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Pruritus: From the Bench to the Bedside

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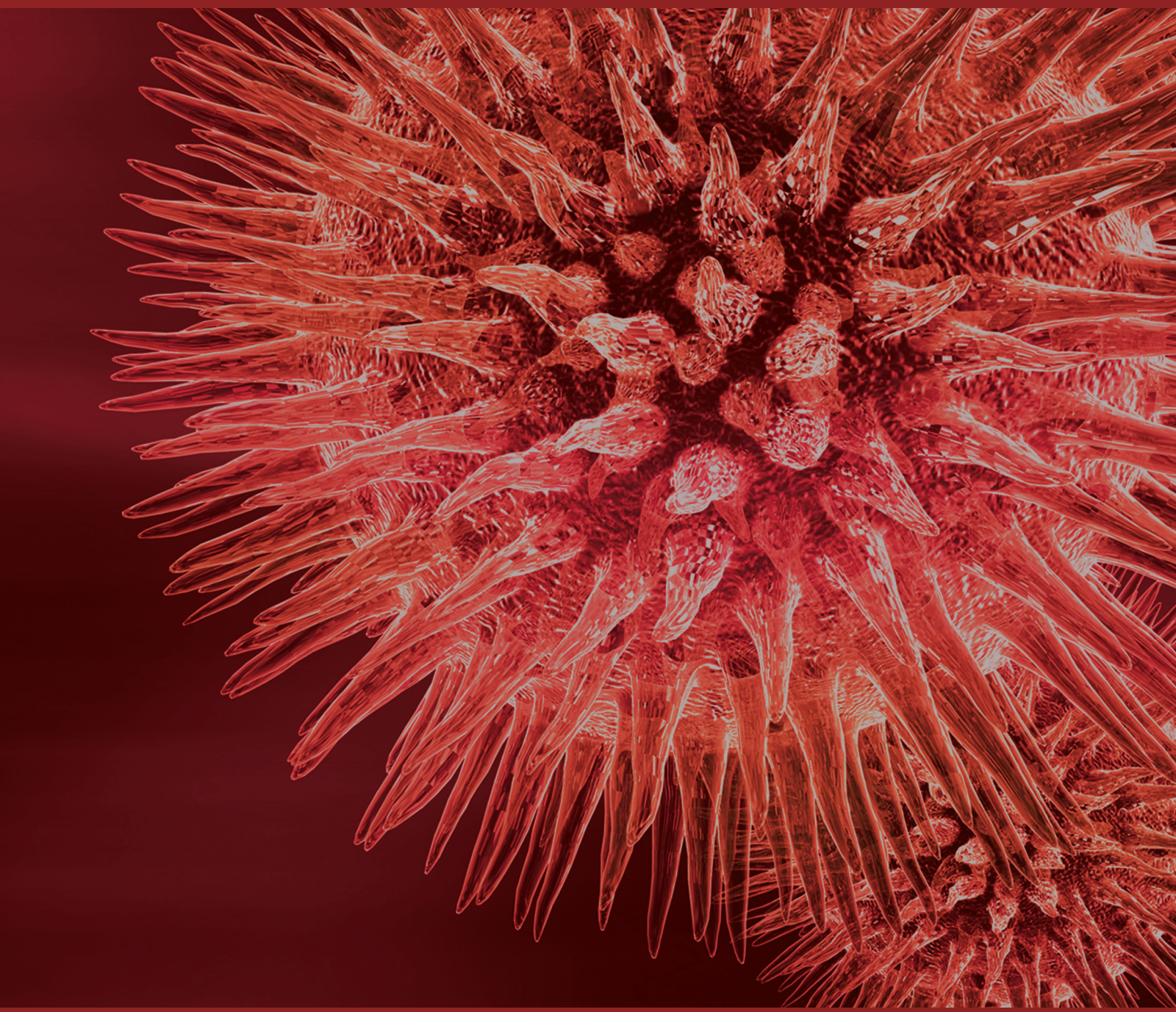

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Editorial

Pruritus: From the Bench to the Bedside

Adam Reich,[1] **Laurent Misery**,[2] **and Kenji Takamori**[3]

[1]*Department of Dermatology, University of Rzeszow, Rzeszow, Poland*
[2]*Department of Dermatology, University Hospital Brest, Brest, France*
[3]*Institute for Environmental and Gender Specific Medicine and Department of Dermatology, Juntendo University Graduate School of Medicine, Urayasu, Chiba, Japan*

Correspondence should be addressed to Adam Reich; adi_medicalis@go2.pl

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Pruritus is defined as a unpleasant sensation that causes a desire to scratch. It may accompany various skin diseases, but it may also be present in many systemic, neurologic, and psychiatric conditions. However, it is often overlooked or its significance is diminished. Remarkably, many studies documented that, for patients, pruritus is often considered as the most bothersome symptom in the course of the diseases they suffer from. Fortunately, the awareness about the relevance of pruritus is steadily growing among physicians and health care professionals. Subsequently, the higher awareness results in a growing interest in studying the underlying mechanisms of pruritus. Hopefully, our growing understanding of its pathogenesis will eventually generate new antipruritic treatment modalities and improve patient care in the near future. The current special issue is focusing on the latest developments in the field of pruritus science, providing new insights into pruritus pathogenesis, showing new data on pruritus clinical manifestation, and discussing new treatment options for pruritic conditions.

A paper by J. Song et al. could be handled as a nice introduction to the current special issue on pruritus, giving the readers an overview of the current understanding on the transmission of pruritic stimuli to the brain, describing the potential mediators of pruritus in the skin, including proteases, cytokines, peptides, and phospholipid metabolites, and explaining the differences between histamine-dependent and histamine-independent signaling pathways.

In 2006 Sonkoly et al. first suggested the role of interleukin 31 (IL-31) in pruritus accompanying atopic dermatitis [1]. Since that time, a number of studies have been undertaken to assess the meaningfulness of IL-31 in pruritus observed among other inflammatory skin conditions, like lichen planus, primary localized cutaneous amyloidosis, primary cutaneous T cell lymphomas, or mastocytosis [2–5]. The relevant role of IL-31 in pruritus pathogenesis has been recently confirmed in the phase II clinical trial with nemolizumab, an anti-IL-31 A receptor monoclonal antibody, in atopic dermatitis patients, showing significant decrease of pruritus intensity in active treatment group when compared to placebo [6]. Subsequent phase III clinical trials are ongoing, recruiting patients not only with atopic dermatitis, but also with other pruritic conditions, like, e.g., prurigo nodularis. Entering into this research trend, in this special issue, L. Kulczycka-Siennicka et al. analyzed the level of IL-31 in autoimmune blistering skin diseases frequently accompanied by pruritus, such as dermatitis herpetiformis and bullous pemphigoid. Surprisingly, they found decreased serum levels of IL-31 in patients suffering from these both conditions compared with healthy volunteers. Based on this observation, it could be suggested that IL-31 might not be the key cytokine mediating pruritus in these conditions; however, next studies are needed to further elucidate this phenomenon.

Interesting results on the itch and pain stimuli processing were also demonstrated by the group of A. I. M. van Laarhoven et al., who investigated whether attention is drawn to the stimulus location in tonic pruritus and pain stimuli. Opposite to their primary hypothesis, they were unable to find any indication for spatial attention allocation towards somatosensory stimuli, despite tonic itch and pain interfering with task performance. Based on these observations they concluded that patients with chronic pruritus or pain may benefit from learning to disengage their attention away from pruritus or pain, focusing attention on the location of pruritus or pain aggravates symptoms.

Several papers published in this special issue focused on the clinical presentation of pruritus in various conditions. V. Vachiramon et al. analyzed the prevalence and clinical manifestations of pruritus in vitiligo patients. Although vitiligo is usually not considered as a pruritic conditions, they found in the group of more than 400 patients that as much as about one fifth of patients with vitiligo may suffer from pruritus, with the highest prevalence in patients with focal vitiligo. Importantly, pruritus often preceded development of skin lesions suggesting that this phenomenon might be related to ongoing inflammatory response leading to destruction of melanocytes in the skin. Many patients with vitiligo experiencing pruritus declared disturbances in daily activity and problems with sleep, suggesting that this symptom should not be overlooked in this group of patients.

Similar situation was also observed among pregnant women, as demonstrated by J. Szczęch et al. Among the cohort of almost 300 women; the point prevalence of pruritus was about 20%, while the prevalence of pruritus during the entire pregnancy was almost 40%. Importantly, in many cases the presence of pruritus could not be attributed to any underlying condition suggesting that, indeed, pruritus may only be due to pregnancy. Frequent location within the abdomen skin suggests that at least in some pregnant women pruritus may be a result of skin stretching and mechanical activation of pruriceptive cutaneous nerve endings. Whether pruritus in pregnancy is also evoked by other mechanisms needs to be elucidated in the future.

Recently, greater attention has also been put on the scalp, as this body area can be very pruritic in such conditions as psoriasis and seborrheic dermatitis. As demonstrated by Yosipovitch group [7], skin on the scalp is highly innervated and as such may be more vulnerable to pruritic stimuli. Some researchers even suggested that pruritus in scalp psoriasis may be responsible for recalcitrant skin lesions due to Koebner phenomenon resulting from scratching.

Last but not least, we would like to put the readers' attention on two other papers related to pruritus assessment and treatment. On one hand, due to a subjective nature of pruritus, its objective measurement in clinical practice still remains a challenge. On the other hand, assessing the efficacy of any treatment options in clinical trials requires a valid instruments that are used to evaluate improvement of pruritus intensity [8]. Frequently, the Visual Analogue Scale or the Numeric Rating Scale are used; however, it is often not sufficient and these scales should be supplemented with other instruments. A. Reich et al. demonstrated a validation study on the new 12-Item Pruritus Severity Scale, which has been used by this group previously in various studies on pruritic diseases. In a number of analyses they showed that this itch severity questionnaire shows strong internal consistency, good reproducibility, and convergent validity and demonstrates significant correlation with patients' quality of life. Based on these observations it could be stated that the 12-Item Pruritus Severity Scale may be potentially used in future clinical trials.

Finally, A. He et al. reviewed current data on aprepitant, a neurokinin 1 receptor antagonists, in the treatment of pruritus and discuss its mechanism of action and adverse effects. Since first reports on its potential activity in chronic pruritus [9, 10], a growing interest is observed regarding neurokinin 1 blockade as a potential promising antipruritic target. Novel derivates with longer half-life time, such as serlopitant or tradipitant are currently investigated in clinical trials.

Summarizing, we hope, that the current special issue on pruritus would bring new insights into pathogenesis of pruritus, its assessment, and treatment, We also hope that the readers find the coverage interesting and important for their clinical practice.

Adam Reich
Laurent Misery
Kenji Takamori

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Review Article

Pruritus: Progress toward Pathogenesis and Treatment

Jing Song[1], **Dehai Xian**[2], **Lingyu Yang**[1], **Xia Xiong**[1], **Rui Lai**[1] and **Jianqiao Zhong**[1]

[1]*Department of Dermatology, The Affiliated Hospital of Southwest Medical University, Luzhou 646000, China*
[2]*Department of Anatomy, Southwest Medical University, Luzhou 646000, China*

Correspondence should be addressed to Jianqiao Zhong; zjq7632@hotmail.com

Jing Song and Dehai Xian contributed equally to this work.

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Pruritus, the most common cutaneous symptom, is widely seen in many skin complaints. It is an uncomfortable feeling on the skin and sometimes impairs patients' quality of life. At present, the specific mechanism of pruritus still remains unclear. Antihistamines, which are usually used to relieve pruritus, ineffectively work in some patients with itching. Recent evidence has suggested that, apart from histamine, many mediators and signaling pathways are involved in the pathogenesis of pruritus. Various therapeutic options for itching correspondingly have been developed. In this review, we summarize the updated pathogenesis and therapeutic strategies for pruritus.

1. Introduction

Pruritus or itching is an unpleasant feeling that causes a desire to scratch, which negatively affects psychological and physical aspects of the life [1]. It is the most common symptom of skin diseases, sometimes trifling or light and sometimes intolerable. It is also the most common reasons for patient to consult dermatologist [2]. The pruritus may exist continuously or occur intermittently. Its site may be local or generalized. Itching is primarily associated with the free teleneuron which distributes in the superficial layers of the epidermis. The most of itching-related skin diseases are contact dermatitis, eczema, urticaria, neurodermatitis, prurigo, and cutaneous pruritus [3]. In addition, the pruritus may emerge from systemic diseases including inflammatory diseases, metabolic diseases, infection, neurologic disorders, endocrine diseases, psychiatric disorders, and cancer [4].

It is generally considered that the cause of itching is extremely complicated and many factors are involved in itching including internal and external factors. The intrinsic factors may be related to chronic infection, block of blood circulation, change of endocrine and metabolism, hereditary tendency to allergies, and so on, while the extrinsic ones are more complex and changeable, consisting of food, inhaled substances, chemical materials, animal hair and fur skin, and so on [5].

Until now, the exact pathogenesis of pruritus remains unknown. Previously, it was thought that histamine mediator was primarily involved in the attack of pruritus [6]. However, recent reports show that some mediators, such as 5-hydroxy tryptamine (5-HT), proteases, opioid peptide, and peptides, play crucial role in the mechanism of itching [7, 8]. Besides, signaling pathways have important effects on it. Accordingly, phototherapy, topical medication, systemic treatment, and traditional Chinese medicine are developed to pave the way for the relief of pruritus [9].

