cord. More treatments have been confirmed to be beneficial in this condition.

localized on the growth cone functioned in penetration into the basement membrane (35). In addition, MMP-8 secreted by nerve fibres was reported to be involved in nerve growth within the dermis (36). The levels of expression of MMP-2 and MMP-8 were upregulated by NGF and down-regulated by Sema3A. The selection and up-regulation of MMPs corresponding to the ECM components surrounding the growing nerve fibres may be required for efficient nerve fibre penetration, suggesting that the coordinated activation of neurotrophin and ECM-integrin signalling is necessary for efficient and long-distance axon extension (37). As class 3 semaphorin signalling inhibits integrin-mediated adhesion signalling, Sema3A stimulation of growing nerve fibres may provide a reverse signalling pathway for these events (38).

Peptidergic fibres. Substance P (SP) and calcitonin gene-related peptide (CGRP) are neuropeptides produced by sensory nerves in the dermis to communicate with different cell populations in the different layers of the skin, which in turn stimulate nerve fibres. An increase in the elongated epidermal peripheral nerve fibres consist of SP/CGRP-containing C-fibres, which usually represent epidermal peptidergic nerve fibres, has been reported in the AEW model (39, 40).

The neuropeptide gastrin-releasing peptide (GRP) is characterized as a neurotransmitter that specifically relays itch signals and specifically expressed in a small subset of peptidergic dorsal root ganglion (DRG) neurones. Genetic ablation of GRP receptor $(GRPR)^{+}$ neurones resulted in significant reduction in the scratching response to multiple pruritogens (41). The transcription factor Tlx3 in the spinal cord was demonstrated to be essential for the development of $GRPR^{+}$ neurones (42). Huang et al. (43) reported that Tlx3 conditional knockout (*Tlx3*$^{F/F}$; *Nav1.8-Cre* mice specifically lost Tlx3 expression in most TrkA-lineage DRG neurones) mice scratched much less compared with controls in the dry skin model, suggesting impairment of dry skin-induced chronic itch in these mice.

Non-peptidergic fibers. C-fibres have been divided into peptidergic and non-peptidergic subsets mainly on the basis of neurochemical criteria. The peptidergic neurones are

mostly marked by neuropeptides, including SP and CGRP, whereas non-peptidergic neurones are commonly labelled by the purinergic P2X3 receptor and the plant lectin isolectin B4 (IB4) (44). On the contrary to previous reports of SP and CGRP involvement in the AEW model, a recent study reported that AEW treatment increased non-peptidergic intraepidermal fibres, but not $CGRP^+$ fibres, suggesting that a specific subset of non-peptidergic fibres function in dry skin itch (45), as is observed in itch behaviour of the imiquimod-induced psoriasis mouse model (46).

Protease-activated receptors (PARs). PARs consist of 4 members: PAR-1, PAR-2, PAR-3, and PAR-4. PARs other than PAR-3 are expressed in cutaneous nerve fibres, keratinocytes, mast cells, and macrophages, and are considered involved in itch (27, 47). Spontaneous scratching behaviour in dry skin-treated animals was significantly attenuated by a PAR-2 antibody either delivered locally to the dry skin area or systemically. In addition, DRG cells from AEW-treated mice exhibited significantly larger responses to the PAR-2 agonist, implicating a role for endogenous agonists of this receptor in chronic itch (27).

Mas-related G protein-coupled receptor family (Mrgpr). The Mrgpr family in mice can be grouped into several subfamilies: MrgprA, MrgprB, MrgprC, and MrgprD-G (48). MrgprA3, MrgprC11, and MrgprD in mice, which are expressed only on small-diameter sensory neurones in the DRG and trigeminal ganglia (TG), and were recently suggested to be involved in the transmission of itch (49–51). The expression of mRNAs encoding MrgprA3 and MrgprC11 was found to be higher in AEW-treated dry skin model mice than in water-treated controls (52). Moreover, the ablation of $MrgprA3^+$ DRG neurones reduced chronic itch induced by AEW treatment, suggesting that MrgprA3 functions in dry skin-related itch (53). The increases in expression of MrgprA3 and MrgprC11 were inhibited in acid-sensing ion channel 3 (ASIC3) knockout mice (52), suggesting that fluctuations in skin pH are involved in dry skin-related itch.

Transient receptor potential family (TRP). The TRP channels are known as polymodal cellular sensors. The ion channel TRP subfamily A member 1 (TRPA1) was previously reported to mediate acute histamine-independent itch, e.g. sensory neurone activation and itch behaviour downstream of 2 histamine-independent pruritogens, chloroquine and BAM8-22 (49, 54). Wilson et al. (55) found that functional TRPA1 is required for the dry-skin-evoked phenotypes, including AEW-evoked scratching, epidermal hyperplasia, and expressional changes in the skin. Among the human disease genes, TRPA1 regulates both scratch-dependent and scratch-independent changes: AQP3, IL-33, chemokine receptor CXCR2, lipocalin, Slc9a3r1, and S100A9 require TRPA1, and are independent of the itch-scratch cycle, whereas CCL27 and Tenascin C (TNC) are scratch- and TRPA1-dependent. These genes play diverse roles in the initiation and maintenance of chronic itch (55).

TRP cation channel subfamily V member 1 (TRPV1) is a heat-sensitive cation channel that is selectively expressed in a population of primary sensory neurones in TG and DRG, which plays an important role in thermal and pain sensations (56). Yu et al. (28) reported an increased innervation density of TRPV1-expressing sensory fibres in the skin of AEW model mice due to expansion of this channel. This may also be partly involved in the induction and/or enhancement of itch in dry skin.

NP clusters of sensory neurones. Usoskin et al. (57) reported 4 neuronal clusters (further divided into 11 fundamentally distinct types of sensory neurones) in single cells of sensory neurones from mouse lumbar DRGs. The first cluster is the NF cluster (including NF1-5), which expresses neurofilament heavy chain (*Nefh*) and parvalbumin (*Pvalb*), and was previously associated with myelinated DRG neurones. The second, the PEP cluster (including PEP1-2), expressed SP (*Tac1*), TRKA (*Ntrk1*) and CGRP, which were previously associated with peptidergic nociceptors. The third, the NP cluster (including NP1-3), expressed *Mrgprd* and *P2rx3*, which were previously associated with non-peptidergic nociceptors. The fourth, the TH cluster, exhibited distinct expression of tyrosine hydroxylase (*Th*) and has been described in a distinct subclass of unmyelinated neurones. Furthermore, NP1, NP2, and NP3 neuronal types were reported to function in itch, and NP3 is likely to sense and transduce inflammatory itch. They detected lysophosphatidic acid–responsive neurones (*Lpar3* and *Lpar5*) in the NP1 class, chloroquine-responsive neurones (*Mrgpra3* and *Mrgprx1*) in NP2, and interleukin (IL)-31 (*Il31ra* and *Osmr*)- and cysteine leukotriene (*Cysltr2*)-responsive neurones, neuropeptides natriuretic peptide, neurotensin, and somatostatin (*Nppb, Nts*, and *Sst*) markers, and a low level of P2X3 in NP3. Histamine receptors (*Hth1*) were found in NP2 and NP3, and serotonin receptors (*Htr1f*, *Htr2a*) were found in NP3 and PEP2. Thus, their data support the existence of at least 3 classes of itch responsive neurones with unique response profiles: lysophosphatidic acid associated with cholestatic disorders may be tuned to NP1 neurones, chloroquine and histamine associated with acute itch may be tuned to NP2 neurones, and mediators, such as IL-31 and cysteine leukotrienes, which are linked to chronic states of inflammatory itch, as well as histamine and serotonin, may engage NP3 neurones (57). These new types and classification of neurones may be closely related to the pathomechanism of dry skin-induced itch.

Keratinocytes

Transient receptor potential cation channel subfamily V member 4 (TRPV4) was reported to be involved in acute itch elicited by exogenously applied histamine and 5-hydroxytryptamine (5-HT) (58, 59). Luo et al. (60) revealed that TRPV4 is selectively expressed by epi-

dermal keratinocytes in mice. Lineage-specific deletion of TRPV4 in keratinocytes reduced itch in AEW-treated mice. Moreover, TRPV4-dependent chronic itch requires 5-HT signalling secondary to activation of distinct 5-HT receptors in AEW as downstream signalling.

AD and allergic contact dermatitis (ACD) are cutaneous diseases characterized by dry skin and chronic itch. Previously, we demonstrated that, possibly through PAR-2 activation in keratinocytes, the cytokine thymic stromal lymphopoietin (TSLP) produced by keratinocytes plays an important role in the development of AD (61). Of note, it was further reported that keratinocytes communicate directly with cutaneous sensory neurones via TSLP to promote itch. Wilson et al. identified the ORAI1/NFAT calcium signalling pathway as an essential regulator of TSLP release from keratinocytes, and TSLP acts directly on a subset of TRPA1-positive sensory neurones to trigger robust itch behaviours (62).

Liu et al. (63) also reported that IL-33 produced and released by keratinocytes is a key cytokine up-regulated in the skin of urushiol-challenged ACD model mice. In this study, IL-33 and its receptor ST2 (expressed in DRG neurones, which innervate the skin) were functionally present in primary sensory neurones and found to lead to pruritus in this model. Studies revealed that hypo-osmotic stress to keratinocytes, such as that noted in AD, and trauma to the skin, such as tape-stripping, promote IL-33 production from keratinocytes (64, 65). Considering the close relationship between itchy-dry skin and AD or ACD, it is highly possible that TSLP and IL-33 produced by keratinocytes play an essential role in the mechanism of dry skin itself.

Spinal cord

Gastrin-releasing peptide system. The GRP and its receptor (GRPR), a $G_{\alpha q}$-protein-coupled receptor (GPCR), were reported as itch-specific signalling molecules and expressed in the spinal cord. Intrathecal GRP acts via GRPR to induce scratching behaviour (41). PI3Kγ, a member of lipid kinases that participate in the intracellular signalling cascade, is activated downstream of GPCRs and is related to itch. In a dry skin model of itch, GRPR blockade or PI3Kγ inhibition by intrathecal or systemic route, attenuated the scratching behaviour, suggesting that GRPR is expressed by the central terminals of DRG nociceptive afferents, which transmit itch via the PI3Kγ pathway. These data suggest that the spinal GRP/GRPR system is partly involved in the induction of itch in dry skin (66).

Chemokines. Chemokines are expressed in the central nervous system, where they regulate its function under both physiological and pathological conditions, including neuronal development, synaptic transmission, and disease-associated neuroinflammation (67). Qu et al. (68) reported that C-X-C motif chemokine ligand 10 (CXCL10) and C-X-C motif chemokine receptor 3 (CXCR3) are increased in the DRG in an ACD model, and CXCL10 directly activates a subset of cutaneous DRG neurones through neuronal CXCR3. Of note, AEW treatment induced the expression of CXCR3 and CXCL10 in the spinal cord, and $CXCR3^{-/-}$ mice had fewer scratching responses than control mice. In addition, AEW-induced astrocyte activation was reduced in $CXCR3^{-/-}$ mice, suggesting that the spinal CXCR3 plays an essential role in the pathogenesis of chronic dry skin-induced itch (69).

Toll-like receptors (TLR). TLR are type I transmembrane proteins that can mediate innate and adaptive immunity via recognition of exogenous and endogenous ligands produced after tissue injury. There is increasing evidence that primary sensory neurones express TLRs, e.g. TLR3 and TLR4 (70, 71), and their important roles, such as spinal cord glial activation in neuropathic pain (72, 73). The AEW mouse model exhibited persistent upregulation of TLR4 mRNA and increased TLR4 expression in GFAP-expressing astrocytes in the spinal dorsal horn. $TLR4^{-/-}$ mice exhibited substantial reductions in scratching and alloknesis, a touch-elicited itch in wild-type mice, after AEW. This model also induced TLR4-dependent astrogliosis (GFAP upregulation) in the spinal cord. Intrathecal injection of astroglial inhibitor L-α-aminoadipate reduced AEW-induced itch and alloknesis. Scratching plays an essential role in spinal astrogliosis because AEW-induced astrogliosis was abrogated by placing collars on the neck to prevent scratching. Intrathecal injection of lipopolysaccharide from *Rhodobacter sphaeroides* (LPS-RS), a TLR4 antagonist, suppressed AEW-induced itch and alloknesis. These findings suggest that spinal TLR4 signalling is important for spinal astrocyte activation and astrogliosis, which may underlie chronic itch and alloknesis (74).

Tumour necrosis factor-α (TNF-α). Emerging evidence suggests that cytokines and chemokines also serve as key itch mediators and/or modulators (75). TNF-α was reported to play a central role in regulating synaptic plasticity in the spinal cord and chronic pain via its receptors, TNFR1 and/or TNFR2 (76). Dry skin itch induced by AEW was reduced by the administration of thalidomide (TNF-α-synthesis inhibitor) and etanercept (TNF-α antagonist), and in TNFR1/R2 double-knockout mice. AEW treatment induced TNF-α expression in the skin, DRG, and spinal cord, and TNFR1 expression only in the spinal cord. Thus, these findings suggest that TNF-α/TNFR1 signalling is partly required for the full expression of chronic itch in dry skin via peripheral and central mechanisms (77).

Others

Zeta chain-associated protein kinase 70. The T-cell signal pathway was reported to function in dry skin pruritus (78). Zeta chain-associated protein kinase 70 (ZAP70),

as a T-cell receptor, may induce IL-2 secretion and promote NGF secretion in skin (79). After AEW treatment, 22-month-old AEW mice exhibited increased spontaneous scratching compared with 5-month-old AEW mice. ZAP70 expression was significantly increased, in addition to the secretion of IL-2 and NGF in 22-month-old AEW mice compared with 5-month-old AEW mice. This study revealed that increased ZAP70 is involved in dry skin in pruritus in elderly people, probably due to increased secretion of IL-2 and NGF (80).

Toll-like receptor 3. TLR3 was found to be an important receptor in murine itch signalling, and is expressed by sensory nerves and DRG in mice. TLR3 is also expressed by mast cells and keratinocytes (81). AEW treatment elicited a marked 25-fold increase in TLR3 expression in the skin, but not in the DRGs. Moreover, AEW treatment induced marked NGF upregulation in the skin, which was TLR3-dependent. Spontaneous itch was eliminated in TLR3$^{-/-}$ mice. Thus, TLR3 and its upregulation in the dry skin are important for the induction and sensitization of chronic itch (82).

Opioids. Previous studies have identified 4 major types of opioid receptors, μ-type (MOR, a receptor for β-endorphins), κ-type (KOR, a receptor for dynorphins), δ-type (a receptor for enkephalins), and nociception (a receptor for nociceptin/orphanin FQ). Activation of μ-opioid receptors is thought to induce pruritus, whereas activation of κ-opioid receptors is believed to have suppressive effects (18, 83). We previously reported that the κ-opioid system was downregulated in the epidermis of patients with AD, and that psoralen-ultraviolet A (PUVA) therapy downregulated the μ-opioid system and restored the κ-opioid system, concomitant with a decrease in the visual analogue scale (VAS) score (84). Spontaneous scratching after AEW treatment was significantly suppressed by subcutaneous injection of μ-opioid antagonists, such as naloxone and naltrexone (26), and the κ-opioid agonist nalfurafine (85), presumably via both peripheral and central mechanisms.

Hyperknesis

The term "hyperknesis" was proposed as an umbrella term encompassing the state in which there is enhanced itch to normally itch-provoking stimuli or lowered itch threshold to a given stimulus (86). The mechanisms of hyperknesis are not clear, and it remains unknown which type of afferents mediate the mild itch resulting from punctate stimuli (87). Hyperknesis may be mediated by type-I Aδ fibres through a central mechanism when secondary to itch provocation or an actively itchy skin lesion (88).

Akiyama et al. (27) reported a significant increase in the number of scratching bouts evoked by intradermal injections of a PAR-2 agonist and 5-HT under dry skin conditions. Moreover, DRG cells from AEW-treated mice exhibited significantly larger responses to the PAR-2 agonist and 5-HT. Furthermore, enhanced responses of lumbar superficial dorsal horn neurones to intradermal PAR-2 agonist in this model have been reported (89). This implies that acute itch elicited by certain pruritogens, such as 5-HT and PAR-2 agonists, is enhanced in chronic itchy skin. This reflects hyperknesis, which is consistent with the sensitization of itch-signalling pathways.