2. Clinical Classification of Pruritus

Pruritus, one of the distressing symptoms, covers a variety of clinic complaints containing dermatologic, neurologic, systemic, and psychiatric diseases [10]. In most cases, the origin of pruritus is in the skin or/and the nervous system. Many mechanisms are implicated in the itching [11]. According to the peripheral and central nervous systemic mechanisms, pruritus is divided into the following categories [3, 12, 13].

2.1. Skin-Derived Pruritus. Skin-derived itching originates from the skin, which is caused by inflammation, dryness, or damage of the skin. It is produced and irritated by the conduction of C nerve fiber. Some typical diseases, such as urticaria, scabies, and insect bite dermatitis, belong to this category [14–16].

2.2. Neuropathic Pruritus. Neuropathic pruritus is associated with pathological alterations in the afferent pathway of sensory nerve fibers. Its coverage is limited to a certain point. Postherpetic neuralgia, for example, is usually accompanied by itching [17–19].

2.3. Neurogenic Pruritus. Neurogenic pruritus is derived from the central nervous system, in which itch is produced by the induction and transmission of mediators and receptors without nerve damage. Bile stasis itching, for instance, is caused by opioid peptides acting on the μ-opioid receptor [20, 21].

2.4. Psychogenic Pruritus. Psychogenic pruritus is a functional itch disorder caused by psychologic factors (some irritating factors, skin dryness, etc.) and psychiatric abnormalities. Parasitic phobia is a common disorder characterized by psychogenic pruritus [22, 23].

2.5. Mixed Pruritus. Mixed pruritus is caused by multiple factors and mediated by two or more mechanisms. For example, atopic dermatitis (AD) is a typical disease involving skin derived itching and neurogenic pruritus [24].

3. Possible Mechanisms of Pruritus

Although the exact mechanism of itching has not been completely clarified, current studies indicate that some mediators are key contributors to the elicitation and aggravation of pruritus [8]. These mediators play different roles in different itchy conditions. Moreover, it has been proved that signaling pathways and neurotransmitters are also responsible for itch sensation. Thus, the related mechanisms are elaborated in detail as follows [25].

3.1. Mechanisms of Mediator-Related Pruritus. Mediator-related pruritus implies that itching is associated with the mediation of mediators including histamine, 5-hydroxy tryptamine, proteases, opioid peptide, peptides, and eicosanoids [26]. There are different mediators involved in the occurrence of pruritus at different stages. It has been found that a variety of mediators, apart from histamine, have much effects on the skin, mainly participating in the occurrence and development of itching [27].

3.1.1. Amines

(1) Histamine. Histamine is a chemical medium stored in the basophilic leukocyte and mast cells. When these cells are activated by immune and nonimmune factors, histamine is induced to release [28, 29]. Its receptors belong to the members of the G protein-coupled receptors (GPCR), in which H1 and H4 receptors (H1R and H4R) play important roles in the appearance of pruritus. Previously, it was considered that histamine dominated the development of pruritus via binding to H1R and activating phospholipase Cβ3 (PLCβ3) and phospholipase A2 (PLA2) [30–33]. Meanwhile, Bell et al. have demonstrated that histamine could increase the calcium influx in the axon terminals of the spinal cord neurons by activating transient receptor vanilloid 1 (TRPV1) receptor and then promote a series of intracellular signal activation and ultimately lead to itching generation [31]. It is currently confirmed that, however, other mediators are greatly important in pruritus occurrence.

(2) Serotonin/5-HT. Serotonin or 5-HT in the skin is derived from mast cells, which may induce pruritus through the peripheral and central nervous mediation. At the periphery, it indirectly facilities itching generation by encouraging mast cells to release histamine; at the center, however, it acts as an itchy mediator to produce the pruritus through opioids participation [34, 35].

3.1.2. Proteases. Proteases perform as any enzyme about proteolysis, which are involved in diverse physiological reactions [36]. It is believed proteases are extremely important substances in causing histamine-independent pruritus. Recent studies have demonstrated that proteases play a crucial role in itching attack by combining to GPCR called proteases-activated receptors (PARs), especially PAR2 and PAR4 [37–40].

3.1.3. Cytokines-Interleukins. Interleukins (ILs) are a group of cytokines containing secreted proteins and signal molecules, which were first discovered to be expressed by leukocytes [41]. Some ILs serve as itchy mediators to trigger and exacerbate pruritus. IL-2 and IL-6 are the typical histamine-dependent mediators of pruritus. In cutaneous T-cell lymphoma, for example, IL-3, IL-4, IL-6, and IL-10 synthesized by T-cells promote the secretion of Th2 cytokines particularly IL-6 [42, 43].

3.1.4. Peptides

(1) Bradykinin. Bradykinin belongs to an active peptide of the kinin group of proteins. It is a potent inflammatory mediator and endothelium-dependent vasodilator, which contribute to the production of inflammatory reaction and the dilation of blood vessels [44]. The receptors of bradykinin comprise receptor B1 (B1R) and receptor B2 (B2R) belonging to the members of GPCR family. By combining with its receptors, bradykinin initiates and induces a variety of physiological and pathological reaction [45]. In their study, Liu et al. confirmed that B1R was a pivotal factor to facilitate the chronic incurable itching in a diphenylcyclopropenone-treated chronic inflammation mice model [46].

(2) Substance P. Substance P (SP) is a neuropeptide widely distributed in the central and peripheral nervous system [47]. After stimulation, SP releases from sensory nerve endings

and conveys the signal to center nerves by binding to the NKl receptor (NKR1) [48]. SP works as a messenger in transmission of signals from terminal neurotransmitters and mast cells. However, Andoh et al. recently found that the scratching behavior of mice after intradermal injection of SP was few of connection with mast cells [49].

(3) Calcitonin Gene Related Peptide. Calcitonin gene related peptide (CGRP), a member of the calcitonin family of peptides, is produced in both peripheral and central neurons and secreted by peptidergic somatosensory neurons [50]. Its effect on the transmission of itching signals was ever controversial. At present, it is deemed that CGRP plays a regulatory role in the signal transduction of itching through binding to its receptors called calcitonin receptor-like receptor (CALCRL) and a receptor activity-modifying protein (RAMP1) [51]. Moreover, recent studies have reported that prurigo nodularis, a typical itchy disorder with intensive pruritus, is closely associated with the increased dermal levels of CGRP and SP [52].

(4) Neurotrophin. Neurotrophin is a large family of physiological activators promoting the growth, differentiation, and maintenance of neurons [53]. It primarily contains nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophic factors-3 (NT-3), and neurotrophic factors-4 (NT-4). Related reports have demonstrated that NGF levels in the itchy lesions of AD and psoriasis significantly increased and correlated with the severity of diseases; NGF, at the same time, upregulated the expression of sensory neuropeptides, which may induce the release of TRPV1, elicit the degranulation of mast cells, and result in pruritus [54–57].

(5) Opioid Peptides. Opioid peptides have peripheral and central itchy effects. They effectively work by activation of μ-receptor and inhibition of κ-receptor in the central nervous system. μ-receptor is the major functional receptor for itching production, but κ-receptor does the opposite. At the periphery, on the other side, morphine induces pruritus generation by eliciting the degranulation of mast cells. Studies further confirmed that all of these opioid peptides could cause itching after intrathecal administration [58–62].

3.1.5. Phospholipid Metabolites

(1) Cannabinoids. Cannabinoids (CB) belong to the derivatives of arachidonic acid, the receptors of which contain CBl receptor and CB2 receptor. CBl receptor is distributed in the central nervous system, while CB2 receptor is distributed in the peripheral tissues [63]. In animal studies, it was found that CB by binding to their receptor could induce the release of 13-endorphins, further to relieve pain and alleviate histamine-induced itching [64]. These results indicate that CB may be involved in the regulation of pain and pruritus.

(2) Eicosanoids. Eicosanoids, as signaling molecules, are produced by enzymatic or nonenzymatic oxidation of arachidonic acid [65, 66]. They are vital to diverse physiological and pathological situations, such as regulating cell growth, controlling inflammation, and inhibiting immune responses. There are multiple subfamilies of eicosanoids, consisting of leukotrienes (LTs), prostaglandins, resolvins, lipoxins, eoxins, and thromboxanes [65]. LTs, most prominently, are important regulators in the modulation of pruritus [67]. Andoh et al. discovered that scratching behavior of mice could be induced after the injection of LTB4 into mice skin [68]. Besides, it was found that the levels of LTB4 significantly elevated in AD and psoriatic lesions which were usually accompanied with pruritus.

(3) Platelet-Activating Factor. Platelet-activating factor (PAF) has a variety of physiological and pathophysiological effects, which acts as an important mediator and activator in anaphylaxis, inflammation, platelet aggregation and degranulation, and leukocyte chemotaxis. Normally, PAF is produced in low quantities by various cells (e.g., platelets, neutrophils, macrophages, endothelial cells, and monocytes), but it emerges in larger quantities from inflammatory cells in response to specific stimulator [69]. Through specific receptors and a series of signal transduction systems, PAF works to induce diverse biochemical responses. It has been demonstrated that PAF initially evoke an inflammatory response in allergic reactions in the skin of mammals and humans [70].

The primary mediators and their receptors as well as the corresponding medicine are summarized in Table 1.

3.2. Mechanisms of Signaling Pathway-Mediated Pruritus.

With important progress in knowledge of itch signaling, the pathogenesis of pruritus to some extent becomes clear. Currently, two signal pathways of itching have been identified. One is histamine-dependent (histaminergic) signaling pathway; another is histamine-independent (nonhistaminergic) signaling pathway [71]. In addition, itching can be produced in the central nervous system without relying on peripheral stimulation.

3.2.1. Histamine-Dependent Signaling Pathway.

The itchy receptors exist in sensory nerve endings located in the epidermal-dermal connection [28]. These receptors can be combined with the specific mediators mainly involving histamine, 5-HT, SP, and prostaglandins [64, 72]. As members of GPCR, four receptors of histamine (H1~4R) have been confirmed. H1R is a chief receptor involved in itch sensation, which may be activated by coupling with Gq proteins and evoking PLC [30–33]. H1R activation enhances calcium levels and irritates lipoxygenase (LOX) and PLA2. By activation of TRPV1, H1R facilitate scratching response to histamine [30–33]. PLCβ3, meanwhile, is critical for mediating histamine-induced scratching behavior through H1R in dorsal root ganglion (DRG) neurons [30]. Moreover, the signaling pathway of PLCβ3 is essential to 5-HT-evoked scratching. These two major signaling transduction pathways are drawn into itch depending on histamine through DRG neuronal mechanism [11].

Besides, various sensory receptors are specially combined with their corresponding ligands to transmit signals and lead

Table 1: Mediators, receptors, and drugs about pruritus.

Mediators	Receptors	Drugs
Histamines	Histamine receptors (H1R, H2R, and H4R)	Antihistamines
5-Hydroxy tryptamine (5-HT)	5-HT receptors (5-HT_2 and 5HT_3)	Paroxetine, Fluoxetine, Mirtazapine, Ondansetron
Proteases	Proteases-activated receptors (PARs, PAR1–4)	Leupeptin, E6005, E-64, Chymostatin
IL-2, IL-3, IL-4, IL-6, and IL-10	IL-2 and IL-6 receptors	Cyclosporine, Dupilumab, Lebrikizumab
Bradykinin	Bradykinin receptors (B1R and B2R)	Icatibant, Bromelain
Substance-P (SP)	NK receptor (NKR1)	Aprepitant, Fosaprepitant, Casopitant, Vestipitant, Orvepitant, Lanepitant, Dapitant, L-733, 060
Calcitonin gene related peptide (CGRP)	CGRP receptors (CALCRL and RAMP1)	Erenumab, Fremanezumab, Galcanezumab
Opioid peptides	μ-receptor, κ-receptor	Naloxone, Naltrexone, Nalfurafine
Cannabinoids	Cannabinoid receptors (CB1 and CB2 receptors)	Palmitoylethanolamine (PEA)
Leukotrienes (LTs)	Leukotriene receptors	Zafirlukast, Pranlukast, Montelukast
Platelet-activating factor (PAF)	PAF receptor	Rupatadine, Apafant

to itching. After stimulation by itchy mediators, specific C fibers convey signals to the dorsal horn of the spinal cord and then through the spinal cord to the lamina nuclei of the thalamus and finally to the cerebral cortex (somatosensory area), further producing itch sensation (Figure 1). These C fibers are scarcely sensitive to mechanical stimuli but only to itchy mediators, which therefore are called mechanically insensitive C-type fibers (CMi) [9, 11]. The nerve endings of CMi mainly distribute in the connection of the epidermis and dermis (Figure 1). Moreover, CMi possess some special characteristics including slow conduction rate, many branches of nerve endings, insensitivity to mechanical stimuli, and high threshold of excitation, which plays crucial roles in itch through histamine-dependent signaling pathway [73].

3.2.2. Histamine-Independent Signaling Pathway. Since a major of chronic refractory itch is resistant to antihistamine therapies, it seems that such a chronic pruritus relies on nonhistaminergic mediation. The nonhistaminergic signaling pathway is usually mediated by a class of mechanically sensitive C-type fibers (CMHs) [74]. The nerve endings of CMHs mainly distribute in the epidermis (Figure 1). Itch signals are transferred to the central nervous system via CMHs (Figure 1). CMHs can be stimulated by a tropical leguminous plant---cowhage, which may produce a strong itch sensation when stuck into the skin. Cowhage is a classic nonhistaminergic pruritogen and it induces itching via histamine-independent signaling pathway; thus antihistamine medication ineffectively works [75, 76]. The active ingredient of cowhage is mainly 36KD-cysteine protease called mucunain, which can stimulate PAR2 and PAR4. Present studies suggest that transient receptor potential (TRP) cation channel is the downstream target of the itch signaling pathway, which could be activated by PAR2 [77, 78]. PAR2 initially sensitizes PLC and then stimulates the downstream target including transient receptor potential cation channel V1 (TRPV1) and TRPA1, ultimately leading to itching sensation (Figure 2).