Alloknesis

Innocuous mechanical stimuli were reported to elicit itch when delivered within a region of normal skin surrounding a site of experimental itch induced by the intradermal injection of histamine, a phenomenon known as itchy skin or alloknesis (90). Alloknesis may reflect a central mechanism in which the activation of low-threshold mechanoreceptors excites sensitized itch-signalling neurones in the spinal cord. Innocuous mechanical stimulation elicited scratching when delivered at the edge of a region of AEW treatment in mice, suggesting the presence of alloknesis in this animal model of chronic dry skin itch (29).

Merkel cells, the touch receptors in the skin, were reported to make "synapse-like" contacts with type I slowly adapting afferents (91). Feng et al. (92) reported that alloknesis in dry skin is associated with a loss of Merkel cells. Targeted genetic deletion of Merkel cells and its associated mechanosensitive Piezo2 channels produced alloknesis. Chemogenetic activation of Merkel cells protected against alloknesis in dry skin. These data suggest that cutaneous Piezo2 channel-Merkel cell signalling is critical in modulating the conversion of touch to itch.

ITCH OF DRY SKIN AND ANXIETY

Chronic itch is clinically correlated with the development of mood disorders, such as anxiety and depression, predominantly in dermatological patients (7). The psychological burden produced by chronic itch was reported with high incidences of suicidal motivation (21.1%) and psychiatric illnesses (70%) (93). Zhao et al. (94) reported that AEW mice developed anxiety-like symptoms 2–3 weeks and depression-like phenotypes 3–4 weeks after AEW treatment, suggesting that mood impairment due to chronic itch evolves over time. The mood impairment behaviours were significantly related to the itch-associated behaviour. They also demonstrated primary disturbance of the hypothalamic pituitary adrenal (HPA) axis function in AEW-treated mice with chronic itch.

The amygdala is the key brain region for the generation of anxiety (95). Recently, Sanders et al. (96) reported that acute itch stimuli, such as histamine, induced anxiety-like behaviour and increased neurone activity in a subpopulation of the amygdala in adult mice. These results highlight the importance of itch-responsive amygdala

neurones in the regulation of itch-related effects and behaviour, which may also apply to chronic itch conditions due to dry skin.

MANAGEMENT OF DRY SKIN-INDUCED ITCH

Since the mechanisms of dry skin-induced itch in animal models were reported, there have been many studies on the management of dry skin-induced itch (Fig. 2 and **Table I**).

Antihistamines

Second-generation H_1-antihistamines (e.g. bepotastine) were reported to be beneficial for pruritus in patients with AD (97). We recently demonstrated that bepotastine downregulated NEFs (NGF and ARTN) mRNA in normal human epidermal keratinocytes. The alteration was mediated by the transcription activity of AP-1- and/or NF-kB-dependent mechanisms via the histamine H_1 receptor. These results provide therapeutic evidence that second-generation H_1-antihistamines may be effective for controlling itch associated with epidermal nerve density in dry skin conditions (98). Another report found that topical application of H_1 (diphenhydramine) and H_2 (famotidine)-antihistamines prevented epidermal hyperplasia in mice whose skin barrier was disrupted by acetone treatment (99). Similar to many intractable pruritic conditions, AEW-induced itch is thought to be histamine-independent; however, antihistamines may partly improve skin barrier function and epidermal hyperinnervation in dry skin conditions.

Emollients

In our previous study, immediate and delayed application of emollients, e.g. hydrophilic petrolatum and heparinoid cream, onto acetone-induced dry skin reduced the number of penetrated intraepidermal nerve fibres and NGF levels in the mouse skin (33). In addition, application of gel-like moisturizing lotion (TSG), which contained water, glycerin, urea, methyl paraben, propyl paraben, and agar, reduced the number of infiltrated intraepidermal nerve fibres, and induced higher expression of Sema3A in the epidermis of AEW-treated mice. This suggests that topical application of TSG attenuates itch induced by chronic dry skin through a mechanism involving the inhibition of epidermal hyperinnervation (100).

Phototherapy

UV-based therapies, such as PUVA and narrowband-ultraviolet B (NB-UVB), are efficacious in the treatment of chronic pruritus in patients with AD (101) and psoriasis (102). In our previous study, PUVA therapy reduces epidermal hyperinnervation in patients with AD (103). Furthermore, in the acetone induced-dry skin mice model, PUVA, PUVA+betamethasone valerate ointment (BV), NB-UVB, and excimer lamp treatments significantly reduced the intraepidermal nerve growth induced in this model. PUVA+BV and NB-UVB also normalized the abnormal expression of NGF and Sema3A in the epidermis (104).

In addition, we reported that excimer lamp irradiation of nerve fibres formed by cultured DRG neurones induced degenerative changes in these fibres. We demonstrated that attaching a cut-off excimer filter (COF) to the lamp, thus decreasing cytotoxic wavelengths, reduced hyperinnervation and the production of cyclobutane pyrimidine dimer, a DNA damage marker, in the acetone-induced dry skin mouse model. This suggests that the antipruritic effects of excimer lamp irradiation with COF are due to the induction of epidermal nerve degeneration and reduced DNA damage (105).

Opioids

Dry skin-related itch in animal models was suppressed by μ-opioid receptor antagonists (26) and κ-opioid receptor agonists (85). Clinically, μ-opioid receptor antagonists and κ-opioid receptor agonists were found to inhibit itch in dry skin-related cutaneous or systemic diseases (106, 107).

Table I. Therapies for dry skin-induced itch

Therapeutic method	Mechanisms of antipruritic effects
Topical treatment	
Emollients • hydrophilic petrolatum, heparinoid cream, gel-like moisturizing lotion	• Reduction in epidermal nerve density
Film dressings	• Reduction in epidermal nerve density • Prevention of mechanical stimulus
Phototherapy • Psoralen ultraviolet A • Narrowband ultraviolet B • Excimer lamp	• Normalization of expression levels of nerve elongation factors and nerve repulsion factors ⇨ Reduction in epidermal nerve density • Induction of cutaneous nerve degeneration
Systemic treatment	
Neurotropin	• Reduction in epidermal nerve density
μ-receptor antagonist & κ-opioid agonist	• μ-receptor antagonist and κ-opioid agonist in the central nervous system
Collagen tripeptide	• Reduction in epidermal nerve density, normalization of axon-guidance factors
Antioxidants	• Inhibition of oxidative stress in the periphery
Fish oil	• Improvement of skin barrier function
Adjunctive treatment	
Second generation of H1-antihistamines, e.g. bepotastine	• Reduction in nerve elongation factors and epidermal hyperplasia

Nalbuphine is a synthetic opioid analgesic, a mix of κ-opioid receptors agonist-μ-opioid receptors antagonist, clinically indicated for moderate to severe pain (108). A systematic review suggested that nalbuphine is a superior treatment option for opioid-induced pruritus because of its antagonistic effects and high affinity to the μ-opioid receptors (109).

Neurotropin

Neurotropin, a non-protein extract isolated from the inflamed skin of rabbits inoculated with vaccinia virus, was reported as an effective treatment for antihistamine-resistant pruritus in a multicentre, open-label, small sample study (110). We found that neurotropin inhibits NGF-induced neurite outgrowth of DRG neurones *in vitro* (111). Moreover, the intraepidermal nerve density in acetone-treated mice was reduced by the intraperitoneal administration of neurotropin, probably through the expression of Sema3A in the epidermis (112).

Phospholipids

Eicosapentaenoic acid (EPA, 20: 5n-3) and docosahexaenoic acid (DHA, 22: 6n-3) are representative omega 3 (n-3) polyunsaturated fatty acids (PUFA). Previous studies suggested that n-3 PUFA and related monohydroxy metabolites play an essential role in skin homoeostasis because their content within the skin regulates the skin barrier function (113, 114). Supplementation of fish oil, a well-known source of n-3 PUFA, in an acetone-induced dry skin rat model restored the skin barrier defects and improved scratching behaviour (115).

Dietary milk-derived phospholipids (MPLs) and milk-derived sphingomyelin have been reported to have beneficial effects on epidermal functions (116, 117), such as increased SC hydration in normal hairless HR-1 mice (116), and improved skin barrier function in the HR-AD mouse model (117). Recently, we reported that dietary MPLs attenuate the penetration of nerve fibres into the epidermis by reducing epidermal NGF levels and increasing the Sema3A level in a mouse model of acetone-induced dry skin. Thus, dietary MPLs may have beneficial effects for the prevention and/or alleviation of dry skin-induced itch by reducing intraepidermal nerve fibre density (118).

Collagen tripeptide

Collagen tripeptide is a highly purified, non-antigenic, low allergenic collagen fraction that is known to have many biological effects, such as enhancing hyaluronic acid production in human dermal fibroblasts *in vitro* and in murine skin *in vivo* (119). Oral administration of collagen tripeptide to acetone-induced dry skin model mice improves dry skin and normalizes axon-guidance factors in the epidermis, in addition to reducing pruritus (120).

Antioxidants

Oxidative stress has long been proposed to play a role in the pathogenesis of itch-related skin and systemic diseases, including AD, psoriasis, and chronic renal failure (121). Oxidants were demonstrated to induce histamine-independent itch via the activation of TRPA1 in mice (122). Zhou et al. (123) reported that antioxidants were systematically effective in reducing the scratching bouts of AEW-treated mice, possibly through the inhibition of oxidative stress in the periphery (affected skin) and suppression of p-ERK activation in the spinal cord. Thus, antioxidants, such as N-acetyl-L-cysteine and N-tert-butyl-a-phenylnitrone, may have therapeutic effects on dry skin-induced itch.

Film dressings

More recently, we reported that the application of film dressings, which are used for wound treatment to provide an appropriately moist environment and act as a barrier to contamination, alleviated the epidermal hyperinnervation and alloknesis in the AEW-induced dry skin model mice. Film dressings may reduce itch hypersensitivity of the skin (124). Consistent with this, we and others found that the level of NGF in the mouse epidermis significantly decreased by occlusion with emollients (33) or a vapour-impermeable membrane (24) after skin barrier disruption by tape-stripping or acetone. This suggests that skin moisturization prevents epidermal hyperinnervation induced by barrier disruption and mechanical stimuli to the skin.

CONCLUSION

This review presented recent knowledge regarding the mechanisms of dry skin-induced itch and its management. A decline in skin barrier function is thought to be the primary cause of dry skin-induced itch, as observed in the AEW model, the most well-known mouse model of dry skin. Many kinds of mediators, receptors, and channels are involved in itch signalling among the skin nervous system, skin cells, and central nervous systems, including Mrgprs, TLR, cytokines, and TRP channels. Continued studies are required to better understand these complex interactions and to develop antipruritic drugs to improve the quality of life of the patients.

ACKNOWLEDGEMENTS

This work was partly supported by Research Fellowship from the Japan Society for the Promotion of Science (18F18410), Strategic Research Foundation Grant-aided Project for Private Universities from MEXT (S1311011), and KAKENHI (18K07396).

The authors have no conflicts of interest to declare.

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Centenary theme section: ITCH AND PRURITIC DISORDERS

REVIEW ARTICLE

Non-dermatological Challenges of Chronic Itch

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Chronic itch occurs in many skin diseases, but also in a variety of systemic, neurological, and psychogenic/psychosomatic disorders, or is caused by drug intake. When several diseases or causes co-exist, chronic itch is categorized as "mixed origin". These patients present with unaltered skin or with chronic scratch lesions including chronic prurigo. Precise diagnostics are necessary to evaluate the underlying aetiology, to enable identification of the best treatment available, and to improve patients' quality of life. This is of particular relevance in elderly people in whom chronic itch is often of systemic or mixed origin. Xerosis cutis is a frequent cofactor contributing to chronic itch of non-dermatological origin. Treatment is frequently multimodal, considering age, comorbidities, current drug intake, quality and intensity of itch. With regard to the demographic situation of the population, characterized by increasing life expectancy and polypharmacy, itch of non-dermatological origin will represent an increasing medical challenge in the future.

Key words: cholestasis; chronic kidney disease; liver; pruritus; systemic disease; uraemic itch.

Accepted Oct 15, 2019; Published Jan 9, 2020

Acta Derm Venereol 2020; 100: adv00025.

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SIGNIFICANCE

Itch (medical term: pruritus) is an unpleasant sensation occurring in many skin diseases, but also in a variety of systemic, neurological, and psychogenic/psychosomatic disorders, or is caused by drug intake. These patients usually present with normal-looking skin or chronic scratch lesions of variable degree, including the clinical picture of chronic prurigo. This review focusses on the systemic causes of chronic itch, in particular liver disease, chronic renal failure, haematological disorders and adverse reactions of drug use. Furthermore, a diagnostic approach is presented, and effective, multimodal treatment options for the different systemic causes are summarized.

Pruritus or itch is an unpleasant sensation that can evoke scratching even in patients who do not currently have a skin disease. These patients usually present with normal-looking skin or chronic scratch lesions of variable degree, including the clinical picture of chronic prurigo (CPG; **Fig. 1**). For a long time it was assumed that itching and scratching must be associated with a skin disease. This may result from previous conditions, in which scratching aimed at extracting mites or other skin infestations. It took medical doctors and researchers some time to realize that chronic itch (CI), aside from dermatological disorders, can also be caused by a number of other diseases/origins. This comprises chronic kidney disease, a variety of hepatobiliary, haematological, and endocrine diseases, as well as so-called drug-induced itch (**Table I**). To date, it is now known to what extent drug intake and, in particular, polypharmacy contributes to CI. The underlying mechanisms of drugs causing pruritus as adverse events are only partially understood, ranging from mainly type-I and type-IV allergy to several other possible mechanisms (1, 2).

Advanced technical and medical care for chronically ill patients prolongs their life expectancy, albeit with an increased number of patients experiencing non-dermatological pruritus. Chronic pruritus further significantly reduces the quality of life in chronically ill patients. These observations represent an important incentive to increase itch research, with the aim of improving medical care for patients with CI with no underlying skin disease (3).

This review summarizes major non-dermatological aetiologies of CI. It also describes neuropathic itch secondary to brain and spinal cord injuries or peripheral nerve damage, as seen in brachioradial itch and notalgia

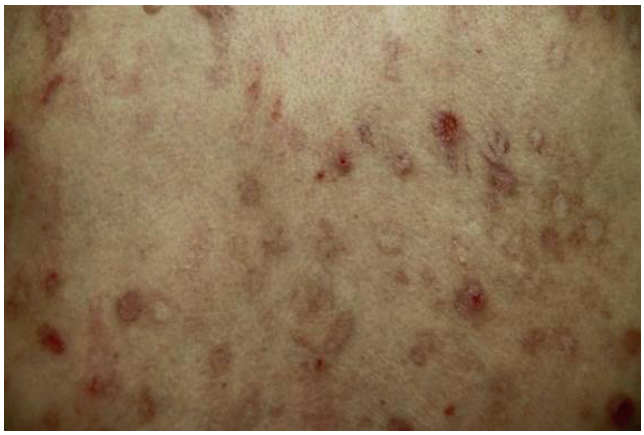

Fig. 1. Chronic prurigo on the upper leg in a patient with haemochromatosis.

Table I. Systemic diseases associated with chronic pruritus

Frequency	Organ system	Diseases
Common	Renal disorders	Chronic kidney failure
	Hepatobiliary disorders	Primary biliary cholangitis, primary / secondary sclerosing cholangitis, IgG4-related cholangitis, drug-induced toxic cholestasis, liver cirrhosis, benign or malignant obstructive cholestasis
	Haematopoietic diseases	Polycythaemia vera, essential thrombocytosis, Hodgkin and non-Hodgkin lymphoma, hypereosinophilic syndrome, mastocytosis
Rare	Endocrine diseases	Hyperthyreoidism, hypothyreoidism, hyperparathyreoidism, carcinoid syndrome, diabetes mellitus
	Malassimilation syndromes	Lactose intolerance, coeliac disease, anorexia nervosa, iron deficiency, vitamin B/D deficiency
	Infectious diseases	Chronic HBV-/ HCV-/ HIV-/ HSV-infection, H.p. infection, VZV-reactivation (post-herpetic), parasitoses
	Solid tumours	Carcinoma of the thyroid gland, ears, nose and throat, breast, lungs, stomach, pancreas, colon, prostate, uterus and sarcoma

paraesthetica. Finally, this review emphasizes that diagnosis and treatment is challenged in daily clinical routine by the fact that several origins frequently contribute to the occurrence of CI of non-dermatological origin.

DIAGNOSING NON-DERMATOLOGICAL ITCH

Identifying the underlying disease or itch-causing drug often represents a clinical challenge for the treating physician, but is a major need for the affected patient. A recent cohort analysis of more than 3,000 patients with CI illustrated that it occurs mainly in older patients and in those with many comorbidities (4). In contrast to previous doctrines, there is no correlation between generalized pruritus and a systemic disease as underlying cause. Patients with generalized pruritus suffer comparably often from systemic as from dermatological disorders (5). Thus, careful and detailed medical history taking, clinical examination and interdisciplinary, laboratory and radiological diagnostics are of significant importance (6). For this purpose a structured pruritus questionnaire has been developed (7).

Pruritus on primarily affected skin hints at a dermatological disease. In addition to clinical skin investigations, bacterial, mycological, allergic and autoimmune-serological analyses should be performed. Skin biopsy might further help to establish a clinical diagnosis (6). Pruritus on primarily unaffected skin is often caused by systemic, neurological or psychiatric/somatoform disorders or drug intake (8, 9). If medical history taking and clinical examination are inconclusive a step-wise approach for diagnosis is recommended, including various laboratory diagnostics (6).

It should be noted that CI may occur prior to manifestation and/or clinical diagnosis of the underlying disease. This so-called premonitory itch may present up to several years prior to diagnosis, as seen in polycythemia vera (10).

In rare cases malignancy is responsible for CI (Table I). Two large cohort studies of 8,744 and 12,813 patients with CI without primary skin changes, respectively, unravelled solely increased rates for haematological and bile duct malignancies (11, 12). In case of CI of unknown origin (PUO) the diagnostic approach should focus on these 2 cancer entities. If no underlying diagnosis could be established an annual repetitive work-up may be performed.

HEPATOBILIARY DISEASES

Chronic pruritus is commonly reported by many patients with hepatobiliary diseases, in particular those with cholestatic features. Prevalence of hepatic itch varies considerably between the different underlying diseases, with 100% as defining symptom in intrahepatic cholestasis of pregnancy, up to 70% in primary biliary cholangitis, primary and secondary sclerosing cholangitis, 15–45% in benign and malignant biliary disorders, and 5–15% in chronic viral hepatitis C infections (13). Affected patients often report the highest intensity on their limbs, in particular the palms of the hands and the soles of the feet, albeit CI may often be generalized (14). In female patients pruritus typically worsens premenstrually, during hormone replacement, and in the last trimester of pregnancy. Hepatic itch presents independently of the severity of cholestasis or liver function.

The pathogenesis of hepatic itch is not yet fully understood. In the past, bile salts, histamine, progesterone metabolites and endogenous opioids have been discussed as culprits, albeit a correlation with itch intensity could not be established (15). Interestingly, the semi-synthetic bile salt obeticholic acid, which has been licensed for the treatment of primary biliary cholangitis (PBC) dose-dependently worsens pruritus. Recent data have suggested that bilirubin and bile salts may mediate cholestatic itch via the mas-related G protein-coupled receptor X4 (MRGX4), albeit human data supporting this observation is lacking (16, 17). Cholestatic patients do not present with histamine-induced skin alternations, such as erythema, urticaria or wheals, and antihistamines are largely ineffective (18). Recently, lysophosphatidic acid (LPA) and its forming enzyme autotaxin (ATX) have been identified as potential mediators of hepatic itch (19). However, drugs inhibiting the ATX-LPA axis have not yet been investigated in hepatic itch to prove this pathophysiological concept.

Treatment should focus primarily on adequate therapy for the underlying hepatobiliary disease, which may

result in relief of hepatic itch. In this regard, itch due to obstruction of the extrahepatic biliary tree is often efficiently ameliorated by endoscopic biliary stenting, transcutaneous or nasobiliary drainage. In contrast, itch due to intrahepatic cholestasis may represent a significant clinical challenge.

Ursodeoxycholic acid (UDCA) is used as anticholestatic baseline treatment in many cholestatic disorders, such as PBC, primary sclerosing cholangitis, and intrahepatic cholestasis of pregnancy (20). UDCA is a safe and effective anti-pruritic therapy in women with intrahepatic cholestasis of pregnancy (21). However, in randomized placebo-controlled trials UDCA did not significantly improve itch intensity. Topical treatment with rehydrating and cooling (e.g. menthol-containing) ointments may mitigate hepatic itch if mild in intensity. If insufficient, cholestatic itch is recommended to be treated with cholestyramine (4–16 g/day) as first-line therapy, followed by rifampicin (150–600 mg/day), naltrexone (25–50 mg/day) and sertraline (75–100 mg/day) according to the current guidelines (13, 20) (**Table II**). Bezafibrate or fenofibrate may be used as alternative approaches (22, 23). Future therapies could be based on inhibitors of the ileal bile acid transporter (IBAT) in the terminal ileum, which are currently investigated in placebo-controlled trials (24). In refractory cases invasive procedures, such as plasmapheresis, albumin dialysis (e.g. MARS®, Prometheus®), transcutaneous or nasobiliary drainage, may be performed. After liver transplantation most patients experience relief of CI.

RENAL DISEASES

Itch in renal disease, also referred to uraemic pruritus (UP), affects patients with advanced stages of chronic kidney disease (CKD), mostly those on dialysis. Epidemiological studies indicate that up to 50% of patients on haemodialysis have CKD-associated pruritus (CKD-aP) depending on the investigated country (25, 26). The underlying pathological mechanism remains elusive. Increased levels of uraemic toxins and parathormone, as well as xerosis and subclinical skin inflammation have been suggested to play a role in the pathophysiology. Furthermore, the endogenous opioid system may play a role, possibly through upregulation of μ-opioid and/or downregulation of κ-opioid activity (27). This may, at least partially, explain the efficacy of μ-opioid antagonists and κ-opioid agonists in the treatment of CKDaP. Recent experimental data suggested central neuropathic and neuroplastic changes in patients with CKD-aP, which may explain the good response to calcium-channel-blockers in these patients (28).

CKD-aP greatly impacts the quality of life of affected patients (25). Retrospective analyses identified risk factors for UP in dialysis patients even before dialysis has begun. These include male sex and certain comorbidities, such as congestive heart failure, chronic hepatitis C virus infection, neurological diseases, depression and higher serum calcium/phosphorus levels (29). When uraemic itch occurs, skin appearance is normal in most patients, except for common changes in skin colour and a frequently observed xerosis. Scratch lesions, such as excoriations with or without impetigo, may be observed in some patients and, in some cases, chronic prurigo (Fig. 1). Medical therapy for CKD-aP remains a clinical challenge. Emollients for skin care and hydration are essential. In early stages gabapentin and pregabalin, although not licensed for this indication, may be helpful (30). Ultraviolet phototherapy may ameliorate itch in uraemic patients (31). Detailed information about drugs and dosages is given in **Table III**.

NEUROPATHIC DISEASES

Neuropathic itch is caused by neuronal or glial damage to peripheral neurones, either localized (e.g. nerve compression) or generalized (e.g. nerve degeneration). Damage to the central nervous system, such as by tumours of the brain or in the spinal cord, rarely causes pruritus.

Several entities can be discerned. Patients with notalgia paraesthetica (NP) perceive itch in the subscapular region, associated with a slightly painful or burning character. The pathophysiology of this entity is unclear, but NP is presumed to be a mononeuritic disease affecting thoracic nerve fibres. Patients with brachioradial itch have localized itch within the dorsolateral parts of

Table II. Therapeutic recommendations for hepatic pruritus

Approach	Drug[a]	Dose
1st line	Colestyramine	4–16 g/day (po)
2nd line	Rifampicin	150–600 mg/day (po)
3rd line	Bezafibrate	400 mg/day (po)
4th line	Naltrexone	25–50 mg/day (po)
5th line	Sertraline	100 mg/day (po)
6th line	Experimental approaches, e.g.	
	Gabapentin	300–3,600 mg/day
	UVB light	1–2×/week

[a]Solely colestyramine is licensed for the treatment of hepatic pruritus; all other drugs are off-label use.
po: per os.

Table III. Therapeutic recommendations for chronic kidney disease associated pruritus

Approach	Drug[a]	Dose
1st line	Gabapentin	After dialysis: 100 mg 3×/week or 300 mg 3×/week or 400 mg 2×/week (po)
2nd line	Pregabalin	75 mg 2×/week–75 mg/day (po)
3rd line	UVB light	1–3×/week
4th line	Capsaicin	3–5×/day (topical)
5th line	Experimental approaches, e.g.	2.5–5 μg/day (po) or 5 μg (iv) after dialysis
	Nalfurafine	2×/day (topical)
	Tacrolimus	500 mg 3×/day
	Curcuma	

[a]All drugs are off-label-use.
po: per os; iv: intravenous.

the forearms and, less frequently, around the shoulders. As in NP, patients report mixed itch and pain sensations. Cervical cord compression or radiculopathies have been observed in these patients (32).

The small fibre neuropathy is a systemic neuropathy of peripheral nerves accompanied by severe pruritus in some patients. This sensory disorder leads to a variety of symptoms, including pain, tingling, numbness, deranged thermoregulation and signs of malfunction of the autonomic nervous system, such as gastrointestinal dysmotility and orthostatic hypotension. The diagnosis is difficult to establish, requiring thermoregulatory sweat testing and skin biopsy with reduced small fibre density (33).

Apart from these entities, neuropathic itch may occur in the course of herpes zoster infections as so-called post-herpetic itch, polyneuropathies and scars induced by trauma or burns.

Treatment of neuropathic itch is difficult. Local treatment with capsaicin or systemic treatment with calcium-channel-blockers, such as gabapentin or pregabalin, may alleviate pruritus (3, 34).

ENDOCRINE DISEASES

CI may occur in association with several endocrine diseases. Whether patients with diabetes mellitus are more frequently afflicted than those without remains a matter of debate. In one study investigating almost 400 patients with diabetes 27.5% reported on generalized itch (35). In another study truncal itch was most prominent in diabetic patients. Of 2,656 patients with diabetes mellitus, 11.3% reported itch located on the trunk, whereas this symptom was present in only 2.9% of 499 age-matched patients without diabetes (36). Further endocrine diseases associated with the occurrence of CI include Grave's disease and multiple endocrine neoplasia type II.

HAEMATOLOGICAL DISEASES INCLUDING AQUAGENIC ITCH

Itching is commonly reported in patients with haematological diseases. Aquagenic pruritus is a typical feature in many of these patients, with a pungent itchy character after contact of the skin with water. Polycythaemia vera is a rare myeloproliferative disease with a clonal dysfunction of pluripotent hematopoietic cells. Affected patients report itch in 30–65% of cases. Aquagenic itch is most commonly observed in patients with a homozygous JAK2 617V mutation (37). Inhibitors of the JAK-STAT pathway, such as ruxolitinib, strongly attenuated pruritus in addition to improving the underlying disease (38, 39). Similarly, patients with essential thrombocytosis and primary myelofibrosis often report aquagenic itch.

Hodgkin's disease belongs to the class of B-cell lymphoma. CI on primarily unaffected skin is reported by 15–50% of patients (40). Severe itch may precede the outbreak of the disease by many years. CI worsens at night, often starts at the lower limbs, and may generalize. After successful anti-tumour therapy, CI may also indicate a relapse of Hodgkin's disease. In patients with non-Hodgkin lymphoma pruritus may affect up to 30% of patients. In leukaemia patients CI is more commonly observed in lymphatic compared with myelocytic leukaemia and in chronic compared with acute forms. Recommended therapy consists of the calcium channel blockers gabapentin (300–2,400 mg/day) and pregabalin (75–600 mg/day), acetylsalicylic acid (300 mg/day) and mirtazapine (7.5–30 mg/day) (**Table IV**) (6).

PARANEOPLASTIC DISEASES AND CANCER

In daily clinical practice the term "paraneoplastic itch" (PI) is used to describe itch in patients with cancer. Itch caused by haematological diseases is described above. In general, PI is considered as a rare disorder. It occurs most commonly in lymphoreticular malignancies, while being rarely reported in patients with solid tumours. Its true frequency remains unknown, as epidemiological data is limited. This may mainly be due to other symptoms receiving more attention and being regarded as more important in cancer patients with paraneoplastic diseases. According to the literature and our own clinical studies CI further impairs quality of life in patients with malignant diseases. In 2012, an interdisciplinary study interest group (SIG) of physicians and researchers was founded, with the aim of generating a clear definition of PI (40).

Previously, several terms have been used to describe the different types of paraneoplastic itch. The SIG states that the term paraneoplastic itch should be used in case itching occurs as a systemic, but not local, reaction in the presence of a solid tumour or haematological malignancy. This term excludes itch induced either by the local invasive growth of cancer cells or by anti-tumour therapy. PI usually disappears with remission of the tumour and may return with its relapse (40).

Diagnosing PI represents a clinical challenge, as it remains difficult to exclude other aetiologies and reasons for CI, such as paraneoplastic skin diseases, skin or non-dermatological diseases occurring in chronically ill patients, as well as adverse drug reactions. The me-

Table IV. Therapeutic recommendations for pruritus of hematopoietic origin

Approach	Drug[a]	Dose
1st line	Gabapentin	300–2,400 mg/day (po)
2nd line	Pregabalin	75–600 mg/day (po)
3rd line	Acetylsalicylic acid	300 mg/day (po)
4th line	Mirtazapine	7.5–30 mg/day (po)
5th line	Experimental approaches, e.g.	
	Aprepitant	125-80–80 mg/week or 80 mg/day
	Naltrexone	50–150 mg/day
	Nalfuraphine	2.5–5 µg/day (po)

[a]All drugs are off-label use.
po: per os.

chanisms of PI are still not understood.

Baseline therapy of PI comprises the treatment of the underlying malignancy. In many cases, cytoreductive therapies are effective. There are no randomized controlled trials (RCTs) for the treatment of PI, which may be explained largely by the rarity and diversity of PI. Topical therapies, including cooling agents, may lead to symptomatic relief. H1-antihistamines are mostly ineffective. PI in lymphoma can improve with oral prednisone (see above) acting via different mechanisms, and longer systemic treatment with prednisone may be considered in PI (3). Serotonin reuptake inhibitors (SSRI), such as paroxetine, up to 20 mg daily, calcium alpha (2)-γ-channel blockers, such as gabapentin and pregabalin, can be used for treating PI as well as thalidomide 50–200 mg daily. Opioid receptor antagonist, such as naloxone (0.8–2 mg i.v./day), naltrexone (50–100 mg/day orally) or neurokinin (NK)-1-receptor-antagonists, e.g. aprepitant, have been used for itch, for example in T-cell lymphoma, solid tumours and itch-related biological cancer treatment (40). It should be considered that patients with cancer frequently receive analgetics that may induce CI as a side-effect.

DRUG-INDUCED ITCH

Itch associated with systemically or locally applied drugs is a common phenomenon (41). Almost every drug may cause localized or generalized itch. Drug-induced itch may emerge as a hypersensitivity reaction towards the drug or, as in many cases, due to another, mostly unknown, pathophysiological process. There is evidence that, with some drugs, the MRGX2-receptor is activated, resulting in a different release of pruritogenic compounds than in IgE-mediated hypersensitivity reactions (42). Identifying the responsible compound remains, for many cases, a clinical challenge, as many patients are taking multiple drugs and there might be a considerable delay between the start of drug intake and the development of itch.

Chloroquine, which is mainly used as an antimalarial drug, can induce itch, probably by activating the MrgprX1-receptor. Interestingly, chloroquine provokes itch mainly in black Africans, while Caucasians are less commonly affected potentially by a strong binding capacity to melanin with significantly higher skin concentrations in Africans (43).

Itching provoked by hydroxylethyl starch (HES) infusion is thought to be caused by HES depositions in peripheral nerves (44). Treatment is cumbersome and mostly frustrating (45).

Opioidergic drugs may cause strong itch, especially when applied epidurally or intrathecally (46) which may be mediated by activation of the isoform D of the μ-opioid receptor (47). It can be treated effectively by μ-receptor-antagonists, such as naloxone.

Along with the expansive development and use of targeted tumour therapies, numerous reports have emerged about therapy-associated chronic pruritus (48–52). The neurokinin-1-antagonist aprepitant seems to have antipruritic potential in such cases (53).