Along with the PARs, there are other kinds of important receptors in mediating histamine-independent itch called Mas-related G protein-coupled receptors (Mrgprs), which specifically distributes in sensory nerves [79]. In 2009, Liu et al. found that the activation of Mrgprs could cause itch sensation, and chloroquine (CQ), another classic non-histaminergic pruritogen which was previously used in malaria as a drug, contributed to inducing pruritus through histamine-independent signaling pathway by binding to its receptors---MrgprA3 in mice and MrgprX1 in humans [80]. Since human proteins fail to match orthologous pairs to rodent counterparts, Mrgprs in human are called MrgprX1-X4 [79]. Besides, other Mrgprs may be involved in CQ-induced itch because CQ-induced pruritus becomes in part weakening in MrgprA3 cluster-deficient mice [80, 81]. After that, many Mrgprs have been identified as receptors for their corresponding pruritogens; for example, bovine adrenal medulla 8-22 peptide (BAM8-22) was a ligand of MrgprC11 in mice and an activator of human MrgprX1 [82]. Recently, SLIGRL, a protease-cleavage product derived from murine PAR2, was thought to evoke itch by activating MrgprC11 instead of PAR2 [83]. Furthermore, one other Mrgpr linked to nonhistaminergic pruritus is MrgprD, which solely activated by β-alanine may elicit itch [84]. Although it is speculated that TRPV1 is maybe involved in the process of β-alanine-induced itch, the specific downstream pathway of MrgprD keeps unclear yet. As the critical downstream target of MrgprA3 and MrgprC11, TRPA1 ablation markedly alleviated CQ or BAM8-22-induced scratching response [85]. MrgprA3 is not coupled to PLC but G$\beta\gamma$ to induce TRPA1 activation, whereas MrgprC11 requires PLC to sensitize TRPA1 [85].

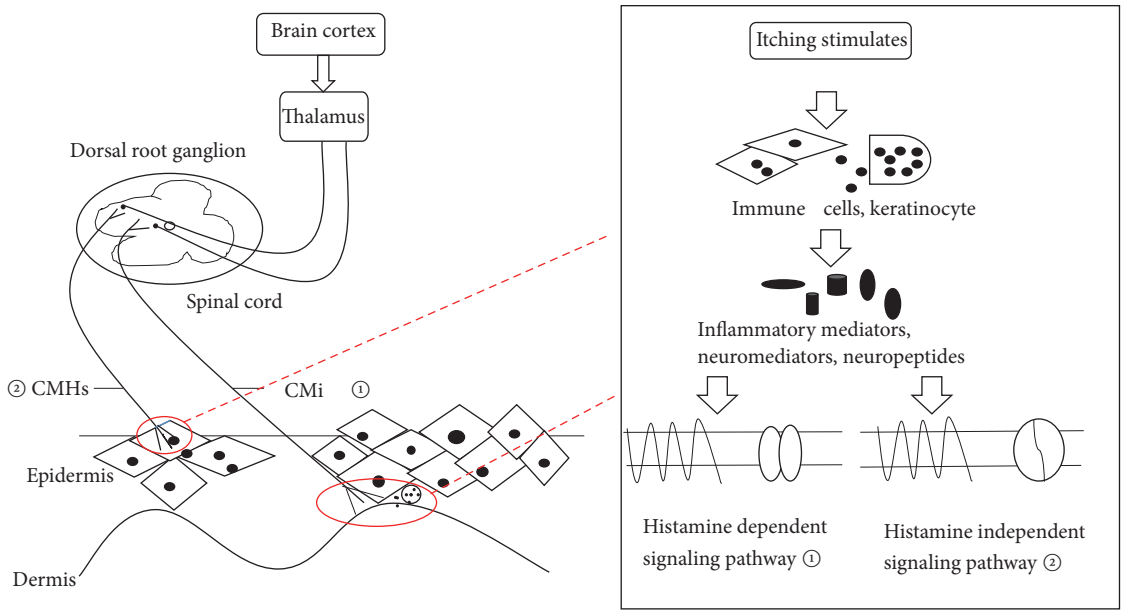

FIGURE 1: *The possible mechanisms and neurological pathways of pruritus*. Itch stimuli initially induce cells (e.g., immune cells and keratinocyte) in the skin to release many itchy mediators including inflammatory mediators, neuromediators, and neuropeptides. Subsequently, these mediators bind to their receptors, further resulting in the activation of itch-specific sensory neurons. The itch signals are transferred from mechanically-insensitive C-fibers (CMi) called histamine-dependent (histaminergic) or mechanically-sensitive C-type fibers (CMHs) called histamine-independent (nonhistaminergic) signaling pathway, through the dorsal root ganglion (DRG) of the spinal cord, across the spinothalamic tract to the thalamus, ultimately getting to the cerebral cortex.

Although the mechanism of Mrgprs mediating itching-related signaling pathways remains elusive, it has confirmed that Mrgprs- and Mrgpr-positive neurons, MrgprA3 in particular, play key roles in mediating chronic pruritus [79, 86]. As we all know, Mrgprs are selectively expressed in primary sensory neurons of the peripheral nervous system. MrgprA3 is specifically expressed in a subset of itch-sensing neurons, called MrgprA3-positive neurons. Other Mrgpr-positive neurons like MrgprD-positive neurons belong to the populations of itch-responsive neurons [79]. MrgprA3-positive neurons are able to be activated by many pruritogens (e.g., chloroquine, BAM8-22, histamine, and cowhage), whereas they fail to respond to β-alanine (MrgprD agonist) [87]. Of note, MrgprA3-positive axons innervate the skin, which is responsible for the considerable relief of pruritoceptive itch after MrgprA3-positive ablation [87]. Both Mrgpr-positive neuron populations are stimulated by the substances released from secondary cells like keratinocytes or mast cells, then they detect a variety of itch-inducing molecules through itch receptors on their cutaneous peripheral axons, and finally convey itch signals to the spinal cord via itch-sensing afferent fibers and cause itch sensation (Figure 2) [79, 86].

At present, it has been proved that there exists itch-associated specific central pathways ascending to the brain via the superficial layer of dorsal horn [88]. Typically, gastrin-releasing peptide (GRP), a bombesin-like peptide, is restricted to expressing in lamina I and the outer layer of lamina II; while its receptor, called gastrin-releasing peptide receptor (GRPR), is found to broadly express the central nervous system [89]. When binding to GRPR, GRP can evoke scratching reaction. Likewise, other neural receptors, B-type natriuretic peptide (BNP) receptor in particular, are involved in spinal itch signals transmitting process. BNP, originated from porcine brain, could elicit scratching response via binding to its transmembrane natriuretic peptide receptor A (NPRA) [89, 90]. It has been verified that both GRP-GRPR and BNP-NPRA systems are overwhelmingly implicated in the process of pruritus in the spinal cord [91]. Moreover, BNP-NPRA may function as the upstream of GRP-GRPR system to regulate neurotransmission of itch in the mouse spinal cord [90, 91]. At the beginning, the secondary neurons located in the dorsal horn of the spinal cord and expressing NPRA are activated by glutamate and BNP released from primary sensory neurons [92]. Next, the secondary neurons start to secrete GRP and then activate GRPR of a third neuron in the spinal cord, which ultimately lead to itch sensation [92, 93].

The possible mechanisms of pruritus are described in Figure 1 and the specific signaling pathways of itching are shown in Figure 2.

4. Pruritus-Related Clinical Diseases

4.1. Pruritus in Dermatoses

4.1.1. AD with Pruritus. Pruritus is outstanding in AD. It is a typical inflammatory skin disease often accompanied with severe and unbearable itching [94]. 10% of children suffer from this disease and it is more popular in adults, especially during pregnancy. Patients with AD tend to have a family history of allergic rhinitis or asthma and be not fully

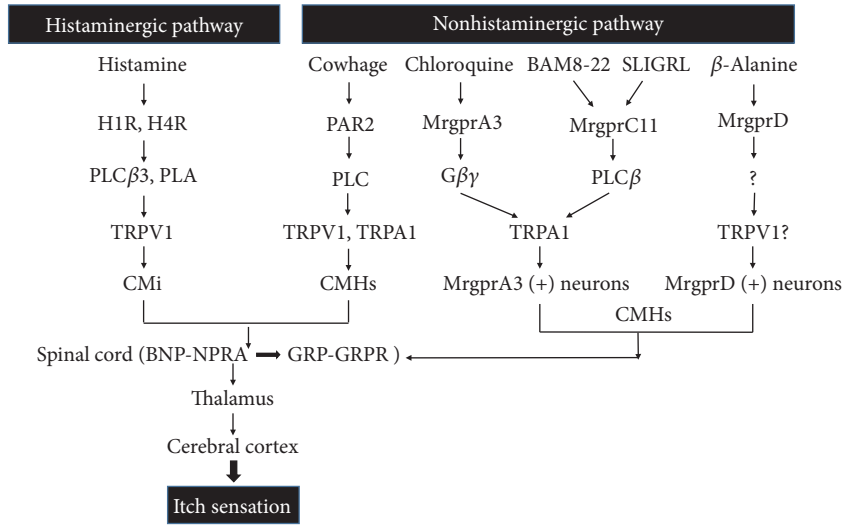

Figure 2: *Schematic illustration of pruritic signaling pathways*. According to different responses to histamine, two signal pathways of itching are covered, namely, histamine-dependent (histaminergic) signaling pathway and histamine-independent (nonhistaminergic) signaling pathway. In the histaminergic pathway, histamine promotes PLCβ3 and PLC activation by binding to their specific receptors, particularly H1 receptor and H4 receptor. These further induce the activation of downstream target TRPV1. Then, itch signals are transferred to the central nervous system via CMi, which finally lead to itchy sensation. On the other side, many pruritogens exist in the nonhistaminergic pathway, such as cowhage, CQ, BAM8-22, SLIGRL, and β-Alanine. Cowhage initially stimulates PAR2, which in turn sensitize PLC. Then the downstream targets including TRPV1 and TRPA1 are activated. Ultimately, itch signals are transferred to the central nervous system via CMHs and itch sensation is produced. At the same time, Mrgprs are linked and activated by CQ, SLIGRL, BAM8-22, and β-Alanine, further coupled to G$\beta\gamma$ or PLC or other; then they promote TRPA1/ TRPV1 activation and Mrgpr-positive neurons detect itch signals; via afferent fibers (CMHs), these signals are sent to the spinal cord and are regulated by GRP-GRPR and BNP-NPRA systems; finally itching sensation is present. PLCβ3, phospholipase Cβ3; TRPV1, transient receptor potential cation channel V1; TRPA1, transient receptor potential cation channel A1; CMi, mechanically insensitive C-fibers; PAR2, protease-activated receptor; CMHs, mechanically sensitive C-type fibers; BAM8-22, bovine adrenal medulla 8-22 peptide; Mrgprs, Mas-related G protein-coupled receptors; GRP, gastrin-releasing peptide; GRPR, gastrin-releasing peptide receptor; BNP, B-type natriuretic peptide; NPRA, natriuretic peptide receptor A.

alleviated by antihistamines alone. Apart from histamine, AD is usually caused and mediated by multiple pruritus mediators including neurotransmitters, ILs, and neuropeptides [95].

4.1.2. Psoriasis with Pruritus. Psoriasis is a common, chronic recurrent cutaneous disorder. Although the etiology of psoriasis is unknown, it is currently proposed that many factors, including genetic, immune-based, and environmental factors, are implicated in the pathogenesis of psoriasis [19]. 80% of psoriasis is accompanied with pruritic symptom and itching often lasts for a long time, especially outstanding at night [96]. Most of antipruritic drugs have little effect on this symptom. The itch mechanism remains unclear, but some mediators, such as SP, CGRP, and ILs, have been found in psoriatic lesions; nerve fibers and nerve polypeptides are in addition associated with itching [97].

4.1.3. Herpes Zoster with Pruritus. Although pain is the most popular symptom in herpes zoster (HZ), pruritus commonly emerges from some cured patients with HZ [98]. In their study, Özdemir and Tüzün found 20 of 178 patients with HZ appeared itch sensation and the damaged peripheral nerve located in itch site [99]. The pruritus mechanism may be associated with the damaged nervous system, which limits the symptom to a point in the afferent nerve and causes pruritus through different transmission pathways [15, 16].

4.2. Pruritus in Systemic Diseases

4.2.1. Uremic Pruritus. Uremic pruritus (UP) is a frequent and wearisome symptom in patients with end-stage renal disease (ESRD) [100]. The etiology of pruritus caused by renal failure keeps unknown, but it is clarified that antihistamines are ineffective for this disease. At present several theories have been proposed for the development of UP, including imbalanced opiate receptors, abnormal calcium homeostasis, enhanced systemic inflammation, and neuropathic dysregulations [101]. Moreover, recent report has showed that pregabalin is quite useful in the control of treatment-resistant UP by decreasing the calcium influx at the nerve endings and the level of SP, glutamate, and noradrenaline [102]. It is speculated that the pathogenesis of UP may be associated with increased SP and calcium influx.