The authors have no conflicts of interest to declare.

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Centenary theme section: ITCH AND PRURITIC DISORDERS

REVIEW ARTICLE

Itch and Psyche: Bilateral Associations

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Beginning from embryological development, skin and psyche are closely related to physiological state regardless of age. Altering the homeostasis of one of these components impacts on the other, thereby substantiating that the relationship between itch and psyche is bilateral. Itch has a complex pathogenesis, which involves the peripheral and central nervous systems, as well as various inflammatory mediators. This paper reviews key aspects of itch pathogenesis, relevant associations with stress, the contagiousness of itch, psychological and psychiatric considerations related to itch, and the burden of itch with respect to impairment of health-related quality of life (HRQoL) and stigmatization. Despite the fact that itch–psyche associations still pose many questions, current knowledge supports the role of a holistic, interdisciplinary approach to these patients in order to improve their well-being.

Key words: itch, psyche, pathogenesis, stress, psychiatry, burden of disease.

Accepted Oct 15, 2019; Published Jan 9, 2020

Acta Derm Venereol 2020; 100: adv00026.

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SIGNIFICANCE

The relationship between itch and psyche is complex and bilateral. Increasing interest in itch and its associations with psyche is indicated by the abundance of experimental and clinical articles published in this field. This review covers the pathogenesis of itch, associations with stress, the contagiousness of itch, psychological and psychiatric aspects related to itch, and the burden of itch with respect to impairment of health-related quality of life and stigmatization.

Beginning with human embryogenesis, skin and brain are organs that are closely connected due to their ectodermal origins (1). These associations continue to unfold after birth, and constitute a foundation for the normal psychosocial development of an individual. According to the *moi-peau* concept (2) (**Fig. 1**) (as extensively reviewed by Dutray & Misery (1)), skin possesses a wide psychological meaning, reflecting various needs of the psyche. Firstly, skin has the function of a "bag" or "container", as it embraces the positive stimuli experienced by a baby during nursing and being cared for. Secondly, skin is an "interface" with the outside world, which serves as a protective barrier against external aggression. Lastly, skin may be considered as a specific "place" or "means of communication" in order to establish relationships, and as a "surface" on which others may leave their trace. It seems substantiated that chronic skin diseases with their rich symptomatology, especially acquired during early childhood, ensue in altering both physical and psychological homeostasis of an affected individual. The impact is always reciprocal: the psyche may predispose to cutaneous complaints (e.g. itch, chronic scratch lesions), whereas dermatological signs and symptoms "scar" the psyche.

Itch is defined as an unpleasant sensation leading to scratching, further classified as acute or chronic (lasting less or more than 6 weeks, respectively) (3). Chronic itch (CI) is a feature of various dermatoses, although it may also stem from systemic, neurological, or psychiatric disorders. Occasionally, the diagnosis of pruritus of unknown origin (PUO) is established. The presence of CI is associated with significant morbidity, mortality, reduction in quality of life (QoL), feelings of stigmatization, stress, impairment of mood, lack of concentration,

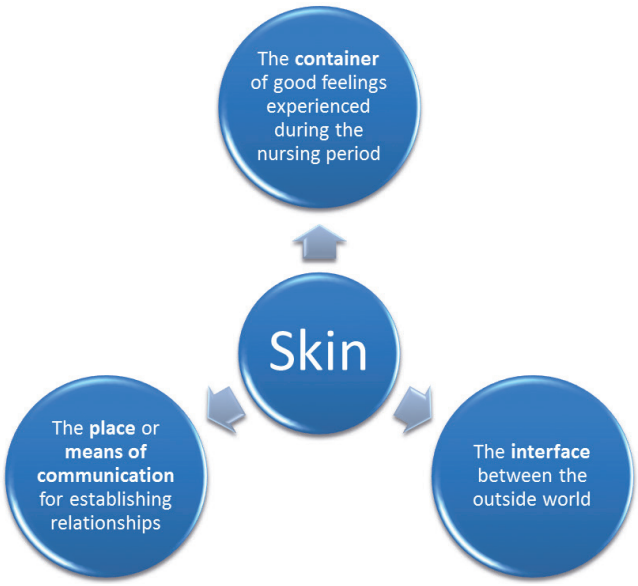

Fig. 1. The moi-peau concept (The Ego-Skin concept) (according to (1)).

reduced sexual desire and appetite, as well as inability to express emotions (alexithymia) (4–9). On the other hand, clinicians are aware that various psychological and psychiatric alterations may contribute to the occurrence or exacerbation of itch. One of the models that aims to explain CI mechanisms in the course of cutaneous disorders is the Biopsychosocial Model, proposed by Verhoeven et al. (10). The occurrence of itch is a result of various factors: internal (associated with personality), external (e.g. stressful environmental stimuli), mediating (e.g. cognitive, behavioural and social) as well as physiological. Tey et al. (11) have clinically classified the itch–psyche interactions as pruritic disorders with psychiatric sequelae (I); pruritic disorders aggravated by psychosocial factors (II); and psychogenic disorders causing itch (III). These complex bilateral associations between itch and psyche support the need for multidisciplinary approach to itch and the associated conditions in the clinical setting (12–14).

This review covers the pathogenesis of itch, cerebral regions associated with pathogenesis of itch, the interplay between itch and stress, the contagiousness of itch, psychological and psychiatric aspects associated itch, and the burden of itch with respect to impairment of QoL and stigmatization.

ITCH PATHOGENESIS

There is growing data concerning the pathogenesis of itch, as this topic is gaining increased attention in the medical literature. From the historical point of view, itch has been perceived as a subtype of pain (15), and it is thought that the symptom might have developed as an evolutionary defence mechanism against various potentially dangerous stimuli, such as parasites, insects, sharp objects, irritants, and allergens (16). However, itch is currently deemed a separate entity from pain. The role of peripheral (PNS) and central nervous system (CNS) is crucial in eliciting CP, starting from free nerve endings in the epidermis. The statement "it is the brain that itches, not the skin" (16) remains valid, as different cortical areas are included in processing itch intensity, location, associated unpleasant feelings, generating the need to scratch, and preparing and executing scratch behaviour (17–20). In a positron emission tomography (PET) study among human participants histamine injection resulted in major activation in the left primary sensory cortex, as well as the primary motor cortex, supplementary motor area and premotor cortex (17). Another study utilizing PET and regional cerebral blood flow (rCBF) revealed that a skin prick test with histamine resulted in activation of the contralateral somatosensory cortex; in addition, both ipsilateral and contralateral motor areas were involved. Itch unpleasantness was associated with the activation of contralateral sensorimotor cortex, prefrontal cortex, posterior insula and ipsilateral supplementary motor area (18). A functional magnetic resonance imaging (fMRI) study demonstrated itching and pain both activated the anterior cingulate cortex, the anterior insula, the basal ganglia and pre-supplementary motor area (20). However, the activity in posterior cingulate cortex and the posterior insula was more prominent in itching than in pain. Moreover, it was proportional to itching sensation. In an experiment with cowhage-induced itch, as demonstrated by fMRI, itching was associated with increased activity in supplementary motor area, premotor cortex, primary motor cortex, and midcingulate cortex (21). The role of the caudate nucleus was also substantiated, as this region is involved in the reward system. Papoiu et al. (22) demonstrated that active scratching was accompanied by higher pleasure and deactivation of anterior cingulate cortex and insula compared with passive scratching. In addition, the activation of ventral tegmentum area (VTA) of the midbrain, as well as deactivation of periaqueductal grey matter (PAG), are associated with the itch-scratch reward system.

ITCH AND STRESS

Stress is a concept frequently mentioned nowadays, yet despite its widespread appearance in various situations it may be described in different ways, e.g. as "the non-specific response of the body to any demand made upon it" (23) or "a relationship with the environment that the person appraises as significant for his or her well-being and in which the demands tax or exceed available coping resources" (24). The bilateral associations of itch and psyche are perfectly reflected by the interplay of itch and stress. Similarly to the vicious itch-scratch cycle, chronic pruritic conditions (e.g. psoriasis, urticaria, atopic dermatitis) generate huge stress levels, which may subsequently perpetuate exacerbation of the disease. Aberrant parasympathetic response may possibly link chronic stress and itch (25), while stress-induced itch is associated with activation of the hippocampus and subcortical regions (corpus callosum and putamen) (26). The itch-stress association does, in fact, pose a certain therapeutic implication towards first-generation H_1-antihistamines and GABA-ergics (gabapentin and pregabalin) (11, 26).

In a large population-based study among Norwegian adolescents mental distress (assessed by the Hopkins Symptom Checklist-10) was correlated with the presence of itch (27). Moreover, the severity of itch correlated with the level of mental distress, regardless of sex. Subsequently, another report linked the presence of itch with low self-efficacy in individuals under higher stress (28). The perceived self-efficacy is a concept of people's beliefs that they can exert control over their motivation, behaviour and social environment (29). Individuals lacking the sense of self-efficacy are not able to manage

demanding situations effectively, despite knowing what to do and possessing the necessary skills. The increase of self-efficacy in psychological interventions may exercise control over stressors due to its immunomodulating properties (30). Recently, Schut et al. (31) employed cognitive behavioural stress management programmes in patients with atopic dermatitis (AD). The study revealed that individuals subjected to these interventions demonstrated diminished cortisol awakening response, while maintaining calm and presenting lower salivary cortisol levels under acute stress. Thereby, various psychological interventions (reviewed in detail by Schut et al. (32)) should be considered as an adjunctive therapy in patients with itch of various origins. The associations between stress and itch in patients with AD constitute a problem of particular complexity and importance and involve the components of the so-called neuro-endocrino-immunocutaneous system (NEICS) and the hypothalamo-pituitary-adrenal (HPA axis). The relevant aspects of this issue are covered in detail elsewhere (33–38), although there is evidence that acute or chronic stress have different impacts on the HPA axis (39).

Regarding patients with psoriasis, our group has demonstrated that patients under heavy or extremely heavy stress more commonly suffer from itch, with the severity of stress and intensity of itch being positively correlated (40). Similar results were observed by Amatya et al. (7). Another study revealed that the self-reported stress reactivity was moderately correlated with the degree of itching (41). Stress-related exacerbation of itch in psoriatic subjects may also be associated with higher expression of substance P receptor, tropomyosin receptor kinase A and calcitonin gene-related peptide receptor in keratinocytes of psoriatic plaques (42). Other reports mentioned the role of stress in pruritic disorders, such as chronic urticaria (43, 44), acne vulgaris (45, 46), hand dermatoses (47) and post-burn itch (48). Recent research reported that patients with generalized CI reported more tension and subjective stress than healthy controls, with the expectation of the acute stress test (49). Notably, "variations of intensity associated with stress" (50) constitute an optional criterion for the diagnosis of functional itch disorder (FID; psychogenic itch).

Itch-stress associations are complex, yet they serve as the foundation of psychological interventions aimed at enhancing coping abilities of the affected individual, e.g. cognitive restructuring (32). A Dutch study reported that a nursing programme "Coping with itch" successfully targeted catastrophizing and helpless itch-related coping (51). Subsequently, it was proven by Evers et al. (52) that patients with AD may benefit from multidisciplinary itch-coping group training. The programme focused on skin care, itch-triggering factors, stress management, long-term goals, relapse prevention, habit reversal and scratch-triggering factors. The training ensued in reducing itch-scratch behaviour, improving skin status, decreasing the need for dermatological visits and treatment. Coping with itch was improved, as the itch-related self-efficacy increased, with decline in catastrophizing. These benefits were regarded both as short-term and long-term.

NOCEBO EFFECT: IS ITCH A CONTAGIOUS PHENOMENON?

The nocebo effect is the negative counterpart of the placebo effect (53). In essence, an individual receives an inert substance or undergoes a neutral procedure, which is intended to induce negative expectations. Interestingly, outbreaks of itch among schoolchildren attributed to epidemic hysteria have been described in the literature (54, 55). Acknowledging the relevant role of psyche in eliciting itch, the nocebo-related concept of "itch contagion" or "contagious itch" was conceived and investigated in different studies. Based on the experience that lectures about pruritic dermatoses induce itching in the listeners, Niemeier et al. (56) proved that a public lecture entitled "Itching – what's behind it?" caused the participants to feel itch and exert scratching behaviour. Subsequent research revealed that patients with AD, when compared with healthy controls, were more prone to scratch themselves after being subjected to histamine or saline injection, followed by watching a short video of people scratching (57). Holle et al. (58) reported that itch contagion is a normative response experienced by most people and its degree may be associated with neuroticism as a personality trait (the impact of personality traits on itch is reviewed below). No association between itch contagion and sex or empathy was established in this study. The fMRI examination revealed that itch intensity correlated with the activation of the left Brodmann area (BA) 44, primary somatosensory cortex and BA6. Lloyd et al. (59) revealed that solitary visual stimulants provoke itch in healthy individuals. Another study demonstrated that the combination of conditioning and verbal suggestion may result in relevant nocebo and placebo effects on itch in healthy individuals (60). It was subsequently proved that nocebo effects regarding the itch sensation may be minimized or reversed via conditioning with verbal suggestion (61). Recently, increased contagiousness of itch in children with autism spectrum disorder was demonstrated (62).

PSYCHOLOGY OF ITCH

The personality of an individual may be defined as a characteristic pattern of behaviours considered in the broad sense, also including thoughts, feelings and motivation (63). One of the most popular models used for the description of personality structure is The Big Five model, which encompasses 5 bipolar dimensions (extraversion, agreeableness, conscientiousness, neuroticism and open-

ness to experience) (64). The impact of personality traits on itch sensation was explored in several reports and supports the role of psychological interventions in aiding affected individuals. In a Swedish study (65) the persistence of post-burn itch was associated with lack of assertiveness, as assessed by the Swedish Universities Scales of Personality (SSP). Moreover, the Coping with Burns Questionnaire (CBQ) scores revealed that itch was more persistent among individuals who sought more instrumental and less emotional support. Patients with prurigo nodularis (PN) exhibited higher neuroticism and lower extraversion traits than controls when examined via the revised Eysenck Personality Questionnaire (EPQ-R) (66). Notably, among subjects with psoriasis, severe itch was significantly associated with somatic trait anxiety, embitterment, mistrust, and physical trait aggression (assessed via SSP) (67). Conversely, Janowski et al. (68) found no differences in basic personality traits regarding psoriatic patients with various frequency of itch (assessed via NEO-Five Factor Inventory; NEO-FFI). However, resignation and self-blame were more common coping strategies among patients experiencing itch more frequently (assessed via the Ways of Coping Questionnaire; WCQ). In a German study, individuals with AD and healthy controls were exposed to videos featuring crawling insects and skin disorders (69). Compared with healthy controls, agreeableness (NEO-FFI) and public self-consciousness (the Self-Consciousness Scale; SCS) were significant predictors of scratching behaviour in subjects with AD. These findings were subsequently replicated (70). Kini et al. (71) investigated patients with CI (recruited from the National Eczema Association and US Veterans Health Administration National Patient Care Database). The authors observed that the lethargic personality style (defined as low extraversion and conscientiousness) (NEO-FFI) was associated with greater mean total ItchyQoL score. On the other hand, higher ItchyQol symptom score was observed both in overcontrolled (high neuroticism and conscientiousness) and undercontrolled (high neuroticism and low conscientiousness) patients.

Another concept that has evolved as a potential paradigm for understanding the influence of emotions and personality on physical illness and health is alexithymia (72). In general, this personality construct defines the inability to identify and verbalize emotions. Our group has investigated alexithymia using the Bermond-Vorst Alexithymia Questionnaire (BVALQ-40) among patients with end-stage renal disease on maintenance haemodialysis (9). It was observed that patients with uraemic itch exhibited lower scores on the fantasizing subscale score. Another group assessed alexithymia via the Toronto Alexithymia Scale (TAS) among individuals with chronic urticaria (73).

PSYCHIATRIC PERSPECTIVE ON ITCH

Taking into account the widespread relationship between itch and psyche, one cannot omit the obvious psychiatric background of itch in certain cases, whereas the presence of itch may frequently ensue in a wide spectrum of psychiatric comorbidities. In a study by Mazeh et al. (74) among a cohort of patients ($n=111$) hospitalized in the psychiatric ward, CI affected 32%. Of those, 45% stated that stress was one of the major aggravating factors of itch. Similarly, our group enrolled inpatients ($n=40$) who were hospitalized with depression (75). Itching was experienced by 17.5% of patients during the depressive episode. Notably, itching disappeared in all affected individuals after the depressive symptoms markedly decreased, whereas recurrent itching was associated with recurrent depressive episodes.

A different approach was presented by Schneider et al. (76), who examined 109 dermatology inpatients with itch and observed that in over 70% of them 1–6 psychiatric diagnoses could be established. In over 60% of patients psychotherapeutic or psychiatric treatment was advised. Ferm et al. (77) evaluated the medical records of 139 patients with CI, among whom 31 (22.3%) had an underlying psychiatric disorder. A recent study among 560 patients with CI who were referred by the dermatologist for a psychosomatic consultation demonstrated that 77.1% had at least one psychosomatic/psychiatric comorbidity (78). The most common comorbidities encompassed psychological/psychosomatic cofactors in itch (F54 according to ICD-10) (74.5%), depression (F32–F34) (30.7%), adjustment disorder (F43.2) (17.8%), dissociative/somatoform disorder/hypochondria (F44–F45) (11.2%), anxiety/compulsive disorder (F40–F42) (6.6%) and others (17%). Notably, patients with the psychiatric/psychosomatic comorbidities presented higher intensity of itch, longer duration and coexistence of chronic scratch lesions. Dermatologists and psychiatrists often utilize psychoactive drugs in order to alleviate itch of different origins; however, itch may also be induced by the use of selective serotonin reuptake inhibitors or neuroleptics (79, 80).

There are also reports in the literature concerning "classic" pruritic disorders, which were also evaluated with regard to psychiatric comorbidities. Gupta et al. (81) linked alleviation of itch in psoriasis with changes in depression scores. Subsequently, Conrad et al. (43) executed a complex study of 41 patients with chronic idiopathic urticaria (CIU) and 44 patients with psoriasis. The investigators assessed the relationship between itch and several domains, including emotional distress and anger (assessed via the Symptom Checklist 90-R (SCL-90-R) and State Trait Anger eXpression Inventory (STAXI) tools, respectively). In patients with chronic

idiopathic urticaria (CIU) anger was a predictor of itch severity, whereas depression seemed to influence itch severity in patients with psoriasis. Regarding patients with CIU, the authors discussed possible pathway involving anger and stress, which stimulate corticotrophin-releasing hormone, subsequently leading to mast cell activation and degranulation of mediators, such as histamine. These aspects might, at least, partially account for the presence of itch accompanying urticarial wheals. In a study by Dazzi et al. (66) 20 subjects with PM were compared with healthy controls with regards to scores in EPQ-R, the Beck Depression Inventory second edition (BDI-II) and the State Trait Anxiety Inventory – form Y (STAI). It was observed that patients with PN exhibited higher scores for the T-anxiety scale (STAI – form y-2; describing how subject feel in general), depression and neuroticism, while lower than the controls concerning extraversion. Subsequently, PN was linked to depression (adjusted odds ratio (OR) 2.82; $p<0.001$), the use of antidepressants (adjusted OR 2,6; $p<0.001$), anxiety (adjusted OR 2.06; $p<0.05$) and the use of anxiolytics (adjusted OR 4.64; $p<0.001$) compared with healthy controls (82). Similar relations were reported in a recent study concerning PN burden with respect to depression and anxiety. In addition, patients with PN more often had suicidal ideation (83). In a previously mentioned study by Remröd et al. (67) ($n=101$) subjects with plaque psoriasis with severe itch presented higher scores for depression and anxiety (as assessed via STAI and BDI-II). A study among 27 patients with AD reported that there is a connection between high scores on the depression scale (Hospital Anxiety and Depression Scale; HADS-D) and higher increase in itch intensity compared with controls (69).

Interestingly, a study by Weisshaar et al. (84) recounted that affective reactions, such as depression and aggression, were more common in German individuals with CI due to dermatological diseases than those with CI associated with underlying systemic disorders ($p=0.04$ and $p=0.03$, respectively). A comparison between German and Ugandan patients with CI was also performed in terms of emotional reactions, revealing that German patients tend to be significantly more aggressive ($p<0.0001$) and more often do not have any drive ($p<0.0001$). In a cohort of patients with end-stage renal disease, the severity of CI (4IIQ) was correlated with depressive symptoms (assessed by BDI) (85). The complicated itch and psyche interplay is elegantly embraced in functional itch disorder (FID; also termed psychogenic itch). This entity was defined as "an itch disorder, where itch is at the centre of the symptomatology, and where psychological factors play an evident role in the triggering intensity, aggravation or persistence of the pruritus" (50, 86) and can be diagnosed according to several criteria. The 3 compulsory criteria encompass: (*i*) localized or generalized itch without primary skin lesions, (*ii*) chronic pruritus of at least 6 weeks' duration, and (*iii*) no somatic cause. In addition, at least 3 out of the following 7 additional criteria have to be found: (*i*) a chronological relationship of pruritus with 1 or several life events that could have psychological repercussions, (*ii*) variations in intensity associated with stress, (*iii*) nocturnal variations, (*iv*) predominance during rest or inaction, (*v*) associated psychological disorder, (*vi*) pruritus that could be improved by psychotropic drugs, and (*vii*) pruritus that could be improved by psychotherapies. Regarding the International Forum for the Study of Itch (IFSI) classification according to its aetiology, FID is associated with the 4th category (psychogenic/psychosomatic origin) (3). Unfortunately, the detailed aspects associated with psyche and well-being of patients with FID in particular have rarely been investigated (87, 88).

Finally, considerations concerning psychiatric associations with itch are nowhere near complete without mentioning the risk of suicide. In a study by Halvorsen et al. (89), 3,682 adolescents responded to a special questionnaire focusing on itch, pain and suicidal ideation. Severe itch was strongly associated with suicidal ideation (OR 3.0). Among the individuals reporting itch, suicidal ideation was reported by 21.1%, in contrast to 8.4% among subjects denying itching. In a large meta-analysis, patients with AD (in which itch is generally considered a constant feature) were 44% more likely to have suicidal ideation and 36% more likely to die by suicide that those without the disease (90).

HEALTH-RELATED QUALITY OF LIFE IMPAIRMENT: THE BURDEN OF SCRATCHING

QoL may be defined as a measure of the goodness of several life aspects, e.g. reactions to life occurrences, disposition, sense of life fulfilment and satisfaction, as well as satisfaction with work and personal relationships (91). Not infrequently, this term is confused with HRQoL, which has multiple definitions. One of the most relevant encompasses "how well a person functions in their life and his or her perceived well-being in physical, mental and social domains of health" (92). The impairment in HRQoL in dermatological patients can be measured with multiple tools, e.g. the Dermatology Life Quality Index (DLQI) (93) or Skindex (94). Impairment in HRQoL stems from various disease-related signs and symptoms, with a special emphasis on CI. Recently, an itch-specific instrument (ItchyQoL) for assessing HRQoL has been validated in several languages (95).

There is recent literature focusing on itch and HRQoL, both in cutaneous and primarily extracutaneous disorders. These issues were studied in detail in subjects with psoriasis. According to Yosipovitch et al. (96), itch bothered 84 (84%) patients, among whom 35% became more agitated, 24% became depressed, 30% had trouble concentrating, and 23% changed their eating habits.

Remarkably, two-thirds of the patients were bothered by difficulties falling asleep and night awakenings due to itch. Moreover, 40% of pruritic subjects reported decreased or non-existent sexual desire, whereas 35% reported decreased or non-existent sexual functions. Subsequently, our group found that HRQoL, assessed via the DLQI, was significantly decreased in patients with itch (6). In addition, the DLQI score correlated with itch intensity assessed via the 4-Item Itch Questionnaire (4IIQ) and visual analogue scale (VAS). The impact of itch on HRQoL in AD is well-documented (35, 97); it is imperative to acknowledge its detrimental influence on children's and their parents' sleep (98). In our study among patients with hidradenitis suppurativa (HS), itch was reported by 62.1% of patients (99). Its presence did not correlate with DLQI scores, whereas its intensity did. Other researchers proved impaired HRQoL in cutaneous T-cell lymphoma (100), dermatomyositis (101), systemic sclerosis (102) and itch following exposure to sulphur mustard (103). Notably, in a large cohort of dermatological outpatients ($n=3,485$), the presence of itching was associated with sexual dysfunction (assessed by the 9th question of the DLQI) (104).

The HRQoL issues associated with itch have also been investigated in relation to underlying systemic disorders. It was observed among German individuals that, compared with dermatological disorders, systemic disorders causing CI were more commonly associated with decreased HRQoL ($p=0.003$) (84). Nevertheless, various systemic conditions afflicting different organs have been associated with CI and impairment in HRQoL. A prominent example is CI due to end-stage renal disease. In a study by Weiss et al. (105), the authors evaluated 860 patients on haemodialysis, revealing that the point prevalence of CI was 25.2%, while the 12-month prevalence and lifetime prevalence were 27.2% and 35.2%, respectively. The SF-12 questionnaire was used to assess HRQoL, revealing that the physical component subscale was significantly more affected among those with CI ($p<0.05$). A subsequent study on the same cohort demonstrated that the mean severity of CI correlated with the total score of the ItchyQoL (106). The strongest correlation with the mean itch severity was observed with respect to the emotions subscale, followed by self-efficacy, functionality and symptoms. Our group has also evaluated CI in 200 patients with end-stage renal disease, among whom CI concerned 38% (85). Patients with uraemic pruritus had significantly lower quality of life according to the 36-item Short Form Health Survey (SF-36) (93.0 ± 20.4 vs. 99.6 ± 19.9 points, $p=0.03$). Among the SF-36 dimensions, general health perception was markedly worse among pruritic subjects ($p=0.0003$). In addition, we found significant negative correlations between the total SF-36 score and itch intensity. The debilitating impact of CI on QoL has also been investigated in other systemic conditions (chronic venous insufficiency (107), Sjogren's syndrome (108), primary sclerosing cholangitis (109), polycythemia vera (110) or HIV infection (111)), although detailed considerations are beyond the scope of this review.

THE SOCIAL WOUNDS: ITCH AND STIGMATIZATION

Stigmatization may be defined as an awareness of social disapproval, discrediting or devaluation, based on an attribute or physical mark and on social rejection (112). Unsurprisingly, stigmatization has been studied in the context of various cutaneous disorders, such as psoriasis, vitiligo, leprosy or acne, to name just a few (113). The role of itch and fatigue in experiencing stigmatization in patients with AD or psoriasis may be associated with higher levels of stress (114). In 1989 Ginsburg & Link (115) explored stigmatization in a cohort of 53 psoriatic subjects via an original questionnaire containing 33 questions focusing on 6 factors (anticipation of rejection, feelings of being flawed, sensitivity to the opinions of others, guilt and shame, positive attitudes, and secretiveness). Ninety-three percent of participants reported itch; it was observed that the extent of bleeding at the time of the study (followed by itching) were the strongest predictors of stigmatization. The possible explanation involves itch as an elicitor of scratching behaviour, which may ensue in bleeding. To the best of our knowledge, this was the first experimental study relating itch to stigmatization. In a study by Lu et al. (114) 131 outpatients with psoriasis and 139 outpatients with AD were evaluated by several tools, including the 6-Item Stigmatization Scale (6ISS) regarding the perceived stigmatization on a 4-point Likert scale. Subsequently, our group investigated the well-being of 102 patients with plaque-psoriasis, among whom itch affected 89.2% (6). The intensity of itch correlated significantly with the level of stigmatization assessed via the 6ISS, as well as the Feelings of Stigmatization Questionnaire. Regarding the latter, the domains "feeling of being flawed", "sensitivity to other attitudes" and "secretiveness" were mostly influenced. Another study among Arabic subjects with psoriasis ($n=108$) revealed that itching (present in 78.7%) predicted stigmatization according to the Feelings of Stigmatization Questionnaire, whereas the intensity of itching significantly correlated with stigmatization level assessed via the 6ISS (116).

CONCLUSION

Despite a constantly increasing volume of data, there are still many unresolved questions about the phenomenon of itch. The known associations between itch and psyche are bilateral and multidimensional, posing challenges for clinicians. Taking into account the abundance of both ex-

perimental and clinical findings, coupled with increasing experience and involving psychiatrists, psychologists and other specialists in the field, is the basis of the holistic approach to the patient. This is a sure recipe for better management of both skin and psyche, as they constitute an unusual union that lasts a lifetime.

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REVIEW ARTICLE

A New Generation of Treatments for Itch

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For decades, antihistamines have been the mainstay of treatment for chronic pruritus, yet they often only work by making patients drowsy and forgetful of their itch. A new era of antipruritic drugs is quickly approaching, presenting more effective treatments for patients suffering from chronic itch. Several treatments have been developed targeting specific receptors in the nervous system, such as the transient receptor potential channels, sodium channels, neurokinin-1 receptors, opioid receptors, and many more. Additionally, antipruritic therapies developed to work on the immune system have become more targeted, leading to greater safety and efficacy measures. These include crisaborole, several interleukin antagonists, and janus kinase inhibitors. The promising results presented with these new antipruritic therapies allow physicians to be better equipped to treat their itchy patients.

Key words: pruritus; antipruritics; cytokines; unmyelinated nerve fibers.

Accepted Oct 15, 2019; Published Jan 9, 2020

Acta Derm Venereol 2020; 100: adv00027.

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Chronic itch can negatively impact sleep, mood, and quality of life (1), causing patients to become desperate for relief. For decades, clinicians have resorted to antihistamines as a primary treatment for itch. However, the majority of chronic pruritus cases do not respond to antihistamines. In fact, they are not at all effective, and only make patients drowsy, forgetting that they are itchy.

With a more profound understanding of the pathophysiology of itch, newer and better targets for treatment have arisen. Medications working on the nerves, such as gabapentin and pregabalin, have improved symptoms, especially in cases of neuropathic itch such as brachioradial pruritus and notalgia paresthetica. Likewise, cases of inflammatory itch, such as psoriasis and recently atopic dermatitis (AD), have been dramatically improved by the advent of immunomodulating therapies.

New treatments for itch are continuously being developed. Herein, we will first discuss new antipruritic therapies working on the nervous system, and next we will discuss the antipruritic therapies targeting the immune system.

SIGNIFICANCE

Itch is a pesky sensation that can be difficult to eliminate. Although a mainstay of anti-itch therapy for many decades, antihistamines are not an effective therapy for patients with chronic, unrelenting itch. With a greater understanding of itch, newer treatments have been developed that are much more effective. These include drugs targeting the neural system and drugs that affect the immune system.

TREATMENTS TARGETING THE NERVES

The sensation of itch is transmitted by unmyelinated C nerve fibers originating in the skin, synapsing in the spinal cord, and traversing the spinothalamic tract to the thalamus, before being further projected to various areas in the brain (2). Yet, the sensation of itch is not that simple. At the levels of the skin, spinal cord, and brain is an additional mechanism referred to as neural sensitization. This phenomenon causes the itch-selective neurons to become hypersensitive to pruritic stimuli (2). In the skin, neuronal sensitization is the result of inflammation, abnormal epidermal innervation, and dysfunction of cutaneous touch receptors. Dysfunction and attenuation of the inhibitory spinal circuits lead to neural sensitization at the level of the spinal cord. Finally, in the brain, chronic pruritus can lead to functional and structural changes in brain connectivity and activation, causing neural sensitization (2–4).

At each step of this pathway is an array of receptors involved in transmitting this pesky symptom. Discovery of the involvement of these receptors and their ligands in itch has led to development of novel targeted therapies. **Fig. 1** diagrams where these antipruritic drugs targeting the nerves act in the skin, spinal cord, and brain.

Neurokinin-1 inhibitors

Neurokinin-1 (NK-1) serves as a receptor for substance P (SP), a known pruritic mediator. NK-1 is located throughout the central nervous system and skin. Activation of NK-1 by SP leads to pro-inflammatory cytokine production and mast cell release of pruritic mediators such as histamine, tumor necrosis factor (TNF)-α, prostaglandin D2, and leukotriene B4 (5).