4.2.2. Cholestatic Pruritus. Pruritus is a common, burdensome, and refractory symptom in patients with cholestasis. The typical itching is extended to the whole body after being localized in the foot joint and palm. At present, the opioid receptor antagonist is the first choice for cholestatic

pruritus [103]. Although the pathogenesis of pruritus in cholestasis remains little understood, it is believed that cholestatic pruritus may be mediated by specific neural pathways and pruritogenic factors including opioids, bile acids, and 5-HT [104]. Meanwhile, studies have demonstrated that cholestatic pruritus is possibly related to various mediators such as endogenous opioid peptide, histamine, bile salts, progesterone metabolites, serotonin, and lysophosphatidic acid (LPA) [105, 106].

4.2.3. Diabetic Pruritus. Pruritus is one of the most common signs of diabetes, which may be associated with secondary problems of diabetes, such as candidiasis and xerosis cutis. Clinically, patients with diabetes often feel generalized intractable pruritus without any lesions. Commonly, itching is the first symptoms of diabetes in elder obese patients [107].

4.2.4. Pruritus of Pregnancy. Pruritus is prevalent in pregnancy and distresses the mother [108]. It mainly involves immune and endocrine mechanism, clinically accompanied with increased estrogen and intrahepatic cholestasis [109]. However, itching could rapidly subside after childbirth. Pregnancy pruritus usually initiates in the abdomen, further extending to the thigh, chest, arms, and buttocks. Some specific dermatoses are easily seen in different time during pregnancy, such as prurigo and folliculitis often occurring in second trimester of pregnancy and urticaria in third trimester [110].

4.2.5. Tumorous Pruritus. Stubborn, wide, and inexplicable itching, particularly in the old people, should be alert to the potential possibility of malignant tumor. Pruritus of tumor is either continuous or transient, characterized by circumscribed and generalized manifestations [111]. The pathogenesis of tumorous pruritus remains unclear, presumably contributing to an immune response caused by tumor cells or cell debris [112]. It may be autoimmune causing cells in other parts of the body to be dissolved and release itchy mediators [113].

4.2.6. Senile Pruritus. Senile pruritus is most popular in the elderly population lack of primary lesions. It is a physiological pruritus resulting from skin atrophy, degeneration, skin gland dysfunction, dry skin, and mood swings [114]. This itching most commonly appears in many disorders, such as diabetes mellitus, chronic renal failure, hyperthyroidism or hypothyroidism, cholestasis, parasitic infections, and malignant tumors [115]. In addition, itching is often associated with other diseases such as thyroid diseases, infectious diseases, and anemia; some environmental, physiological, and dietary factors are involved in pruritus including drinking, mood changes, irrational diet structure, bathing frequently, and exposure to allergic substances.

5. Strategies for Management of Pruritus

Because of its complicated etiology and pathogenesis, pruritus is often difficult-to-treat and requires interdisciplinary measures. Although not all itching could be successfully controlled by antihistamines, particularly refractory pruritus from malignant tumor and kidney or liver diseases [116], a variety of interdisciplinary therapeutic tools have been developed and applied in clinic during recent decades. These vehicles partly have achieved good results and exhibit promising potential in management of itching.

5.1. General Treatment. In general, regular measures should be taken according to the therapeutic principle: finding causative factors, treating original diseases, avoiding all irritating factors, preventing skin dryness, and keeping skin moist [117].

5.2. Phototherapy. Ultraviolet B (UVB) has an ability of relieving pruritus through reducing the number of nerve fibers activated by CGRP in peripheral nervous system [118]. Moreover, UVB is extremely effective in control of itching caused by inflammatory skin diseases, uremia, primary cholestasis, globulism, Hodgkin lymphoma, and other systemic diseases [119].

5.3. Topical Medication. In clinical practice, many topical medications are frequently used to alleviate the itching. Low-PH cleansing agents, moisturizers, and lubricants are greatly effective in increasing cutaneous irritation [120]. Coolants, at the same time, could transfer the cold to cover the itching via stimulation of the nerve endings [22]; for example, liquid nitrogen is often successfully applied in pruritic dermatoses in our department. Moreover, local anesthetics have better efficacy in moderate pruritus, especially combined with coolants [121]. Owing to their capability of blocking H1 receptors, topical antihistamines are beneficial and usually used for resistance to itching, particularly in the treatment of urticaria and mosquito bites; for example, doxepin is the most useful topical antihistamine [122]. As the most effective topical anti-inflammatory agents, corticosteroids are often used in relief of pruritus from dermatoses caused by itchy mediators, but they always fail to control systemic itching [123]; they should be used only for a short interval, because long-term use would make skin atrophy and dry, sometimes accompanied with corticosteroid-induced acne, rosacea, or perioral dermatitis [124]. Recent immunosuppressants, such as pimecrolimus and tacrolimus, have similar effectiveness to corticosteroid in management of itching, but few significant side effects appear [125]. In addition, optical capsaicin can effectively alleviate pruritus by preventing the synthesis, transmission, and release of SP [126].

5.4. Systemic Therapy. Apart from traditional antihistamines, new drugs recently have been developed with further understanding of pruritus mechanisms. These medicines involve many mediator receptor antagonists as follows: opioid receptor antagonists, including naloxone, naltrexone, and nalmefene, have been demonstrated to alleviate pruritus in cholestasis, uraemia, and dermatologic diseases [103, 127–129]. Tricyclic antidepressant, such as doxepin, amitriptyline, trimipramine, and nortriptyline, is effective in resistance to

itch of AD [130]. Selective Serotonin Reuptake Inhibitors (SSRI), for example, paroxetine and fluvoxamine, are available to relieve pruritus [131]. Besides, Mirtazapine may attenuate pruritus of patients with ESRD, cholestasis, advanced cancer, and nocturnal itch [132].

In addition to these medicines mentioned above, other drugs, consisting of calcium channel modulator (pregabalin), thalidomide, benzodiazepines (alprazolam), antipsychotic drugs (pimozide), and ondansetron, work well in relief of itching [133, 134].

5.5. Chinese Traditional Treatment. Based on the perspective of whole and dialectical therapy, traditional Chinese medicine has great advantages on all kinds of itching. At present, traditional Chinese medicines in management of pruritus mainly cover oral herbal medicine, herbal fumigation, external washing, and acupoint therapy, all of which have obvious effects in relief of pruritus [135]. More importantly, we have demonstrated in our study that tripterygium hypoglaucum hutch, a kind of traditional Chinese medicine, is a good choice for relieving the pruritus of chronic urticaria [136].

6. Conclusions

In summary, pruritus clinically covers five categories and extends to a variety of pruritus-related clinical diseases. Although itching mechanism is still unclear, it probably involves various mediators and receptors, the specific nerve fiber, neurotransmitters, and signaling pathways. In spite of poor efficacy in intractable itch with histamines, Hl receptor antagonists, at present, are still widely used as first-line drugs. However, the interaction between H4 and H1 receptors and the development of H4 receptor antagonists should not to be put a high premium. In addition, many molecules are involved in the pathogenesis of itch. Such a complex mechanism indicates that the search for satisfactory vehicles remains a great challenge, and several future strategies for pruritus should be employed such as comprehensive treatment and interdisciplinary measures.

Disclosure

Jing Song and Dehai Xian are coauthors.

Conflicts of Interest

No financial or other conflicting interests exist.

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Clinical Study

Do Tonic Itch and Pain Stimuli Draw Attention towards Their Location?

Antoinette I. M. van Laarhoven,[1,2,3] Stefaan van Damme,[4] A. (Sjan) P. M. Lavrijsen,[5] Dimitri M. van Ryckeghem,[4,6] Geert Crombez,[4,7] and Andrea W. M. Evers[1,2,3]

[1]*Health, Medical, and Neuropsychology Unit, Faculty of Social and Behavioral Sciences, Leiden University, Leiden, Netherlands*
[2]*Leiden Institute for Brain and Cognition (LIBC), Leiden University, Leiden, Netherlands*
[3]*Department of Psychiatry, Leiden University Medical Center, Leiden, Netherlands*
[4]*Department of Experimental-Clinical and Health Psychology, Ghent University, Ghent, Belgium*
[5]*Department of Dermatology, Leiden University Medical Center, Leiden, Netherlands*
[6]*Faculty of Humanities and Social Sciences, Research Unit INSIDE, Institute of Health and Behaviour, University of Luxembourg, Esch-sur-Alzette, Luxembourg*
[7]*Centre for Pain Research, University of Bath, Bath, UK*

Correspondence should be addressed to Antoinette I. M. van Laarhoven; a.vanlaarhoven@fsw.leidenuniv.nl

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Background. Although itch and pain are distinct experiences, both are unpleasant, may demand attention, and interfere with daily activities. Research investigating the role of attention in tonic itch and pain stimuli, particularly whether attention is drawn to the stimulus location, is scarce. *Methods*. In the somatosensory attention task, fifty-three healthy participants were exposed to 35-second electrical itch or pain stimuli on either the left or right wrist. Participants responded as quickly as possible to visual targets appearing at the stimulated location (ipsilateral trials) or the arm without stimulation (contralateral trials). During control blocks, participants performed the visual task without stimulation. Attention allocation at the itch and pain location is inferred when responses are faster ipsilaterally than contralaterally. *Results*. Results did not indicate that attention was directed towards or away from the itch and pain location. Notwithstanding, participants were slower during itch and pain than during control blocks. *Conclusions*. In contrast with our hypotheses, no indications were found for spatial attention allocation towards the somatosensory stimuli. This may relate to dynamic shifts in attention over the time course of the tonic sensations. Our secondary finding that itch and pain interfere with task performance is in-line with attention theories of bodily perception.

1. Introduction

Itch and pain are common somatosensory sensations, which, in acute form, function to protect body integrity, for example, penetration of the skin or stinging insects [1]. When chronic, for example, due to chronic inflammatory conditions of the skin, joints, or viscera, they often have a serious impact on quality of life and performance in daily activities [2–4]. One of the primary reasons for this burden is that itch and pain demand attention in order to perform their protective role [1, 5–7]. For example, when we touch a sharp object or red ants crawl on our skin, fast detection and identification of the threat along with interruption from a concurrent task are adaptive as we can impose action to prevent bodily damage. The interplay between attention and pain has frequently been investigated. The interplay between attention and itch, however, has barely received attention.

Leading cognitive frameworks on pain, which might to some extent also apply for itch, propose that pain draws attention and as such interrupts ongoing task performance and goal pursuit [7–12]. Overall, studies indicate that patients with chronic pain attend more to pain-related stimuli than control participants and have difficulties disengaging their attention away from pain [5, 6]. Such impaired ability to

disengage attention from pain or pain-related information is believed to detrimentally affect functioning in daily activities [5–7]. Pain interferes with task performance [13–18], probably by directing attention to the location where the pain is expected and/or experienced. More recently, studies have focused upon the spatial attention allocation in pain [19–27]. It was found that attention was directed to the bodily location where threatening somatosensory stimuli were expected to occur [23–25]. It is reasonable to assume that individual differences in catastrophizing, worrying, and pain-related fear amplify the threat value of somatosensory stimuli and thus lead to a stronger prioritization of attention [5, 15, 28–32]. Also attempting to control pain leads to a similar allocation of attention towards the location where somatosensory stimuli are expected to occur [21, 26]. A heightened level of attention for pain and its location may then intensify the pain sensation or its impact upon daily functioning [5, 26]. These processes may also play a role in patients with chronic pain or itch [9, 10, 33, 34]. With regard to attention and itch, there are only some indications that itch-related information (e.g., words or pictures) draws attention [35–38] and that more bodily attention is related to heightened itch sensitivity [39]. However, research into spatial allocation of attention while experiencing itch is limited [38].

The investigation of spatial attention in pain and itch requires the use of specific paradigms. For example, spatial attention allocation has been investigated while participants perceive somatosensory pain stimuli on different locations while focusing on and responding to the location of tactile/visual/auditory target stimuli that are ipsilateral or contralateral to the pain location (e.g., [19–27]). Attention allocation to the stimulation location is inferred when participants respond faster to visual targets displayed ipsilaterally than on targets displayed contralaterally to stimulation, as can be deduced from the attentional bias index (i.e., the difference in response time to the contralateral minus the ipsilateral targets [20]). Enhanced focusing on the ipsilateral location is indicative for an attentional engagement, whereas faster responses on the contralateral location are indicative for disengagement of attention away from the stimulus, and when the attentional bias index significantly deviates from zero, there is an attentional bias. It has generally been found that pain draws attention towards its location, that is, attentional engagement [19–27]. Most of these studies, with the exception of [27], use phasic stimuli (≤1 s). However, patients often experience symptoms for a longer duration, stressing the importance of being able to disengage attention from pain and focus on activities in daily life. This is not only relevant for the study of pain, but also for itch, which is a sensation that is often prolonged by attentional processes, given its contagiousness [40]. For itch, we developed a somatosensory attention task (SAT) [38] with tonic itch stimuli of 35 s during which participants responded as quickly as possible to visual targets located at the stimulated or nonstimulated location. We did not find that healthy participants focused their attention towards the itch location; instead, we found some indications that participants disengaged their attention away from the itch location during the second half of the 35 s itch stimuli [38]. However, given the discrepancy with previous findings for pain showing that pain draws attention to its location, additional research involving both tonic itch and pain is required.

The aim of the present study was to investigate whether healthy participants focus their attention at or away from the tonic itch and pain stimulus location. It was expected that the participants' attention would be drawn to the location of the itch and pain stimuli early on but later on during the stimulation would disengage their attention from the stimulated location. Additionally, the relationship between attentional processing of itch and pain and other psychological characteristics, specifically self-reported catastrophizing, neuroticism, perceived threat of the somatosensory stimuli, attention for bodily sensations, and attentional disengagement from itch and pain was explored.