Aprepitant, an NK-1 inhibitor originally developed to treat chemotherapy-induced nausea, is effective for treatment-refractory pruritus, as well as prurigo nodularis

doi: 10.2340/00015555-3347
Acta Derm Venereol 2020; 100: adv00027

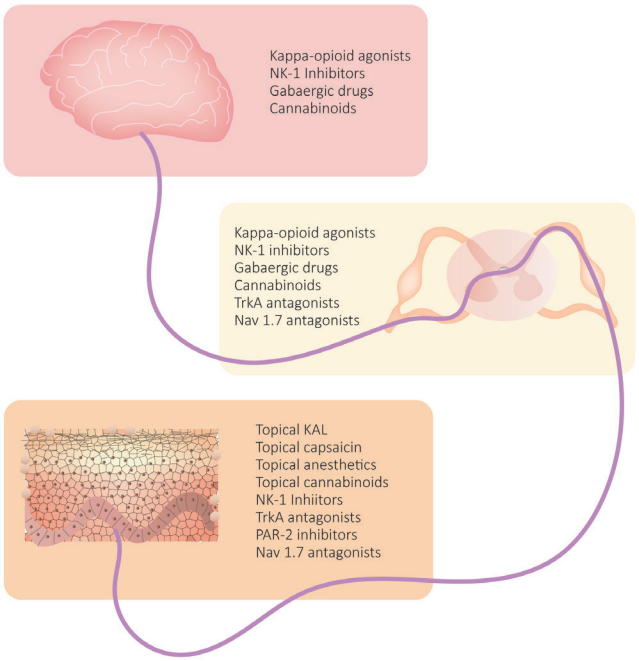

Fig. 1. Site of action of new antipruritic drugs targeting the neural system. NK-1: meurokinin-1; TrkA: tropomyosin receptor kinase A; PAR-2: protease-activated receptor-2; KAL: ketamine-amitriptyline-lidocaine; Nav1.7: voltage-gated sodium channel 1.7.

and cutaneous T-cell lymphoma (5, 6). Unfortunately, aprepitant is expensive and has a multitude of potential drug interactions, making it difficult to administer to patients (2, 7)

Serlopitant and tradipitant, newer NK-1 inhibitors, may be better alternatives and are currently being assessed in clinical trials (**Table I**). In randomized, placebo-controlled, phase II clinical trials, serlopitant exhibited a statistically significant decrease in pruritus in patients with treatment-refractory itch as well as prurigo nodularis (8, 9). In patients with AD, tradipitant showed a statistically significant decrease in itch in a randomized, placebo-controlled, phase II trial (10).

Opioids

Opioids are classically thought of as highly effective pain medications, but more recently, opioids have also been shown to play a significant role in the treatment of pruritus. μ-, κ-, and δ-opioid receptors exist throughout the central and peripheral nervous systems, including the peripheral nerve fibers in the skin (11). In the spinal cord, imbalance in the activation status of μ- and κ-opioid receptors result in neuronal sensitization, which can lead to chronic itch (2). Similarly, an imbalance can occur in the periphery, for example a decrease in the expression of κ-opioid receptors seen in the epidermis of patients with AD (12).

μ- and κ-opioid receptors have been well-studied as they relate to pruritus, while the role of δ-opioid receptors in itch remains poorly understood (11). Specifically, μ-opioid antagonists and κ-opioid agonists are effective in treating itch.

Mixed μ-opioid antagonists and κ-opioid agonists. Butorphanol, both a μ-opioid antagonist and κ-opioid agonist, treats pruritus of varying etiologies with high efficacy. It is administered intranasally and has a rapid onset of action. Most importantly, it has little abuse potential (13). Butorphanol presents a great treatment option especially in cases of refractory chronic itch. However, its mode of intranasal administration is not something that dermatologists feel comfortable to use.

More recent developments are similar drugs like nalbuphine, a mixed μ-opioid antagonist and κ-opioid

Table I. New antipruritic drugs targeting the neural system with corresponding ongoing clinical trials

Category	Drug name	Indication	Phase	Administration	NCT #
Neurokinin receptor-1 inhibitor	Serlopitant	Prurigo nodularis Atopic dermatitis Psoriasis	3	Oral	NCT03540160
		Chronic pruritus of unknown origin	2	Oral	NCT03841331
		Prurigo nodularis	3	Oral	NCT03677401 NCT03546816
		Epidermolysis bullosa	2	Oral	NCT03836001
	Tradipitant	Atopic dermatitis	3	Oral	NCT03568331
μ-opioid antagonist/κ-opioid agonist	Nalbuphine	Prurigo nodularis	2/3	Oral	NCT03497975
κ-opioid agonist	Nalfurafine	Uremic pruritus		Oral	
	Asimadoline	Atopic dermatitis		Oral	
	CR845	Uremic pruritus	3	IV	NCT03998163 NCT03636269 NCT03281538
		Chronic kidney disease	2	Oral	NCT03617536
		Cholestatic pruritus	2	Oral	NCT03995212
		Atopic dermatitis	2	Oral	NCT04018027
	MR13A9	Pruritus in hemodialysis patients	2	IV	NCT03802617
	SHR0410	Pruritus in hemodialysis patients	1	IV	NCT03857568
TrkaA antagonist	CT327	Psoriasis		Oral	
PAR-2 inhibitor	Doxycycline	Hives	2	Topical	NCT03968562
γ-aminobutyric acid analog	Pregabalin	Recessive dystrophic epidermolysis bullosa	3	Oral	NCT03928093
Ileal bile acid transporter inhibitor	GSK2646264	Cholestatic pruritus	2	Oral	NCT02966834

agonist. Clinical trials measuring its efficacy in treating uremic pruritus and prurigo nodularis have shown encouraging results (Table I) (14, 15).

K-opioid agonists. Nalfurafine, a κ-opioid agonist available in Japan, is an effective antipruritic agent in patients with uremic pruritus (16). In the United States, no κ-opioid agonists have yet been approved by the U.S. Food and Drug Administration (FDA) for the treatment of pruritus; however, clinical trials are underway. In a phase II clinical trial (17), intravenous (IV) CR845, a κ-opioid agonist, had significant antipruritic effects for pruritus associated with end-stage chronic kidney disease. Specifically, patients receiving CR845 three times a week after dialysis had a 68% greater reduction from baseline in worst itch scores compared to those receiving placebo (17). Clinical trials evaluating use of CR845 in other pruritic conditions are currently underway (Table I).

Asimadoline, a κ-opioid agonist originally developed for irritable bowel syndrome, completed phase II trials for pruritus associated with AD, but results have not yet been published (18). Likewise, SHR0410 and MR13A9 are undergoing phase I and II clinical trials, respectively, for treatment of pruritus in hemodialysis patients.

Tropomysin receptor kinase A antagonists

Epidermal keratinocytes and eosinophils release nerve growth factor (NGF), which binds to its receptor, tropomyosin receptor kinase A (TrkA). This leads to neural sensitization of transient receptor potential vanilloid 1 (TRPV1) and increased nerve sensitivity to SP, calcitonin gene-related peptide (CGRP), and brain-derived neurotrophic factor. Furthermore, NGF causes sensitization of the skin to nonhistaminergic cowhage-induced itch. Together, the TrkA-NGF pathway leads to hypersensitivity of peripheral sensory nerves to pruritic stimuli, and therefore presents a compelling target for antipruritic treatment (2).

In a phase IIb clinical trial of patients with psoriasis, CT327, a topical TrkA antagonist, demonstrated a statistically significant reduction in pruritus (19). Another Phase IIb trial with the same TrkA antagonist (SNA-120) also showed a robust reduction of pruritus, with 58% of patients receiving a meaningful itch reduction of 4.3 in Numerical Rating Scale (NRS). However, the vehicle also had significant anti-pruritic effects with 53% of patients receiving reduction in their itch, and the difference was not statistically significant (20).

Protease activated receptor-2 inhibitors

Protease-activated receptor-2 (PAR-2) is a type of G-protein coupled receptor activated by proteolytic cleavage of its extracellular N-terminus. For example, cowhage, the well-known inducer of nonhistaminergic itch, contains the protease mucunian, which activates PAR-2, as well as PAR-4, causing pruritus. Several other proteases can similarly activate PAR-2, causing symptoms of itch and making it a good target for treatment (2).

PZ-235, a pepducin that inhibits PAR-2, showed efficacy in the reduction of itching behaviors in a mouse model of AD (21). In humans, a one-time application of a different topical PAR-2 inhibitor led to a significant reduction in ratings of cowhage-induced itch intensities in a placebo-controlled study (22). Randomized, placebo-controlled clinical trials are warranted to determine whether the efficacy of PAR-2 inhibitors in treatment of various chronic itch conditions.

Interestingly, doxycycline, an antibiotic, has shown antipruritic properties in the treatment of acne vulgaris. In addition to its ability to reduce inflammation, its antipruritic mechanism is most likely due to its attenuation of the PAR-2 interleukin (IL)-8 pathway (23).

GABAergic drugs

Gabapentin and pregabalin, analogs of γ-aminobutyric acid (GABA) (an inhibitory neurotransmitter), have proven effective in treating various types of neuropathic itch (24). More specific GABAergic drugs are currently in development. In mice, targeting inhibitory α2 and α3 $GABA_A$ receptors reduced acute histaminergic and non-histaminergic pruritus. Furthermore, this α2/α3 $GABA_A$ modulator reduced chronic pruritus in a mouse model of AD and in dogs who were sensitized to house dust mites (25). Most importantly, these antipruritic effects seemed to come without any unwanted adverse effects (25).

Nav 1.7

An antibody inhibiting voltage-gated sodium channel (Nav) 1.7 with high selectivity suppressed chronic and acute itch in mice (26). This study indicated that Nav 1.7 is in fact involved in both histamine-dependent and -independent pruritus, and modulates spinal cord synaptic transmission for both itch and pain (26). Currently, Nav 1.7 antagonists are still in clinical development. NeuP12, a Nav 1.7 antagonist, is currently being studied in phase I clinical trials for neuropathic pain (27), and will be interesting to see if it has an effect on itch.

TREATMENTS TARGETING THE IMMUNE SYSTEM

The immune system plays an important role in itch, especially in inflammatory pruritic conditions. Classically, systemic immunosuppressive agents, such as glucocorticoids, methotrexate, cyclosporine, and azathioprine were the most effective therapeutic agents available, and although still often used as first-line treatment, can come with some potentially serious adverse effects.

Recently developed immunosuppressive treatments have a more specified mechanism of action, producing a

higher level of efficacy and safety. Moreover, the era of biologic therapies is still ongoing and vastly expanding to include various itchy skin conditions, with clinical trials steadily underway (**Table II**) (28).

Phosphodiesterase-4 inhibitors

Crisaborole is a topical non-steroidal phosphodiesterase-4 (PDE4) inhibitor approved for the treatment of moderate-to-severe AD. Applied as an ointment, crisaborole has proven to be effective in rapidly reducing pruritus in these patients. Pruritus relief was observed in significantly more patients receiving crisaborole ointment than vehicle in a *post hoc* analysis of two phase III clinical trials (29). This study showed that this rapid antipruritic effect was seen as early as day 2, and that 20% of patients receiving crisaborole experienced complete relief of their pruritus by day 6 (29).

Furthermore, a significant and strong link has been seen between pruritus and dermatology-specific quality of life scores. In a *post hoc* analysis of two phase III clinical trials, as patients' itch improved with the help of crisaborole, so did their quality of life scores (30).

Similarly, improved quality of life scores and greater reductions in pruritus as measured by a visual analogue scale (VAS) were achieved in patients with plaque psoriasis receiving apremilast, an oral PDE4 inhibitor (31). The efficacy of apremilast as an antipruritic therapy in patients with scalp psoriasis is currently being studied in phase IV trials (Table II).

Interleukin antagonists

Interleukins (IL) are cytokines which help mediate immune responses and inflammation. Cytokines can act on a number of different targets including immune cells,

Table II. New antipruritic drugs targeting the immune system with corresponding ongoing clinical trials

Target	Drug name	Indication	Phase	Vehicle	NCT #
Phosphodiesterase-4	Apremilast	Scalp psoriasis Psoriasis vulgaris	4	Oral	NCT03553433
		Plaque psoriasis	3	Oral	NCT03721172
	Crisaborlole	Atopic dermatitis		Topical	
Interleukin-4Ra	Dupilumab	Chronic spontaneous urticaria	2	Subcutaneous	NCT03749135
		Cholinergic urticaria	2	Subcutaneous	NCT03749148
	Pitrakinra	Atopic dermatitis		Subcutaneous	
Interleukin-13	Tralokinumab	Atopic dermatitis	3	Subcutaneous	NCT03587805 NCT03761537 NCT03526861
	Lebrikizumab	Atopic dermatitis		Subcutaneous	
	Nemolizumab	Prurigo nodularis		Subcutaneous	
Interleukin-31RA	Nemolizumab	Atopic dermatitis	2	Subcutaneous	NCT03921411
		Atopic dermatitis	3	Subcutaneous	NCT03989206 NCT03985943 NCT03989349
Oncostatin M receptor-β	KPL-716	Prurigo nodularis	2	Subcutaneous	NCT03816891
		Chronic idiopathic urticaria Chronic idiopathic pruritus Lichen planus Lichen simplex chronicus Plaque psoriasis	2	Subcutaneous	NCT03858634
Interleukin-17A	Secukinumab	Atopic dermatitis	2	Subcutaneous	NCT03568136
	Ixekizumab	Psoriasis, genital pruritus		Subcutaneous	
Janus kinase 1/JAK 2 or 3	Baricitinib	Atopic dermatitis	3	Oral	NCT03435081 NCT03733301 NCT03334435 NCT03428100 NCT03952559
	Ruxolitinib	Atopic dermatitis	3	Topical	NCT03745651 NCT03745638
	Tofacitinib	Psoriasis Atopic dermatitis		Oral Topical	
Janus kinase 1	Upadacitinib	Atopic dermatitis	1	Oral	NCT03646604
		Atopic dermatitis	3	Oral	NCT03607422 NCT03569293 NCT03568318 NCT03738397
	Abrocitinib	Atopic dermatitis	2	Oral	NCT03915496
		Atopic dermatitis	3	Oral	NCT03575871 NCT03627767 NCT03422822 NCT03720470 NCT03796676
IgE	Ligelizumab	Chronic spontaneous urticaria	3	Subcutaneous	NCT03580356 NCT03580369
Histamine 4 receptor	ZPL389	Atopic dermatitis	2	Oral	NCT03948334 NCT03517566

keratinocytes, and even sensory nerves (**Fig. 2**) (32). Some of the newer cytokines used as targets in regard to treating itch are discussed below and include IL-4, IL-13, IL-31, and IL-17.

IL-4. Dupilumab is a monoclonal antibody targeting the α subunit of the IL-4 receptor, blocking the signaling of cytokines IL-4 and IL-13, key cytokines involved in T-helper (Th) 2 immunity. Dupilumab has revolutionized the treatment of AD, significantly improving clinical symptoms of AD, rapidly reducing itch, and improving patients' quality of life (33, 34).

Currently, the use of dupilumab in other pruritic conditions is of great interest. Case reports have shown that dupilumab can be helpful in the treatment of patients with prurigo nodularis (35–37), uremic pruritus (38), and bullous pemphigoid (39). However, randomized, placebo-controlled trials are necessary to evaluate its true efficacy in other pruritic conditions. Clinical trials assessing its efficacy in chronic spontaneous urticaria and cholinergic urticaria are currently underway (Table II).

Similar to dupilumab, pitrakinra also targets the IL-4 receptor α subunit, inhibiting IL-4 and IL-13 signaling (40). Pitrakinra has mostly been studied in the treatment of asthma (41). Subcutaneous administration of pitrakinra in moderate to severe AD was investigated in a phase II clinical trial, however results have not been published (40, 42).

IL-13. This cytokine produced by Th2 lymphocytes, is implicated in the pathway of AD. Development of therapies targeting this cytokine are of great interest in treating AD. Two biologic drugs targeting IL-13 that are under investigation for treatment of AD include lebrikizumab and tralokinumab.

Lebrikizumab targets soluble IL-13 and binds with high affinity, preventing binding to the IL-4 receptor α subunit and subsequent signaling (28, 43). In a phase II randomized, placebo-controlled trial (43), patients receiving lebrikizumab in combination with topical corticosteroids showed a significantly greater achievement of 50% reduction in eczema area and severity (EASI) score when compared to placebo. As for pruritus, mean percent reductions in baseline itch as assessed by VAS were not statistically significant when compared to placebo in this study (43). However, in a phase IIb study, lebrikizumab showed dose-dependent improvements in pruritus as early as day two, continuing until day 16 (44).

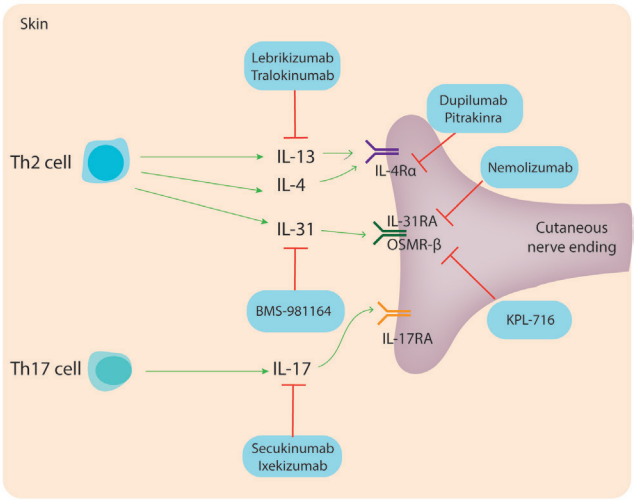

Fig. 2. Effect of interleukin (IL) antagonists on sensory nerves in the skin. OSMR: oncostatin M receptor.

Tralokinumab potently binds to IL-13, prohibiting its binding to IL-13 receptor subunit α-1 and IL-13 receptor subunit α-2, neutralizing its effects (45). Results from a phase II study have indicated promising results for patients with moderate to severe AD treated with tralokinumab (46). At a dose of 300 mg administered subcutaneously every other week, patients received clinically significant improvements in EASI score, Scoring of Atopic Dermatitis (SCORAD), and the Dermatology Life Quality Index (DLQI). Additionally, a significant decrease in pruritus assessed by NRS was seen in patients treated with tralokizumab compared to placebo (46). Phase III trials are currently underway (Table II).

IL-31. This cytokine is heavily implicated in the pathophysiology of chronic pruritus. Increased levels of IL-31 have been associated with a variety of itchy conditions such as AD, prurigo nodularis, cutaneous T-cell lymphoma, mastocytosis, chronic spontaneous urticaria, and bullous pemphigoid, making it a desirable pharmacological target for treatment of these patients (4, 47).

Nemolizumab, the first drug developed to inhibit IL-31 signaling, works by binding to IL-31 receptor A, which is located on a variety of cells including neurons, keratinocytes, macrophages, dendritic cells, and basophils (48). Thus far, nemolizumab has only been studied as a treatment for AD and prurigo nodularis. Pruritus was significantly improved in patients with moderate to severe AD in a phase II, randomized, double-blind, placebo-controlled clinical trial (49). As for prurigo nodularis, a phase II trial was recently completed with positive results (50).

BMS-981164, a monoclonal antibody targeting circulating IL-31, has completed a phase I clinical trial in AD, but no results have been published to date (51).

KPL-716, a monoclonal antibody against oncostatin M receptor beta (OSMR-beta), interferes with IL-31 and oncostatin M (OSM) signaling and has shown an antipruritic effect in patients with AD (52). A phase II clinical trial is currently recruiting patients with prurigo nodularis to assess the efficacy of KPL-716 in reducing their itch (53). Additionally, a pilot phase II study is assessing the efficacy of KPL-716 in reducing pruritus associated with chronic idiopathic urticaria, lichen planus lichen simplex chronicus, plaque psoriasis, and chronic idiopathic pruritus (Table II) (54).

IL-17. This is a pro-inflammatory cytokine that is primarily produced by Th17 cells, along with neutrophils and possibly mast cells. Keratinocytes are stimulated by IL-17A to secrete other pro-inflammatory mediators, which recruit neutrophils, Th17 cells, dendritic cells, and lymphoid cells (55). Drugs in this category are currently FDA-approved for the treatment of plaque psoriasis, and based on current studies, have shown the largest magnitude of effect in reducing psoriatic itch (5).

Secukinumab is a monoclonal antibody that selectively binds and neutralizes IL-17A (55). Two phase III, double-blind clinical trials assessing the efficacy of secukinumab in psoriasis showed that secukinumab was significantly more effective in reducing itch compared to placebo and etanercept, a TNF-α inhibitor (55, 56). In fact, in a pooled analysis of these two phase III trials, patients taking secukinumab achieved a significantly greater reduction in itching as early as the second week of treatment, demonstrating its rapid effect (57).

Phase II clinical trials assessing the role of secukinumab in treating AD are currently ongoing (Table II) (58, 59).

Ixekizumab is a high affinity monoclonal antibody also targeting IL-17A. Ixekizumab has proven to be effective in treating psoriasis, especially psoriatic itch in which phase III trials showed rapid, significant improvements. As early as the first week of treatment with ixekizumab, a significantly greater percentage of patients receiving the drug reported improvement of pruritus compared to those receiving etanercept or placebo (60).

In a long-term extension study of this trial, patients receiving ixekizumab maintained improvements in itch severity through the end of the study. By week 60, 48.2% of patients receiving ixekizumab every 4 weeks throughout the study achieved an itch NRS of 0. Similarly, after being switched to ixekizumab at 12 weeks, 45.1% and 45.3% of patients originally receiving placebo or etanercept, respectively, achieved an NRS of 0 at week 60 (61).

Additionally, ixekizumab is also effective in rapidly reducing genital pruritus. In a phase III, randomized, double-blind, placebo-controlled trial, a greater percentage of patients with genital psoriasis receiving ixekizumab achieved a significantly greater clinically meaningful itch reduction (greater than or equal to 3 point reduction on a numerical rating sale) than patients receiving placebo (59.7% versus 8.3%, $p < 0.001$) (62). Furthermore, a significant improvement in genital itch was seen as early as week 2 in those treated with ixekizumab (62).

Janus kinase inhibitors

Pruritus induced by cytokines is mediated at least partially by the janus kinase (JAK)/signal transducer and activation of transcription (STAT) pathway (2). JAK inhibitors block the JAK/ STAT pathway, which mediates signal transduction of cytokines and growth factors. When ligands bind to their receptors, JAKs are activated which lead to phosphorylation of STATs, which enter the cell nucleus to regulate transcription of target genes (63).

JAK inhibitors are commonly used in the treatment of inflammatory conditions such as rheumatoid arthritis. More recently, these medications are being investigated for use in chronic inflammatory skin conditions, such as AD and psoriasis (Table II).

Tofacitinib, an oral JAK inhibitor, works by blocking JAK1 and JAK3. It has been investigated for the treatment of psoriasis, with results from two randomized phase III trials showing that tofacitinib improved itch in patients with psoriasis, as soon as one day after treatment initiation (64, 65). Patients receiving tofacitinib also achieved a significant improvement in health-related quality of life, which were maintained through the end of the study at week 52 (64). Topical tofacitinib has also been effective for treating pruritus in both patients with psoriasis as well as AD (66, 67).

In a mouse model of psoriasis, tofacitinib significantly decreased mRNA expression of itchy cytokines IL-22, IL-23, and IL-31. This study also demonstrated that tofacitinib increased peptidergic epidermal nerve fiber density, which may aid in rescuing inhibitory itch mechanisms, proposing a novel mechanism for itch reduction by tofacitinib (68).

Additionally, JAK inhibitors may show promise in treating other cases of itch, even non-inflammatory causes of pruritus. In five patients with refractory, chronic idiopathic pruritus, oral tofacitinib led to marked improvement in their itch after only one month (69).

Baricitinib selectively inhibits JAK1 and JAK2. In a phase II, double-blind, randomized trial, baricitinib significantly improved AD and resulted in decreased pruritus (70). Phase III studies are currently underway (Table II).

Upadacitinib is a newer JAK inhibitor whose mechanism of action is selective for JAK1. In a phase II, randomized, placebo-controlled trial, upadacitinib significantly decreased ratings of itch in patients with AD (71). Phase III trials measuring the efficacy of upadacitinib in AD are currently in progress (Table II) (72).

Abrocitinib, another JAK inhibitor specifically targeting JAK1, has demonstrated excellent results in the treatment of AD. In a phase III randomized, double-blind, placebo-controlled trial, a statistically significant greater proportion of patients taking abrocitinib achieved a 4 point or larger reduction in itch NRS versus those taking placebo. Likewise, patients taking abrocitinib achieved a statistically significantly greater magnitude of decrease in the Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) compared to patients receiving placebo (73).

Histamine-4 receptor antagonists

Antihistamines, most of which are antagonists to the histamine-1 receptor, are often given to patients endor-

sing itch despite no clear evidence of their effectiveness as antipruritic therapies. Antihistamines specifically targeting the histamine-4 receptor (H4R), however, have shown some promise in treating itch (74). In a mouse model of AD, pretreatment with an H4R antagonist attenuated scratching responses in a dose-dependent manner (75).

ZPL389, an oral H4R antagonist, is currently being studied as a treatment for AD (Table II). However, results from a phase II randomized, double-blind, placebo-controlled study did not show a significant difference in pruritus reduction between patients taking ZPL389 and those receiving placebo (76).

Anti-IgE

A monoclonal anti-IgE antibody, ligelizumab, is undergoing phase III clinical trials to investigate its efficacy in treating chronic spontaneous urticaria (Table II). Studies have shown that ligelizumab has a much higher affinity to bind IgE in comparison to omalizumab (77), and thus it will be interesting to see its effect on pruritus in these patients.

CONCLUSION

New therapies for itch are continuously being developed. A new era of antipruritic drugs targeting specific neural receptors, itchy cytokines, and small molecules is swiftly approaching. Now that the pathophysiology of pruritus is better understood and research into new targets and mechanisms is perpetually underway, discovery and development of newer and better treatments for itch is ongoing. Unfortunately, treatment for chronic itch is not always simple and every patient requires individualized therapy. With education and development of new targets, clinicians can obtain a greater arsenal of treatment for their patients, to successfully treat them and improve their quality of life.

ACKNOWLEDGEMENT

GY has been a consultant or Ad Board member of AbbVie, Kiniska, Menlo, TREVI, Sienna, Galderma, Sanofi, Regeneron, Novartis, Eli Lilly, Pfizer, Bayer, Cerave and received research grants from Sun Pharma, Pfizer, Leo, Kiniska, and Menlo.

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Centenary theme section: ITCH AND PRURITIC DISORDERS

REVIEW ARTICLE

Challenges in Clinical Research and Care in Pruritus

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Chronic pruritus is a frequent global condition. The pathophysiology, underlying aetiology, clinical manifestation, associated burden and response to therapy of chronic pruritus varies from patient to patient, making clinical research and management of this condition challenging. There are still several unmet needs, such as the need to standardize translational research protocols, diagnostic and therapeutic procedures and to enhance the knowledge of the humanistic and economic burden associated with chronic pruritus. Basic and clinical research is of the utmost importance to target these matters. Clinical research has the potential to identify new relevant mechanisms in affected patients, which may lead to identification of novel therapy targets. This article discusses in depth current shortcomings in the daily care of patients with chronic pruritus and the challenges clinical researchers and physicians treating chronic pruritus face in addressing these matters.

Key words: itch; patient-reported outcome; guideline; clinical trials; clinical research.

Accepted Oct 15, 2019; Published Jan 9, 2020

Acta Derm Venereol 2020; 100: adv00028.

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Chronic pruritus (CP), defined as pruritus lasting for 6 weeks or longer, is highly prevalent, affecting approximately one-sixth of the population in Germany (1). Population-based analyses of the nationwide search volume of pruritus on Google suggest an even larger number of individuals suffering from CP within Germany and the USA (2–4). Those affected often report a substantial burden and a relevant impairment of their quality of life (QoL) (5, 6). The aetiology, clinical manifestation, diagnostic measures and therapeutic response to CP vary from patient to patient, which contributes to the challenging management of CP (7). Although recent years have witnessed a marked increase in basic and clinical research efforts in this field, CP researchers and physicians treating CP currently face several challenges when targeting unmet needs that impact on clinical routine. The aim of this review is to highlight and discuss methodologies used in CP research, as well as current challenges and unmet needs in clinical care.

SIGNIFICANCE

Itch lasting for 6 weeks or more is considered chronic and represents a high burden for those affected. Various aspects of chronic itch, including the underlying origin of the itch, symptoms, skin manifestations, response to therapies and impairment of quality of life vary from patient to patient, constituting a challenge for clinicians and clinical researchers. Unmet needs, such as the standardization of experimental and clinical research protocols, diagnostic procedures and therapeutic regimens, as well as a better understanding of associated burdens and the development of novel effective therapies should be targeted by physicians and researchers dealing with chronic itch.

CHRONIC PRURITUS: A MULTIDIMENSIONAL CONDITION

CP is a heterogeneous condition in terms of demographics, clinical presentation and underlying origin. Although the prevalence of CP increases with age, patients of all age groups, including children, may be affected (8). Moreover, patients of both sexes and all ethnic backgrounds may suffer from CP. According to the International Forum for the Study of Itch (IFSI), CP may present on inflamed skin (IFSI I), on normal appearing skin (IFSI II), or accompanied by chronic scratch lesions, such as chronic prurigo or lichen simplex chronicus (IFSI III) (9). As for the underlying aetiology, CP may arise from dermatological, systemic, neurological or psychiatric/psychosomatic conditions. Some patients show multiple causes for the pruritus (multifactorial CP), while in few cases the origin of the pruritus remains unknown despite extensive diagnostic work-up (9). Recent studies have further suggested a substantial impact of climate and weather on the prevalence of pruritus, especially involving specific localizations on the body, but these issues have yet to be examined in epidemiological studies (2–4). Adding to these factors, patients with CP vary in terms of medical history, comorbidities, co-medication, socioeconomic backgrounds and therapy goals, contributing to the complexity of the management of these patients.

UNMET NEEDS IN CLINICAL RESEARCH

Due to the complexity and multidimensional nature of CP, clinical research investigating several aspects of pruritic diseases and its management is needed. In particular, clinical research contributes to a better understanding of pathophysiological mechanisms involved in the development and chronicity of CP in humans. Moreover, clinical researchers should focus on various aspects of clinical management, such as standardizing diagnostic and therapeutic procedures, and assessing the humanistic burden and impact of CP on affected patients. Another important area is the performance of longitudinal translational studies, clinical trials investigating novel agents for the treatment of CP, and psychometric research. It should also be investigated how the care of patients with CP is integrated into the health system in order to identify shortcomings and to adopt innovative strategies, as, for example, digital tools to improve care. The next section of this article discusses the challenges and difficulties with regard to these issues.

CHALLENGES IN CLINICAL RESEARCH AND CARE

Understanding the pathophysiology

Basic and clinical research has led in recent decades to a better understanding of the mechanisms underlying CP. In clinical-translational research, different methods investigating specific pathophysiological features that augment data obtained from morphological and molecular biological research have been established and validated. The collaboration with biostatisticians and experts of medical informatics is essential for the interpretation of data and for obtaining a comprehensive understanding of the results. An overview of these methods is given in **Table I**.

Several methodologies have been developed in order to investigate the functions of peripheral nerves. Skin stimulation with pruritogens (e.g. histamine, capsaicin, cowhage, β-alanine) has led to the characterization of several subpopulations of C-fibres. Histamine activates mechano-insensitive C-fibres (CMi-fibres), while cowhage and β-alanine activate heat and mechano-sensitive C-fibres (CMH-fibres) (10). Hyperknesis related to cowhage-induced pruritus, but not histaminergic pruritus, is present in several types of CP compared with controls, arguing for sensitization of CMH-fibres in CP (11). One limitation of this methodology is the high inter-individual variability, while intra-individual variability is low (12). Another method, transcutaneous electrical stimulation, allows the selective activation of subpopulations of peripheral nerve fibres. For example, using the Neurometer® C, Aδ and Aβ fibres are activated by electrical stimulation at a frequency of 5, 250 and 2,000 Hz, respectively (13). Higher itch intensities could be induced upon stimulation at 5 and 2,000 Hz in patients with CP of different origins compared with healthy individuals, arguing for hyperknesis in patients with CP (14). Of note, patients are often anxious when undergoing experimental procedures with electrical stimulation, which leads to biased ratings of evoked sensory symptoms, thus constituting a limitation of this method. Another functional well-established diagnostic tool that is used for clinical itch research is quantitative sensory testing (QST). It is a battery of psychophysical tests, in which response to graded thermal and mechanical stimuli is assessed (15). This procedure, originally developed for determination of neuropathic pain, informs about gain or loss of function of different peripheral nerve fibre subpopulations and hints at possible signs of central sensitization. In itch research it could be shown that patients with CP of different origins have an altered QST profile, arguing for disordered peripheral neuronal mechanisms (11). Although QST is widely used in neurological routine care, it has some limitations. It is time-consuming, requires highly qualified personnel, as well as the collaboration of patients. Morphological methodologies for investigation of the anatomy of cutaneous cells and expression of receptors and mediators are essential in clinical itch research. In particular, determination of the intraepidermal nerve fibre density is useful in order to reveal potential epidermal neuroanatomical alterations (16). In this examination, a skin biopsy is obtained and intraepidermal nerves are stained with the axonal marker protein gene product 9.5 (17). This simple method, which is also used in routine care, has some limitations.