2. Methods

2.1. Participants. Fifty-three healthy volunteers (45 female/8 male; mean age of 22.0 years, SD = 2.2; range 18.6–29.4 years) were included. Participants were recruited through advertisements at Leiden University and the Leiden University Research Participation system (SONA systems Ltd., Tallinn, Estonia). Inclusion criteria for participation were being aged between 18 and 30 years (with the intention to include a homogenous group since reaction times increase with age [41]) and fluent in Dutch language. Exclusion criteria for participation were being a patient with chronic itch or pain, severe morbidity (e.g., multiple sclerosis, diabetes mellitus, heart or lung disease, and vasculitis), psychiatric disorders (e.g., depression), use of pacemaker, current use of medication (e.g., analgesics, antihistaminics), and pregnancy. Of the participants, 73.6% were following or had finished tertiary education, 24.5% were following or had finished secondary education, and 1.9% had followed primary education. The protocol was approved by the local Medical Review Ethics Committee and all participants provided written informed consent prior to testing.

2.2. Itch and Pain Induction. Itch and pain were induced electrically by means of a constant current stimulator (Isolated Bipolar Constant Current Stimulator DS5, Digitimer, United Kingdom) [37, 38, 42]. For itch induction, two surface electrodes were attached to the center of the lateral side of the wrist, a disk electrode (ø 1 cm, VCM Medical, The Netherlands) 1.5 cm proximal to the triquetrum, and a reference electrode (ø 2 cm, VCM Medical, the Netherlands) 2 cm proximal [37, 38, 42]. For pain induction, two surface electrodes (two disk electrodes of ø 1 cm, VCM Medical, the Netherlands) were attached at the center of the dorsal side of the wrist [20], one 1.5 cm proximal to the processus styloideus ulnae and the other 2 cm proximal. In accordance with our previous studies with electrically induced itch [37, 38, 42], the stimulus characteristics for the itch stimuli were 50 Hz frequency, 0.1 ms pulse duration, and a ramping of 0.05 mA/s. The itch stimuli lasted for at maximum 35 seconds, the duration of the stimuli in the SAT. For pain, the stimulus characteristics were partly based on previous studies (e.g., [24, 43]) and partly determined by extensive piloting of the

methods since electrical pain stimuli are not regularly applied for 35 seconds. Eventually, pain stimuli were applied also at 50 Hz frequency and 0.4 ms pulse duration. Alike our previous studies [37, 38, 42], the maximum current for all stimuli was 5.00 mA. The levels of itch and pain evoked by each electrical stimulus were scored on a numerical rating scale (NRS) ranging from 0 (no itch/pain) to 10 (worst itch/pain ever experienced).

2.2.1. Determination of the Intensity of the Itch Stimuli. In order to determine the individual intensity at which the 35 s baseline itch stimulus and the itch stimuli during the SAT were delivered, a step-up procedure was executed with 35 s stimuli starting at 0.25 mA, with 0.50 mA increments for every step. For example, the first stimulus started at 0.25 mA and, as a consequence of the ramping, ended at 2.00 mA; the second started at 0.75 mA and ended at 2.50 mA. Because the first step ended relatively high, just before the itch step-up, familiarization with the stimulation took place by assessing two perception thresholds starting at 0.01 mA and ending when the participant reported "the moment that you experience a sensation for the first time" [42]. The step-up procedure finished when the aimed NRS itch was at least 5 or the maximum defined current intensity of 5.00 mA was reached (i.e., stimulus from 3.25 to 5.00 mA). However, in the case the NRS itch exceeded 7, the current intensity was decreased with 0.5 mA (when NRS itch $\geq$ 8) or 0.25 mA (when NRS itch $\geq$ 7) up until the NRS itch was between 5 and 7. In this study, the determined starting current intensity for the baseline and SAT itch stimuli was on average 2.36 (SD = 1.26) mA.

2.2.2. Determination of the Intensity of the Pain Stimuli. In order to determine the individual intensity at which the 35 s baseline pain stimulus and the pain stimuli during the SAT were delivered, a step-up procedure was executed with 10 s stimuli (in order to keep stimulation time better comparable to the itch step-up procedure which consisted of less steps) that increased by 0.50 mA per step. The first stimulus was given at 0.50 mA, the second at 1.00 mA, and so on. The step-up procedure was finished when the aimed NRS pain was at least 5 or the maximum defined current intensity of 5.00 mA was reached. However, in the case the NRS pain exceeded 7, the current intensity was decreased with 0.5 mA (when NRS pain $\geq$ 8) or 0.25 mA (when NRS pain $\geq$ 7) up until the NRS pain was between 5 and 7. In this study, the determined current intensity for the 35 s baseline pain stimulus before the SAT and the pain stimuli during the SAT was on average 3.70 (SD = 1.59) mA.

2.3. Somatosensory Attention Task. The somatosensory attention task (SAT) as used in our previous study [38], which was based on an attention task developed for pain [20], was adopted to investigate attention allocation towards both an itch and pain stimulation and their location (see Figure 1 for a schematic representation of the setup). A plastic black curved screen of ca. 50 cm height with 3 LED lights at 10 cm height (middle green fixation LED, the left and right were red target LEDs placed at 25 degrees from the middle LED) was placed

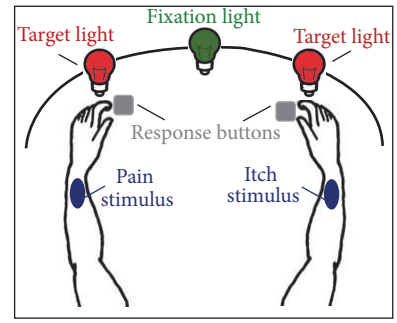

Figure 1: Schematic representation of the setup of the somatosensory attention task. The side of itch stimulation was contralateral to the pain stimulation (randomized across participants). During a block, an itch (itch block) or pain (pain block) stimulus was applied, or no stimulation (control blocks), while, after short onset of the fixation light, one of the target lights illuminated. Participants responded to the target light location using response buttons right below both target lights, at either the ipsilateral or the contralateral location as opposed to the somatosensory stimulation.

in front of the participant. The LEDs were controlled using E-prime software version 2.0 (Psychology Software Tools Inc., Sharpsburg, PA, USA) on a Dell optiplex 3010 computer with Philips Brilliance 225 TFT screen (Resolution 1280 × 1024 at 60 Hz). Right below the left and right LED there was a platform with finger response buttons (Pushbutton Switch, SPDT, Off-(On)) at a fixed position, attached to a serial response box (Psychology Software Tools Inc. Sharpsburg, PA, USA).

The SAT consisted of 12 blocks of 35 seconds each, of which 4 blocks with pain stimuli (pain blocks), 4 blocks with itch stimuli (itch blocks), and 4 blocks without somatosensory stimulation (control blocks). The order of blocks was randomized by E-Prime for each participant. The standard interval between two blocks was 1 minute, which was extended by 1 minute up to a maximum of 5 minutes in the case the NRS pain or NRS itch exceeded 2.0. During each block 10 trials with visual targets were administered, in which first the fixation light (green LED light) was turned on for 1000 ms and extinguished, and then either the left or right target (red LED light) was turned on for 200 ms [38], while unilaterally administering itch (itch blocks) or pain (pain blocks) stimuli, or no stimulation (control blocks). The response window for participants to press a button was 1500 ms. The 10 target stimuli in each block were given in random order with random time interval (varying between 0 and 2000 ms) before the next trial. Half of the visual targets were presented at the wrist where the electrodes were attached and itch or pain was applied in the case of itch and pain block, respectively ("ipsilateral trials"), and half of the visual targets were presented oppositely ("contralateral trials"). Conforming previous research (e.g., [20]), the difference in participants' responding to ipsilateral versus contralateral trials is a measure of spatial attention allocation towards the somatosensory stimulus, with faster responses to ipsilateral trials being indicative for an attentional bias.

2.4. Self-Report Questionnaires. The following self-report questionnaires were administered in Dutch using the online system Qualtrics (Provo, Utah, USA).

The *presence of physical symptoms* was assessed by visual analogue scales (VAS) for itch and pain from the Impact of chronic skin disease on daily life (ISDL) [44], inquiring about the levels of itch and pain during the past two weeks on a scale from 0 (no itch/pain) to 10 (worst itch/pain experienced).

Psychological distress was measured with the *Hospital Anxiety and Depression Scale (HADS) [45]* and a short version of the *Positive and Negative Affect Schedule (PANAS)* [46]. The HADS consists of 7 items measuring the subscale depression (Cronbach alpha in the present study was 0.67) and 7 items measuring the subscale anxiety (Cronbach alpha 0.71), scored on a scale from 0 to 3. The total score was obtained by summing the items per subscale. The PANAS consists of 5 positive items (PANAS-PA; Cronbach alpha 0.59) and 5 negative items (PANAS-NA; Cronbach alpha 0.35) scored on a 5-point Likert scale from 1 to 5. Due to the low reliability, the PANAS was excluded from data analyses.

Catastrophizing about physical sensations was measured using the *Pain Catastrophizing Scale* [47], adjusted for physical sensations (PCS-A) in order to make it also applicable to itch (i.e., by substituting the word "pain" for "physical sensations" for all concerning items). The questionnaire contained 13 items, which were scored on a 5-point Likert scale from 0 to 4. The Cronbach alpha for the PCS-A in the present study was 0.87.

Neuroticism was measured with the *Eysenck Personality Questionnaire revised short scale* (EPQ-RSS) [48], consisting of different subscales, including the subscale neuroticism (Cronbach alpha = 0.72), which consists of 12 items rated on a dichotomous scale (yes = 1/no = 0).

Fear of pain was measured using the Fear of Pain Questionnaire III (FPQ-III) [49], with 30 items assessing the degree of fear participants would likely experience in potentially painful situations, subdivided in the categories severe pain, minor pain, and medical pain. The items are rated on a 5-point scale from 1 (not at all fearful of this pain) to 5 (extremely fearful of this pain). Cronbach alpha of the FPQ-III in the present study was 0.90.

Attentional focus on bodily sensations was measured using the Body Vigilance Scale (BVS) [39, 50], the *Body Sensations questionnaire* [39, 51], and the *Pain Vigilance* and Awareness Questionnaire [52] adjusted for physical sensations (i.e., by substituting the word "pain" by "physical sensations" for all concerning items) *(PVAQ-A)* in order to make it broadly applicable to physical sensations, including itch and pain. The BVS, used to measure attentional focus on bodily sensations, contained 4 items, of which the fourth item consisted of 13 subitems about anxiety-related bodily sensations. All items were rated on a VAS from 0 to 10. Cronbach alpha of the BVS in the present study was 0.79. Additionally, two items had been added that assess one's attention directed towards itch and pain. Of the BSQ, the 15 items concerning bodily sensations (omitting the 2 items concerning derealization) were used to measure of attentional focus on the occurrence of bodily sensations when in a nervous or feared situation (e.g., heart palpitations, dizziness or sweating). Participants used a 5-point Likert scale that ranged from "the sensation never occurs" (0) to "the sensation occurs almost always or always" (4). Cronbach alpha of the BSQ in the present study was 0.79. The PVAQ-A was used to measure attention to bodily sensations by asking subjects to consider their behavior in relation to physical sensations. The PVAQ-A (Cronbach alpha 0.85) consisted of 16 items, for example, "I focus on physical sensations." Items were scored on a 6-point Likert scale (0 never to 5 always).

Attentional disengagement from itch and pain was assessed using two Likert scales ranging from 1 (not at all able to disengage attention) to 5 (always able to disengage attention).

In addition to these online questionnaires, participants indicated the perceived threat of the stimuli applied in the experiment on a scale from 0 (not threatening) to 10 (very threatening). Participants also rated the extent to which they were distracted by the itch or pain stimuli or other factors during their responses to the visual targets in the SAT on 5-point Likert scales ranging from 1 (not at all distracted) to 5 (distracted to very large extent).

2.5. Procedure. Potential participants were informed about the study via written information. When interested in participation, they clicked on an online link to fill out several questions. These concerned demographic variables, absence or presence of medical or psychiatric conditions, intake of medication during the past 4 weeks, the VAS for itch and pain, HADS, PCS-A, EPQ-RSS, FPQ-III, BSQ, PVAQ-A, and attentional disengagement from itch and pain (see Section 2.4). Based on the online assessment, eligibility screening was performed on inclusion and exclusion criteria. Uncertainties about eligibility were solved by telephone contact. Eligible participants made an appointment for participation. Participants were instructed to refrain from intake of alcohol and drugs 24 hours before attending the experiment. Upon arrival at the test facility, participants were verbally informed about the procedure and told that they were free to terminate the experiment at any time. Then participants signed the informed consent. In the lab, subjects also rated their current levels of spontaneous itch and pain as well as perceived fatigue on an NRS ranging from 0 (no itch/pain/fatigue) to 10 (worst itch/pain/fatigue ever experienced) and filled out the BVS and PANAS.

In order to standardize the participants' wrist temperature, which could influence electrical conductivity [53], subjects held their wrists for 3 minutes in a warm water bath made at 34°C [see also [37, 42]], before the electrical stimulation. The side of itch and pain stimulation (left and right wrist or vice versa) was randomized across participants. Then, the step-up procedures for itch and pain were carried out in random order to determine the individual intensity of the itch and pain stimuli. At the individually determined intensity, baseline itch and pain stimuli were applied for 35 seconds. Right before the SAT, participants were asked to position their index fingers of the left and right hand on the left and right response button, respectively. They were instructed to focus on the visual stimuli and to respond as quickly as possible to the location of a target LED illuminating, by pressing the response button at the ipsilateral

side. Before each block, participants were informed whether they would receive a pain stimulus (i.e., pain block), an itch stimulus (i.e., itch block), or no stimulus at all (i.e., control block). At the start of each block, the experimenter counted down from 3 to 0, to indicate the onset (at 0) of a block. Directly following each block, participants were asked to retrospectively report the levels of itch and pain that were evoked (irrespective of any ongoing spontaneous itch or pain) during the block on NRSs ranging from 0 (no itch/pain) to 10 (worst itch/pain ever experienced). After all measurements, participants indicated the perceived threat of the itch and pain stimuli and the extent to which they were distracted during their task performance to respond to the visual targets. After a short debriefing, participants received a monetary reimbursement.

2.6. Statistical Analyses. Reaction times (RT) for trials with RT ≥ 150 ms (0.2% of the trials were excluded) and trials with correct responses (0.6% of the trials were excluded) were extracted from E-prime. Data of two participants were excluded [fire alarm evacuation ($n = 1$), problems with itch stimulation ($n = 1$)] because ≤70% of the RT data was available [38]. Using Matlab and Statistics Toolbox Release 2012b (The MathWorks, Inc., Natick, Massachusetts, USA) the mean RT per trial type (i.e., ipsilateral and contralateral trials during pain, itch, and control blocks) were calculated per participant. Participants' accuracy for the SAT was checked, and no one's data had to be removed based on the criterion of >30% mistakes [38]. Additionally, RT per trial type were calculated for three consecutive time segments of the 35 s SAT blocks. Three was the maximum number of segments the blocks could be split into to remaining sufficient observations per trial type.

All variables to be included in the statistical analyses were checked for normal distribution and transformed when necessary. Transformation did not result in normal distribution of the NRS itch and pain scores during the control blocks and assumptions for the majority of psychological characteristics were not met. In addition, there were two participants displaying outlying RT (i.e., >3 SD of the overall mean) for the majority of the trial types. Therefore, the analyses were conducted both in all 51 participants and after excluding the two outliers ($n = 49$) combined with log-transforming variables.

A manipulation check, to confirm that the intended sensations had been induced in the respective blocks, was conducted comparing the NRS itch and pain scores for the itch and pain blocks, respectively, to the control blocks using nonparametric sign tests. Similarly, NRS unpleasantness ratings were exploratorily compared across the different block types. An attentional bias index (AB-index) was calculated for itch and pain [20] using the formula $RT_{contralateral} - RT_{ipsilateral}$, during itch and pain blocks, respectively. A positive AB-index indicated that attention was directed ipsilaterally to the stimulus location (attentional engagement), while a negative AB-index indicated that attention was directed contralaterally to the stimulus location (attentional disengagement). One-sample t-tests were conducted to assess whether the AB-indices significantly differed from zero, that is, implying attentional bias. In order to test the main hypothesis of whether participants focused attention on the itch and pain location, two repeated measures analyses of variance (RM-ANOVAs) were carried out with the within-subjects factors location (ipsilateral versus contralateral) and block type (either itch or pain versus control). Separate analyses for itch and pain were required because the factor location in the control blocks referred to the location of the attached itch and pain electrodes, which were oppositely attached, and, consequently, for control blocks, the ipsilateral location was indecisive. Main effects of location and block type were calculated, as well as location × block type interactions. Exploratorily, a similar RM-ANOVA was conducted to compare the RT for the itch versus pain blocks (control blocks were not included). In order to investigate the course of attention allocation over time, 2 × 2 × 3 RM-ANOVAs were conducted, for itch and pain separately, with the within-subjects factors location (ipsilateral versus contralateral), block type (either itch or pain vs. control), and time (first, second, and third time segment of blocks). Main effect of time and location × block type × time interactions were calculated. For all RM-ANOVAs, a generalized eta squared was calculated [54, 55].

Finally, Pearson correlation coefficients were calculated between the AB-indices for itch and pain. Nonparametric correlation coefficients (Spearman) were calculated between the psychological characteristics (EPQ-RSS-n, BVS, BSQ-f, PVAQ-A, PCS-A, FPQ-III, attentional focus on and disengagement from itch and pain, and perceived threat of the stimuli) and itch and pain AB-indices.

Statistical analyses were conducted using SPSS 23.0 software (IBM SPSS Statistics for Windows, Armonk, NY, USA). All values displayed are means ± SD, unless stated otherwise. A $p < 0.05$ was considered statistically significant.

3. Results

3.1. Participants. The baseline levels of itch, pain, and fatigue and outcomes of self-report questionnaires measuring the psychological characteristics of the 53 participants included are displayed in Table 1. The reasons for baseline spontaneous itch levels >0 ($n = 10$ in total, $M_{NRS\text{-}itch>0} = 1.1 \pm 0.5$, ranging from 0.5 to 2.0) were talking/thinking about itch as a result of this specific question ($n = 5$), dry skin ($n = 2$), sweating due to traveling ($n = 1$), epilated armpit ($n = 1$), and some skin irritation ($n = 1$). The reasons for baseline spontaneous pain levels >0 ($n = 8$ in total; $M_{NRS\text{-}pain>0} = 1.1 \pm 0.5$, ranging from 0.3 to 2.0) were sore throat ($n = 2$), muscle ache ($n = 2$), back ache ($n = 1$), knee pain resulting from surgery some weeks ago ($n = 1$), menstruation pain ($n = 1$), and finger cut ($n = 1$).

3.2. Manipulation Check: Induced Itch and Pain. The itch, pain, and unpleasantness scores for the baseline itch and pain stimuli and those during the SAT blocks are displayed in Table 2. Nonparametric sign tests showed that median NRS itch scores were significantly higher during itch than control blocks of the SAT and median NRS pain scores were significantly higher during pain than control blocks

Table 1: Total scores of self-reported questionnaires ($n = 53$).

	Mean score ± SD	Range
Level of spontaneous itch at baseline	0.2 ± 0.5	0.0–2.0
Level of spontaneous pain at baseline	0.2 ± 0.4	0.0–2.0
Level of fatigue at baseline	1.8 ± 1.3	0.0–5.5
Affect		
Anxiety (HADS-Anxiety)	2.4 ± 0.5	0.9–3.0
Depression (HADS-Depression)	2.7 ± 0.3	1.9–3.0
Personality characteristics		
Neuroticism (EPQ-RSS)	3.2 ± 2.5	0–11.0
Attention to bodily sensations		
Attentional focus on itch	2.2 ± 1.9	0–6.5
Attentional focus on pain	3.3 ± 2.4	0–8.0
BVS	2.8 ± 1.5	0.2–6.8
BSQ	2.0 ± 0.5	1.3–3.3
PVAQ-A	24.2 ± 9.5	4–45
Catastrophizing		
PCS-A	7.5 ± 6.4	0–29
Fear of pain		
FPQ-III	63.3 ± 15.9	36–101
Attentional disengagement from		
Itch	4.3 ± 1.0	1–5
Pain	4.0 ± 0.9	1–5

HADS: Hospital Anxiety and Depression Scale (theoretical range 0–21 per subscale); EPQ-RSS: Eysenck Personality Questionnaire revised short scale (theoretical range 0–12 neuroticism subscale); Single items assessing attentional focusing on itch and pain (theoretical range 0–10); BVS: Body Vigilance Scale (theoretical range 0–10); BSQ: Body Sensations Questionnaire (theoretical range 1–5); PVAQ-A: Pain Vigilance and Awareness Scale, adjusted for physical sensations (theoretical range 0–80); PCS-A: Pain Catastrophizing Scale, adjusted for physical sensations (theoretical range 0–52); FPQ: Fear of pain questionnaire (theoretical range 30–150); single items about attentional disengagement (theoretical range 1–5).

Table 2: Means ± standard deviations of NRS itch, pain, and unpleasantness scores at baseline and during the pain, itch and control blocks of the somatosensory attention task (SAT) ($n = 51$).

	NRS itch	NRS pain	NRS unpleasantness
Baseline itch stimulus	**3.5 ± 2.2**	0.6 ± 1.1	2.3 ± 2.0
Baseline pain stimulus	0.9 ± 1.3	**3.9 ± 1.7**	3.4 ± 1.8
SAT itch blocks	**1.8 ± 1.6**	0.2 ± 0.4	1.2 ± 1.5
SAT pain blocks	0.5 ± 0.8	**3.0 ± 1.7**	2.7 ± 1.7
SAT control blocks	0.1 ± 0.2	0.0 ± 0.1	0.0 ± 0.1

Note. The electrical current at which the itch and pain stimuli were applied was tailored to individual sensitivity and was identical during baseline measurements and the SAT. NRS: numerical rating scale.

(both $p < 0.0005$). Median NRS unpleasantness scores were significantly higher during itch and pain blocks than during control blocks (both $p < 0.0005$) and also significantly higher during pain blocks than during itch blocks ($p < 0.0005$).

3.3. Perceived Threat of the Stimuli. The induced pain and itch were, on average, perceived as 2.8 ± 2.4 and 1.5 ± 1.8 threatening, respectively. With regard to the degree to which participants were distracted from the task to respond to the visual targets, they indicated to be distracted by the itch and pain stimuli on average 3.2 ± 1.0 and 2.5 ± 1.1, respectively, and 1.8 ± 0.6 by other factors.

3.4. Behavioral Outcomes. With regard to the accuracy, the average number of mistakes made during the SAT over all participants was 0.6 ± 1.3 (range 0 to 8; theoretical maximum 120), with overall 0.5% mistakes during itch blocks, 0.4% mistakes during pain blocks, and 0.6% mistakes during control blocks. The mean RTs (of correct responses) during itch, pain, and control blocks for the ipsilateral and contralateral trials are displayed in Table 3.

The location × block type interaction effect was of primary interest to this study as this indicated whether attention was drawn to the stimulus location. For itch, the RM-ANOVA comparing the ipsilateral and contralateral trials

Table 3: Mean reaction times (in ms) ± standard deviation for the ipsilateral and contralateral trials of the somatosensory attention task (SAT) during itch, pain, and control blocks ($n = 51$).

	Mean reaction times (ms) of ipsilateral trials	Mean reaction times (ms) of contralateral trials
Itch blocks	466.2 ± 91.0	463.7 ± 84.4
Pain blocks	470.7 ± 81.8	472.5 ± 80.9
Control blocks	450.4 ± 81.2[1]	457.4 ± 88.5[2]

[1]Reaction times during control blocks (no somatosensory stimulation) ipsilateral to attached itch electrodes location. [2]Reaction times during control blocks (no somatosensory stimulation) ipsilateral to the attached pain electrodes location.

(factor 1: location) during the itch and control blocks (factor 2 block type) did not show a significant location × block type interaction effect ($F(1, 50) = 0.78$, $p = 0.38$, $\eta_G^2 = 0.0014$). There was, however, a significant main effect of block type ($F(1, 50) = 12.80$, $p < 0.001$, $\eta_G^2 = 0.019$), with longer RT for itch blocks than control blocks. The main effect of location was not significant ($F(1, 50) = 0.13$, $p = 0.72$, $\eta_G^2 = 0.0003$). For pain, the RM-ANOVA did not show a significant interaction effect of location × block type ($F(1, 50) = 0.71$, $p = 0.41$, $\eta_G^2 = 0.00012$). Again, there was a significant main effect of block type ($F(1, 50) = 21.29$, $p < 0.0001$, $\eta_G^2 = 0.05$), with longer RT for pain blocks than for control blocks, but no significant main effect of location ($F(1, 50) = 0.16$, $p = 0.69$, $\eta_G^2 = 0.00032$). After removing the two outliers, similar levels of significance were obtained. In line with the main findings of the nonsignificant location × block type interaction, no significant attentional biases were found as the AB-indices for itch ($t(50) = -0.51$, $p = 0.61$) and pain ($t(50) = 0.18$, $p = 0.86$) did not significantly differ from zero.

Explorative comparison of the itch and pain blocks showed no significant interaction effect of location × block type ($F(1, 50) = 0.13$, $p = 0.72$, $\eta_G^2 = 0.00036$), nor a significant main effect of location ($F(1, 50) = 0.004$, $p = 0.952$, $\eta_G^2 = 0.00001$), but the overall RT were significantly longer for the pain than for the itch blocks ($F(1, 50) = 5.26$, $p = 0.026$, $\eta_G^2 = 0.0109$).

3.5. Time Course of Attention during the SAT. In a further analysis of the data, Figure 2 displays the RT for the ipsilateral and contralateral trials during the itch (Figure 2(a)), pain (Figure 2(b)), and control (Figure 2(c)) blocks, which are subdivided into three equal time segments. For itch, there was no significant location × block type × time interaction ($F(2, 100) = 2.01$, $p = 0.140$, $\eta_G^2 = 0.0068$), but a significant main effect of time ($F(2, 100) = 3.77$, $p = 0.026$, and $\eta_G^2 = 0.015$) emerged. Simple contrast analyses showed that RT were significantly faster in the second than in the first segment ($F(1, 50) = 6.73$, $p = 0.012$ and, $\eta_G^2 = 0.006$). There were no significant differences in RT when comparing the second with the third segment, although a nonsignificant trend was observed ($F(1, 50) = 4.03$, $p = 0.050$, and $\eta_G^2 = 0.038$), or when comparing the first and the third segment ($F(1, 50) = 0.48$, $p = 0.494$, and $\eta_G^2 = 0.0094$). For pain, there was no significant location × block type × time interaction ($F(2, 100) = 0.41$, $p = 0.662$, and $\eta_G^2 = 0.0012$), nor a significant main effect of time, although a trend was observed ($F(2, 100) = 2.99$, $p = 0.055$, and $\eta_G^2 = 0.012$).