Table I. Clinical research methodologies used in itch research

Methodology	Mechanism
Cutaneous stimulation with histamine	Chemical-evoked itch via activation of mechano-insensitive C-fibres (CMi-fibres), mast cell degranulation
Cutaneous stimulation with cowhage or ß-alanine	Chemical-evoked itch via activation of mechano and heat-sensitive C-fibres (CMH-fibres) as well as A-fibres.
Hyperknesis	Increased itch in response to (chemical, electrical) pruritogens or pinprick stimulation
Alloknesis	Itch response to non-pruritogenic stimuli: touch/brush strokes. Functional testing of itch sensitization phenomena with punctuate or dynamic mechanical stimulation (von Frey filaments, cotton swab)
Transcutaneous electrical stimulation	Electrical-evoked itch via selective activation of peripheral nerve fibre classes
Quantitative sensory testing	Psychophysical testing of subpopulations of peripheral nerve fibres (C-fibres, Aδ-fibres, Aβ-fibres) and signs of central sensitization using graded thermal and mechanical stimuli
Functional magnetic resonance imaging/positron emission tomography	Identification of activated and deactivated cerebral centres upon pruritic stimulation
Conditioned pruritic modulation	Central descending inhibition of pruritus
Intraepidermal nerve fibre density	Morphological determination of epidermal nerve fibre numbers (skin biopsy)

The skin probe is sensitive to the fixative and needs to be processed in a timely manner in the laboratory. In addition, reference values are available only for the distal lower leg (18, 19), thus interpretation of values from other body sites is difficult. It is a purely morphological examination, which does not inform on functional alterations of peripheral nerve fibres.

Central processing of pruritus is very challenging. Most current knowledge on spinal transmission of itch was obtained from animal studies (20). Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have been used to investigate transmission and processing of pruritus in upper centres. Most studies have been performed on healthy volunteers exposed to pruritic stimulation during the scans. Brain regions associated with sensory recognition, cognition, motor response and emotional states are activated in response to pruritus (21). Interestingly, both overlapping and distinct brain areas are activated upon histaminergic and non-histaminergic pruritic stimulation, pointing to differences in cerebral processing of distinct pruritus types (22). Patients with CP also show differences in brain activation upon stimulation with histamine compared with healthy individuals, arguing for central sensitization in CP (23). Also, structural changes in grey matter have been observed in patients with CP, showing the neuroplasticity in chronic states (24). Although functional imaging studies have enhanced our understanding of cerebral processing of pruritus, this methodology has some pitfalls. fMRI and PET are very expensive methodologies, which are available only in specialized centres. In addition, patients with claustrophobia, ferromagnetic prostheses or implanted devices (e.g. defibrillator) cannot undergo an MRI examination, while others (e.g. children) have difficulty lying still during the procedure, leading to poor imaging quality. More imaging studies, enrolling patients with CP of different origins, are needed in order to establish similarities and differences in cerebral brain processing of pruritus across distinct CP conditions.

Upper centres exert a descending inhibitory modulation via a noradrenergic and a serotonergic pathway, as shown by imaging studies (21, 25). The paradigm of conditioned pain modulation (CPM), in which a noxious stimulus inhibits pain elsewhere in the body, can be used experimentally to assess descending inhibition (26). In patients with CP, as in those with chronic pain, CPM is impaired, which may contribute to the chronicity of the pruritus (11). An analogous paradigm of conditioned pruritic modulation, in which a pruritic stimulus inhibits pruritus elsewhere in the body, has also been investigated, with conflicting results regarding its effect (27, 28). More studies are needed to enhance the understanding of the mechanisms of descending modulation in CP and its role in the chronicity of the disease.

Standardization of assessment instruments

Since pruritus has a subjective dimension, patient-reported outcomes (PRO) play a pivotal role. A plethora of standardized questionnaires and scales have been developed in order to gather information on several aspects of CP, including pruritus characteristics, course of the disease, QoL, reactive disorders, such as anxiety, depression and sleep impairment, and therapy goals.

Pruritus characteristics (e.g. onset, duration and distribution of pruritus, as well as accompanying sensory symptoms and scratching behaviour) can be assessed using general patient-oriented itch questionnaires (29, 30). Mono-dimensional scales, namely the visual analogue scale, the numerical rating scale and the verbal rating scale, have been validated to assess the intensity of pruritus (31). Intensity scales are also validated for the use in electronic diary applications (32). The interpretation of itch intensity scales is challenging, since scores vary from patient to patient according to external factors, such as sex or ethnic background (1, 33). Some efforts have been put into understanding the minimal clinical relevant difference of itch intensity change, e.g. after initiating a therapy (34). However, many factors (e.g. the aetiology of the pruritus, recall period, socioeconomic background) may influence the minimal clinical relevant difference, making the interpretation of results difficult. An overview of other instruments for the assessment of itch is shown in **Table II**.

As for secondary conditions arising due to CP, standardized questionnaires are used to screen for anxiety and

Table II. Examples of instruments for itch assessment

Instrument	Description
Visual analogue scale (VAS)	Monodimensional scale for assessment of itch intensity; used in clinical trials and routine care (electronic and paper versions available)
Numerical rating scale (NRS)	Monodimensional scale for assessment of itch intensity; used in clinical trials and routine care (electronic and paper versions available)
Verbal rating scale (VRS)	Categorial scale for assessment of itch intensity; used in clinical trials and routine care (electronic and paper versions available)
Labelled magnitude scale (LMS)	Monodimensional scale for assessment of itch intensity; used in experimental research (paper version)
Itch Severity Scale (ISS)	Multidimensional scale for assessment of itch intensity; used in clinical trials (paper version)
Dynamic Pruritus Score (DPS)	Patient global impression of change for assessment of itch improvement; used in clinical trials and routine care (electronic and paper versions available)
5-D itch scale (5 dimensions itch scale)	Multidimensional questionnaire for assessment of itch characteristics; used in clinical trials (paper version)
ItchyQuant	Monodimensional scale for assessment of itch intensity; combination of VAS and cartoon depictions of scratching; developed for populations with cognitive limitations (elderly, children); used in routine care (paper version)

depression (e.g. Hospital Anxiety and Depression Scale (35)), to assess sleep disorders (36, 37) and to measure the impairment of QoL (e.g. Dermatological Life Quality Index (38) and pruritus-specific ItchyQol (39)).

PRO measures are usually collected via paper and pencil questionnaires, but electronic PRO systems are emerging. Computerized collection of PRO measures offers a couple of advantages compared with paper questionnaires: reduction of errors emerging through typewriting, reduction of missing data by requiring completion, and reduction of invalid data by implementation of skip patterns (40). Furthermore, electronic assessment can increase the compliance of completing questionnaires at home by up to 70%, using, for example, computerized reminder functionality (40). To overcome the drawbacks of paper questionnaires, an electronic PRO system, enabling the patient to complete the PRO measures via digital survey, may be implemented (41–43). Since most PRO measures have been validated as paper tools, it cannot be assumed that the electronic version of the same PRO measures deliver the same results for a patient encounter. Gwaltney et al. (40) showed that "as long as substantial changes are not made to the item text or response scales, equivalence studies should not be necessary to demonstrate anew the equivalence or validity of a computerized measure". However, in order to ensure the validity of electronic measures, it would be preferable if the concrete implementations were examined using test–retest or alternate-forms reliability.

Standardization of itch assessment instruments across centres treating patients with CP is of great importance, since it would allow the comparability of data. A first step was already taken by the Task Force Pruritus of the European Academy of Dermatology and Venereology. In a consensus conference, it was agreed that pruritus intensity and QoL should be regarded as the 2 most important parameters to be assessed in routine care. The visual analogue scale and the ItchyQol were regarded as the instruments of choice (44). Another important task is the validation of the assessment tools into various languages in order to be used in clinical trials and routine care across different countries. Future clinical research should focus on showing which instruments have better utility for the clinical practice and which tools are better accepted by patients and physicians.

Understanding the humanistic and economic burden

CP, similarly to chronic pain, can lead to a severe impairment of QoL (45–47) and has negative effects on mood, ability to concentrate, quality of sleep, everyday life and work productivity (48, 49). Some patients have mental health problems, such as depression, in response to CP, and are at significantly higher risk of suicide (50, 51). QoL is a highly subjective construct and is influenced by various factors, such as pruritus intensity, but also duration, frequency and localization of pruritus. Another challenge in understanding the impact of pruritic conditions on affected patients is that cross-cultural factors influence the reported intensity of pruritus and QoL rather than the specific dermatological diagnosis. This could be found in a study in 9 European countries enrolling more than 500 patients with CP due to different dermatoses (6). Clinical research should take the cultural background of patients with CP into account when investigating the humanistic burden of pruritic conditions.

In addition to limiting QoL, there are often psychiatric complications. Patients with CP and with a psychosomatic/psychiatric comorbidity suffer more from CP and its consequences. Interestingly, even if their symptoms improve, psychological suffering is higher in these patients (52). In order to cope with these associated disorders, individual multimodal medical care is needed, not only for diagnosing the underlying disease of CP and for symptomatic antipruritic therapy, but also for adjunct therapy against, for example, sleep disorders or mental health conditions. An important challenge for clinical researchers is to detect risk factors for developing mental diseases in patients with CP and thus identify patients at risk. This would aid attending physicians in redirecting vulnerable patients to mental health professionals and ultimately to improve care.

Definition of treatment goals

As a multifactorial chronic disease, CP requires complex and cost-intensive therapy. Knowledge of the treatment goals of patients with CP is therefore of great importance in order to plan an efficient therapy regimen. Therapy goals were recorded and evaluated in 2,474 patients with CP using the Patient Benefit Index – Pruritus (PBI-P), which was validated in 2009 for patients with CP and consists of 27 items, including various aspects, such as physical and mental well-being, professional and everyday performance, social and leisure activities, and QoL in general. The relevance of these items is calculated on the basis of a 5-step Likert scale (0="not at all important" to 4="very important") (53). It was shown that, in addition to demographic data such as sex and age, the CP IFSI group, pruritus intensity and QoL had a significant impact on different patient needs. Women considered the reduction in physical and psychological symptoms, such as depressive feeling, nervousness, or burning sensations, as more important (54). For men, an important goal was the improvement in aspects of social life, such as social contacts, partnership, and sex life. Patients with CP on inflamed skin (IFSI I) or pruritus with chronic scratch lesions (IFSI III) considered the healing of the skin lesions as a very important treatment goal (54). Overall, it has been shown that therapeutic goals relate to the diagnosis and medical therapy. Reduction in pruritus or confidence in therapy were considered important or very important

by the majority of patients with CP. However, patients with CP focus not only on symptom relief, but also on trustworthy and efficient medical action. Their overall need level seems to be higher than in other dermatological patients as, for example, patients with atopic dermatitis (54). The complexity of patients' needs constitute a challenge for clinical researchers, since patients' needs and goals influence how they perceive their disease and the efficacy of a therapy. Patients' needs should thus be taken into consideration when planning studies involving patients with CP.

Standardization of diagnostic and therapeutic procedures

Owing to the heterogeneity of CP conditions, it is difficult to achieve a standardized diagnostic and therapeutic approach across specialized centres and physicians treating patients with CP. The first guideline addressing CP was published in Germany in 2006 (55) and constituted an important first step in this regard. Since then, the German guideline has been regularly updated (56), while a European guideline was also developed and recently updated (57).

There is still a lack of randomized controlled trials investigating anti-pruritic drugs, and therefore many of the recommendations of current guidelines are based on case series, case reports and expert opinion. Another challenge that guidelines face is the heterogeneity of CP aetiologies. For instance, while antihistamines are effective in the treatment of urticaria, they do not reduce pruritus in other diseases, such as atopic dermatitis or systemic pruritic conditions (58). Therefore specific therapeutic recommendations are needed for the various pruritic conditions. Clinical trials targeting different pruritic diseases (e.g. atopic dermatitis, uraemic pruritus, cholestatic pruritus, paraneoplastic pruritus) are of the utmost importance in order to generate quality data on which to base therapeutic recommendations.

Dermatologists are usually the first specialists consulted for CP and play a key role in the management of CP. Their job is not only to treat the CP, but also to assign the patient to local physicians of other specialties for specific diagnostic procedures (e.g. medical imaging). However, due to time constraints, taking a comprehensive medical history in patients with CP is challenging in a dermatological practice. Reactive disorders of CP, such as depression and anxiety, need to be considered, as possible causative factors and skin findings, comorbidities and medication must be well documented. The consultation of patients with CP in specialized pruritus centres can offer an important advantage in the management of CP, especially when refractory to basic therapeutic measures, such as antihistamines, topical steroids and the use of emollients. However, the centres are scarce and more are needed for the current demand (7). Pruritus centres should work on an interdisciplinary basis together with medical specialties other than dermatology, such as internal medicine, neurology, pain medicine, psychosomatics, radiology, and medical informatics (59). In addition to outpatient care, specialized centres should also offer the possibility of inpatient care for highly complex patients who require extensive diagnostic procedures or who have relevant psychosocial factors, such as suicidal ideation or severe sleep impairment (59).

Guideline-based treatment of patients with CP at specialized centres can significantly reduce costs, both in the inpatient and outpatient sectors. This is the result of a recent study in which data from 300 patients with CP were analysed regarding their QoL, health economic burden and therapeutic benefits. Six months after the start of treatment at a specialized pruritus centre there was not only a significant improvement in the pruritus intensity, QoL and therapeutic benefit (PBI-P), but also a significant reduction in all costs (60).

Need for novel effective therapies

Owing to a better understanding of the mechanisms underlying CP, new promising agents with an anti-pruritic effect have been identified and are being tested in randomized controlled trials. These include monoclonal antibodies (e.g. nemolizumab, tralokinumab), neurokinin-1 receptor antagonists (e.g. serlopitant, aprepitant), opioid modulators (e.g. nalbuphine, nalfurafine), phosphodiesterase-4 inhibitors (e.g. apremilast, crisaborole), janus kinase inhibitors (e.g. tofacitinib) among other novel agents.

The development of innovative drugs faces important challenges. So far, clinical trials have been performed only for a few indications, especially atopic dermatitis, chronic prurigo, uraemic and cholestatic pruritus. For many other pruritic conditions clinical trials are lacking, and thus no novel drugs are available.

Since these new agents represent a high cost for the healthcare system, it is important to select the patients who can profit the most from them. Clinical trials and observations from routine care should inform which target population is suitable for each drug.

At present, innovative drugs being tested in clinical trials are available in only a few centres and thus not all patients have access to them. Licensing of these drugs is needed in order to extend the availability of these promising agents to patients in need. Hence, clinical research should focus on producing high-quality data on the safety and efficacy of novel anti-pruritic drugs, so that regulatory agencies can approve these medications.

CONCLUSION

Clinical research efforts in CP have increased in recent years, leading to better understanding of this condition, and ultimately to better care. However, the multidimen-

sional nature of this condition and the heterogeneous population affected by CP pose a challenge for clinical researchers and attending physicians. Unmet needs, such as the shortage of knowledge on chronicity mechanisms, insufficient standardization of a diagnostic and therapeutic approach to CP patients, and the development of novel promising drugs for refractory CP, ought to be targeted by researchers and physicians dealing with CP.

ACKNOWLEDGEMENTS

This article was supported by the German Research Foundation (DFG, No. FOR2690 to KA and SST) and by the European Academy of Dermatology and Venereology (EADV, No. 2016-012 to MP and SST).

The authors have no conflicts of interest to declare.

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