After removing the two outliers, similar results were obtained in the 2 × 2 × 3 RM-ANOVA for itch. For pain results were also comparable after removing the two outliers, although now a significant main effect of time ($F(2, 96) = 3.17$, $p = 0.047$, and $\eta_G^2 = 0.015$) was found. Simple contrast analyses showed significantly faster RT in the second than in the first segment ($F(1, 48) = 7.30$, $p = 0.010$, and $\eta_G^2 = 0.026$), but no significant differences in the second compared to the third segment ($F(1, 48) = 1.43$, $p = 0.237$, and $\eta_G^2 = 0.011$) nor in the first compared to the third segment ($F(1, 48) = 1.54$, $p = 0.221$, and $\eta_G^2 = 0.019$).

3.6. Exploratory Analyses: Association between Individual Characteristics and Attentional Bias towards Itch and Pain. The AB-index for itch was on average −2.9 ± 39.9 and ranged from −80.1 to 90.2; 39.2% of the participants displayed a positive AB-index (i.e., towards the itch stimulus location). The AB-index for pain was on average 1.0 ± 41.0 and ranged from −79.5 to 86.5; 54.9% of the participants displayed a positive AB-index (i.e., towards the pain stimulus location). The AB-indices for itch and pain were not significantly correlated ($R = -.252$, $p = 0.074$). The AB indices were generally not significantly correlated with the psychological characteristics neuroticism (EPQ-RSS), catastrophizing of physical sensations (PCS-A), fear of pain (FPQ-III), self-reported attention to itch and pain and to bodily sensations in general (BVS, BSQ, PVAQ-A), attentional disengagement from itch and pain, and the perceived threat of the induced itch and pain. Only four significant correlations were observed. There were positive associations between the AB-index for itch and catastrophizing ($r_S = 0.40$, $p = 0.003$), neuroticism (EPQ-RSS-n) ($r_S = 0.37$, $p = 0.008$), and the threat value of the itch stimulus ($r_S = 0.29$, $p = 0.04$). There was a negative association between the AB-index for pain and the threat value of the pain stimulus ($r_S = -0.30$, $p = 0.03$).

4. Discussion

The present study investigated whether attention of healthy volunteers would be spatially drawn to the stimulus location early on during tonic itch and pain stimuli, and, whether they would disengage their attention away from the stimulated location later on during stimulation. In the somatosensory attention task, participants received tonic somatosensory itch or pain stimuli or no stimulation while responding to the location of visual targets, either ipsi- or contralaterally displayed to the somatosensory location. In contrast with our expectations, no significant differences were found between

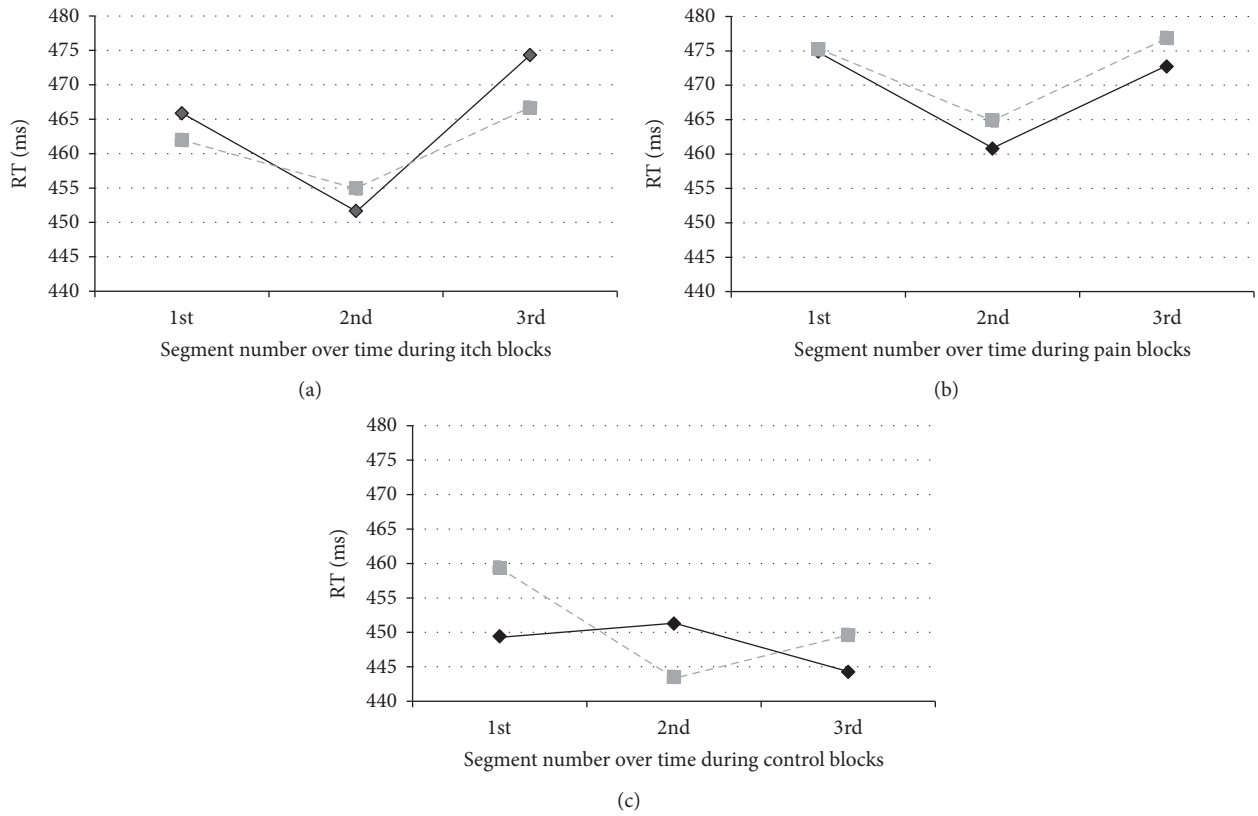

Figure 2: Reaction times (in ms) for participants ($n = 51$) responding to the visual target lights during the 35 s somatosensory itch (a) or pain bocks (b) or in control blocks, in which no somatosensory stimulation was applied (c). Visual targets were displayed either at the side of the itch or pain stimulation (i.e., ipsilateral trials, solid black line) or at the opposite side (i.e., contralateral trials, dashed grey line). In the case of control blocks, the solid black line is indicative for trials ipsilaterally to the attachment of the itch electrodes and the dashed grey line is indicative for trials ipsilaterally to the attachment of the pain electrodes.

responding to visual targets ipsilaterally compared to contralaterally to the stimulation, neither over the total duration of stimulation nor across the three successive time segments during the tonic itch and pain stimuli. Of further note, we observed that itch and pain stimulation slowed down participants' task performance (i.e., responding to visual targets) compared to no stimulation, indicating towards attentional interference by itch and pain. Overall, these results seem to indicate that itch and pain affect attentional processes, but that attention is not systematically directed towards nor disengaged from the location of tonic itch and pain stimulation.

There were no indications that attention was directed away from or towards the location of the itch and pain stimulation: reaction times for ipsilateral and contralateral trials did not significantly differ, nor was there a significant difference in spatial attention allocation between itch and pain. The indications for an attentional disengagement effect during the last part of the 35 s itch stimulation in our previous study [38] could not be confirmed here. In addition, we were also not able to replicate previous findings that pain directs attention towards its spatial location [19–27]. However, most of these studies used phasic pain stimuli with each trial consisting of one pain stimulus and one target stimulus [19–26] or pain stimuli of maximally 10 seconds [27]. It could be that the 35 s somatosensory stimuli in the present study along with multiple trials of visual targets during that stimulus may not draw attention to the stimulus location for the entire time frame. Attention likely continuously shifted between the somatosensory stimuli and visual targets. This process may have been enhanced because the participants were aware that the visual targets could be displayed ipsilateral or contralateral to the stimulation and the central fixation light before each trial could have influenced attention allocation. Moreover, the intensity of the itch and pain stimuli and the threatening character of the stimuli were relatively mild, and therefore the stimulus saliency may have been limited. Generally, in the present and the previous study there was a time effect showing that participants responded faster after the first segment. This may be owing to a learning effect as the participants learned to respond faster to the visual targets, leaving less attention to focus on the itch and pain sensations. This effect was, however, irrespective of the spatial location of the somatosensory stimuli. It could be that somatosensory stimuli only draw attention to the spatial location in the very beginning. However, the current segmentation of three time

segments might not be sufficiently fine-grained to determine continuous attentional shifts.

Of further note, our study did show that participants were generally slower in task performance of responding to the targets during itch and pain, which is indicative for attentional interference by itch and pain. The fact that pain interferes with attention has previously been demonstrated [13–18] although most studies used stimuli with a duration shorter than 35 s. Surprisingly, in our previous study with itch stimuli similar to those in the present study we did not find such an interference effect [38]. Exploratory findings indicate that pain may interfere more in attentional processing than itch, as overall reaction times (i.e., independent of stimulus location) were slower during pain than during itch. Explanations for this may include that pain is evolutionarily more aversive, as indicated by the higher reported threat value and unpleasantness of the pain stimuli presented here and, consequently, a higher saliency [10, 12]. However, it could also be related to the lower levels of evoked itch than pain. Reversely, participants may have better been able to ignore the itch and therefore perceived itch less intense during the attention task, akin previous findings showing that focusing away from pain can result in less intense pain [27, 56]. Support for this explanation comes from the large decline in itch when comparing the itch stimuli, at the same intensity, given at baseline and during the attention task. Another possible explanation could be that people habituate more easily to itch than to pain, but this has, to our knowledge, not yet been investigated.

Of the psychological characteristics the individual levels of catastrophizing of physical sensations and neuroticism were related to a higher attentional bias index for itch. However, given the nonsignificant association between catastrophizing and the attentional bias index for pain, these findings should be interpreted with caution. There were also some indications that higher perceived threat of the itch stimulus was related to a higher attentional bias index for itch, but higher perceived threat of the pain stimulus was associated with a lower attentional bias index for pain, which is contrary to what would be expected. Other psychological characteristics, including fear of pain and self-reported attention to and disengagement from physical sensations and itch and pain in particular, did not play a role in attention allocation towards the itch and pain stimuli. Future research should further investigate the role of individual characteristics in spatial attention allocation towards itch and pain.

This study has several limitations. First, the levels of itch induced during the attention task were relatively low and not directly comparable to pain. Second, after each block in the SAT, participants retrospectively rated the intensity of itch and pain during the somatosensory stimulation. It cannot be ruled out that participants also intentionally focused on the stimulation while responding to the visual targets. Third, the current design did not allow the investigation of fast attentional switches between somatosensory and visual stimuli. Future research may use more fine-grained time segments. Fourth, the included group was homogenous with respect to age but this limits extrapolation to other age groups.

5. Conclusions

This study showed that although tonic itch and pain stimuli interfere with task performance, attention is not consistently drawn towards their spatial location, probably because attention shifts over the time course of tonic stimuli. Additional research focusing more closely on time aspects of attention allocation is required to elucidate how tonic itch and pain stimuli are being processed in healthy participants and in clinical populations. When focusing attention on the location of itch or pain aggravates symptoms, patients with chronic itch and pain may benefit from learning to disengage their attention away from itch or pain, respectively.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Research Article

12-Item Pruritus Severity Scale: Development and Validation of New Itch Severity Questionnaire

Adam Reich,[1,2] Agnieszka Bożek,[1] Katarzyna Janiszewska,[1] and Jacek C. Szepietowski[1]

[1]*Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland*
[2]*Department of Dermatology, University of Rzeszów, Rzeszów, Poland*

Correspondence should be addressed to Adam Reich; adi_medicalis@go2.pl

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Introduction. A validated assessment of pruritus intensity is an important but still difficult clinical problem due to a subjective nature of this sensation. *Objective*. The aim of this study was the creation and validation of new itch severity questionnaire assessing pruritus intensity. *Material and Methods*. A total of 148 patients with pruritic dermatoses were asked to assess pruritus intensity using 12-Item Pruritus Severity Score (12-PSS) and Visual Analogue Scale (VAS). Patients were also asked to complete the Dermatology Life Quality Index (DLQI) and Hospitality Anxiety and Depression Scale (HADS). Test-retest comparison of 12-PSS was conducted in 102 subjects who completed the itch questionnaire twice with the 3- to 5-day interval. *Results*. We have created the 12-PSS assessing pruritus intensity (two questions), pruritus extent (one question) and duration (one question), influence of pruritus on concentration and patient psyche (four questions), and scratching as a response to pruritus stimuli (four questions). A maximum scoring was 22 points. The results showed strong consistency (Cronbach α coefficient 0.81). A significant correlation was observed with VAS ($r = 0.58$, $p < 0.001$) and quality of life level according to DLQI ($r = 0.53$, $p < 0.001$). Test-retest comparison in 102 subjects revealed a satisfactory reproducibility of achieved results (ICC = 0,72). *Conclusions*. The newly developed pruritus severity questionnaire may be used in daily clinical practice in the future.

1. Introduction

Pruritus is defined as an unpleasant sensation leading to the desire to scratch. It can be distinguished as acute (<6 weeks) or chronic (i.e., pruritus lasting 6 or more weeks). Chronic pruritus, which can be distressing and often refractory to treatment, is associated with many diseases. It is a primary symptom of various dermatological diseases, including atopic dermatitis, psoriasis, and urticaria. It is also a common feature of several systemic diseases, such as chronic kidney failure, cholestatic liver diseases, human immunodeficiency virus (HIV) infection, and haematopoietic disorders [1–3]. Chronic pruritus is often accompanied by a high level of psychiatric comorbidities and sleep disturbances with considerable impact on the health-related quality of life (QoL) [4]. Pruritus is a subjective symptom and, therefore, it is difficult to be accurately measured in an objective way. However, developing and validating measures are becoming increasingly important in dermatological research. The development of new therapeutic approaches requires an objective assessment of diseases. The assessment of the antipruritic effect is, to date, based solely on patient reports on the course of pruritus or measurements of scratch movements [4]. Assessing the intensity of pruritus as objectively as possible is extremely important, not only for research purposes, but also in clinical practice. However, an ideal scoring system for all the purposes is not available. Currently, several assessment methods are available to evaluate pruritus severity: monodimensional Pruritus Severity Scales (e.g., Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), and Verbal Rating Scale (VRS) [5]), multidimensional questionnaires (like the 5-D Pruritus Scale [2], Pruritus Severity Scale [3], and the Eppendorf Pruritus Questionnaire [6]), and the measurement of sensory threshold or scratching activity [7].

Based on the recently published consensus, it is recommended to use the VAS or NRS in daily clinical practice and at

least two independent methods in research studies or clinical trials [4]. However, no widely accepted, standardized, and validated questionnaire for objective measuring of pruritus is currently available [8]. The Visual Analogue Scale (VAS) is considered as the most reliable and valid pruritus assessment scale. However, it is clear that the use of a single measure of pruritus intensity does not ensure an adequate and comprehensive assessment of chronic pruritus, as pruritus may differ not only regarding its intensity, but also, for example, its duration or extent [8]. Numerous different methods were used for assessment of the intensity of pruritus in the past. However, most of them did not undergo proper validation and reliability testing. The lack of reliable pruritus assessment tools that would evaluate various aspects of pruritus has motivated us to develop and validate a new pruritus severity questionnaire that would assess pruritus intensity, scratching response, and the influence of pruritus on patient's mood and concentration.

2. Materials and Methods

2.1. Subjects. A total of 148 patients (81 females and 67 males) between ages 18 and 91 years (mean age, 50.0 ± 15.7 years) with chronic dermatological pruritus (>6 weeks) were included in the study. Pruritus was associated with lichen planus in 78 cases (52.7%), psoriasis in 31 cases (20.9%), atopic dermatitis in 25 cases (16.9%), and other skin diseases in 14 cases (9.5%). All patients were Caucasians. The patients were recruited from inpatients and outpatients attending regular visits at the Department of Dermatology, Venereology and Allergology, Wroclaw Medical University. Inclusion criteria for the study included (1) pruritus associated with one of the chronic skin diseases, (2) chronic pruritus defined as lasting for at least 6 weeks, (3) age over 18 years, (4) ability to give informed consent, and (5) ability to complete the questionnaire. All included subjects agreed to participate in the study and signed a written informed consent prior to any further procedures.

2.2. Development of 12-Item Pruritus Severity Scale. Creation of the 12-Item Pruritus Severity Scale (12-PSS) was based on the review of the literature concerning existing pruritus assessment tools, discussion with patients, and our own clinical experience in the diagnosis and treatment of patients with chronic pruritus. The development of our questionnaire has also been based on a consensus paper of the Special Interest Group (SIG) initiated by members of the International Forum on the Study of Pruritus (IFSI) to determine which domains and structure of pruritus questionnaires need to be implemented to assess chronic pruritus in a better way [8]. The 12-PSS is a one-page instrument consisting of 12 items that assess different aspects of pruritus. The items were grouped into five domains: pruritus intensity (2 questions: Q9, Q10), pruritus extent (1 question: Q11), frequency and duration of pruritus (1 question: Q1), impact of pruritus on daily activities and mood (4 questions: Q2–Q5), and scratching assessment as a response to pruritus (4 questions: Q6–Q8 and Q12) (Table 1). Total scores can range from 3 (minimal pruritus) to 22 (most severe pruritus).

2.3. Data Collection. After providing written informed consent, patients were asked about their demographics, medical diagnosis, course of disease, and comorbidities. Afterwards, all subjects meeting inclusion criteria completed a questionnaire package which included the 12-PSS, the VAS [9], and the Dermatology Life Quality Index (DLQI) [10]. In addition, the Hospitality Anxiety and Depression Scale (HADS) were given to 75 patients to assess the level of anxiety and depressive mood [11]. Only patients who did not start any treatment for current exacerbation of the skin disease were included into the study. All assessments in the first round were completed prior to treatment initiation. One hundred and two patients who returned 3–5 days after enrollment for reassessment were asked to complete the questionnaires to evaluate test-retest reliability.

2.4. Statistical Analysis. Statistical analysis was performed using Statistica 12.0 (Statsoft, Kraków, Poland). Groups were compared with Student's t-test or with analysis of variance (ANOVA) with Scheffé post hoc test, where appropriate. Correlations between the individual components of 12-PSS and the total score of 12-PSS were calculated using Spearman's rank order correlation test. Spearman's correlation coefficient (ρ) was interpreted as follows: ρ = 0–0.1, no correlation; ρ = 0.1–0.29, weak correlation; ρ = 0.3–0.49, moderate correlation; ρ = 0.5–0.7, strong correlation; $\rho >$ 0.7, very strong correlation [10]. The correlations between the 12-PSS, VAS, and DLQI were calculated using Pearson's correlation coefficient and interpreted as follows: $r \leq 0.3$, weak correlation; $r > 0.3$ but $r < 0.5$, moderate correlation; and $r \geq 0.5$, strong correlation [12]. Differences between the first and the second assessments were verified with paired Student's t-test. Intraclass correlation coefficient (ICC) was calculated to assess test-retest reliability. ICC < 0.4 indicated poor reliability, 0.4 ≤ ICC < 0.75 fair to high reliability, and ICC ≥ 0.75 excellent reliability [13]. Internal consistency was determined using Cronbach's alpha coefficient. Coefficient scores >0.7 generally indicate high internal reliability [14]. p values less than 0.05 were considered significant.

3. Results

3.1. Distribution and Discriminant Validity of 12-Item Pruritus Severity Scale. The mean scoring of 12-PSS for all patients was 11.7 ± 4.5 points (range 3–21 points). The total scoring showed wide, almost equal distribution of achieved responses, except the most outer results (Figure 1). Neither ceiling nor bottom effect was observed.

Comparison of the mean pruritus severity between various dermatoses revealed that with 12-PSS we were able to detect significant differences between subjects with atopic dermatitis (mean pruritus severity: 14.8 ± 4.2 points), psoriasis (12.9 ± 3.7 points), and lichen planus (10.0 ± 4.1 points; $p < 0.001$) (Figure 2(a)). Interestingly, such difference was not observed, when pruritus severity was measured with VAS (atopic dermatitis: 4.0 ± 2.5 points, psoriasis 4.5 ± 2.3 points, and lichen planus 3.4 ± 2.5 points; $p = 0.12$) (Figure 2(b)).

Table 1: 12-Item Pruritus Severity Scale.

	Question	Possible answers	Scoring
(1)	How often did you feel pruritus within the last 3 days?	(i) All time	3 points
		(ii) All morning/afternoon/evening/night long itch episodes	2 points
		(iii) Occasionally, short itch episodes	1 point
(2)	Did pruritus hinder your ability to do simply things, like watching TV, hearing music, etc.?	(i) Yes	1 point
		(ii) No	0 points
(3)	Did you feel irritated or nervous because of your itching?	(i) Yes	1 point
		(ii) No	0 points
(4)	Did your pruritus cause you depressed?	(i) Yes	1 point
		(ii) No	0 points
(5)	Did your pruritus impede your work or learning abilities?	(i) Yes	1 point
		(ii) No	0 points
(6)	Did you scratch your skin because of itching?	(i) Yes	1 point
		(ii) No	0 points
(7)	Did scratching bring you relief?	(i) Yes	0 points
		(ii) No	1 point
(8)	Were you able to refrain from scratching?	(i) Yes	0 points
		(ii) No	1 point
(9)	Did you wake up during last night because of pruritus?	(i) No	0 points
		(ii) Yes, 1-2 times	1 point
		(iii) Yes, 3-4 times	2 points
		(iv) Yes, 5 and more times	3 points
(10)	Could you assess the severity of your pruritus within last 3 days?	(i) Very mild	1 point
		(ii) Mild	2 points
		(iii) Moderate	3 points
		(iv) Severe	4 points
		(v) Very severe	5 points
(11)	Could you indicate pruritus location?	(i) Single locations of pruritus	1 point
		(ii) Large body areas	2 points
		(iii) Generalized pruritus	3 points
(12)	Are excoriations or other scratch lesions present?	(i) Yes	1 point
		(ii) No	0 points

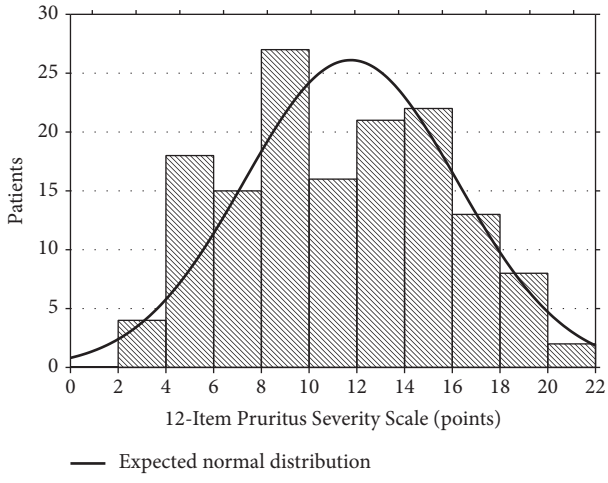

Figure 1: Distribution of the total scorings of 12-Item Pruritus Severity Score.

With 12-PSS, we were also able to detect significant differences between patients having various levels of QoL impairment assessed according to DLQI ($p < 0.001$) (Figure 3(a)). Based on these findings, we may conclude that 12-PSS is able to detect changes between patients suffering from pruritus of different intensity supporting the discriminant validity of 12-PSS. The VAS scoring was much less discriminative regarding various QoL categories (Figure 3(b)).

3.2. Internal Consistency. The assessment of internal consistency was performed based on 148 questionnaires. The results of our study have shown that the different items of the questionnaire are interrelated with one another. Cronbach's alpha coefficient was 0.81 indicating strong internal consistency.

3.3. Convergent Validity. Correlation of individual components and the total score of the 12-PSS by Spearman's correlation coefficient showed statistically significant values. Most of the questions showed strong correlation with the total score ($r > 0.5$). Only one question (Q7) demonstrated weak, albeit statistically significant correlation ($r < 0.29$) and two questions (Q4 and Q6) moderate correlation (Table 2). Overall, it could be concluded that the 12-PSS shows satisfactory convergent validity.

3.4. Correlations of the 12-Item Pruritus Severity Scale with the VAS, DLQI, and HADS. The 12-PSS demonstrated significant

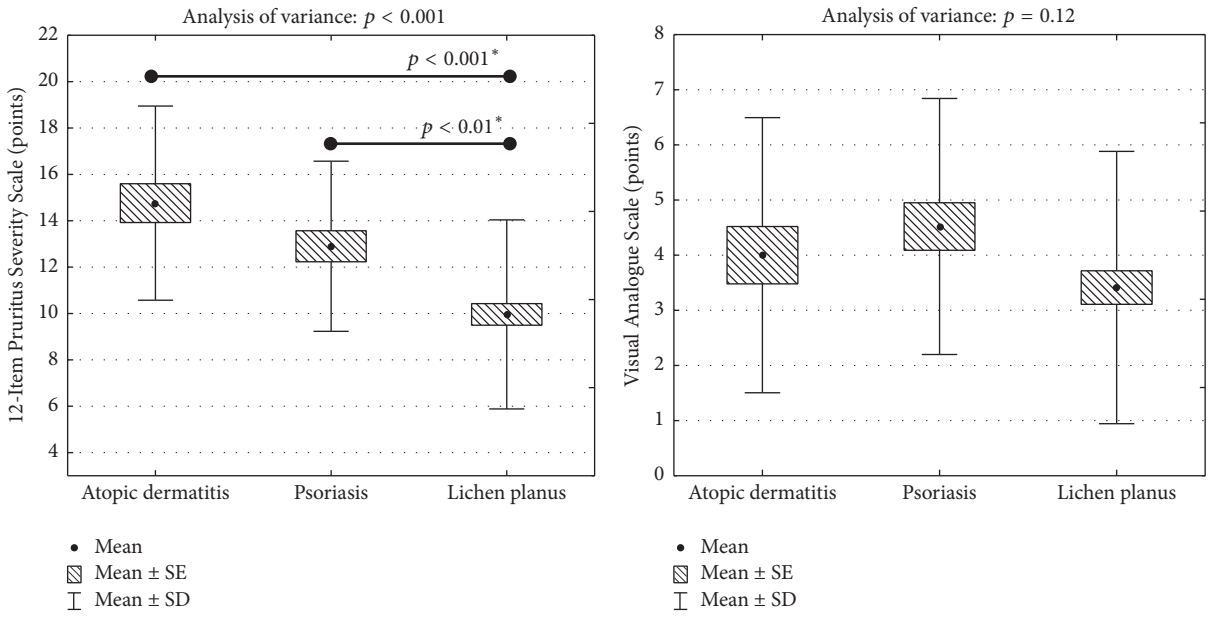

Figure 2: (a) Comparison of pruritus severity assessed according to 12-PSS in various dermatoses (SE: standard error of mean; SD: standard deviation, $^*p$ values according to Scheffé post hoc test). (b) Comparison of pruritus severity assessed according to VAS in various dermatoses (SE: standard error of mean; SD: standard deviation).

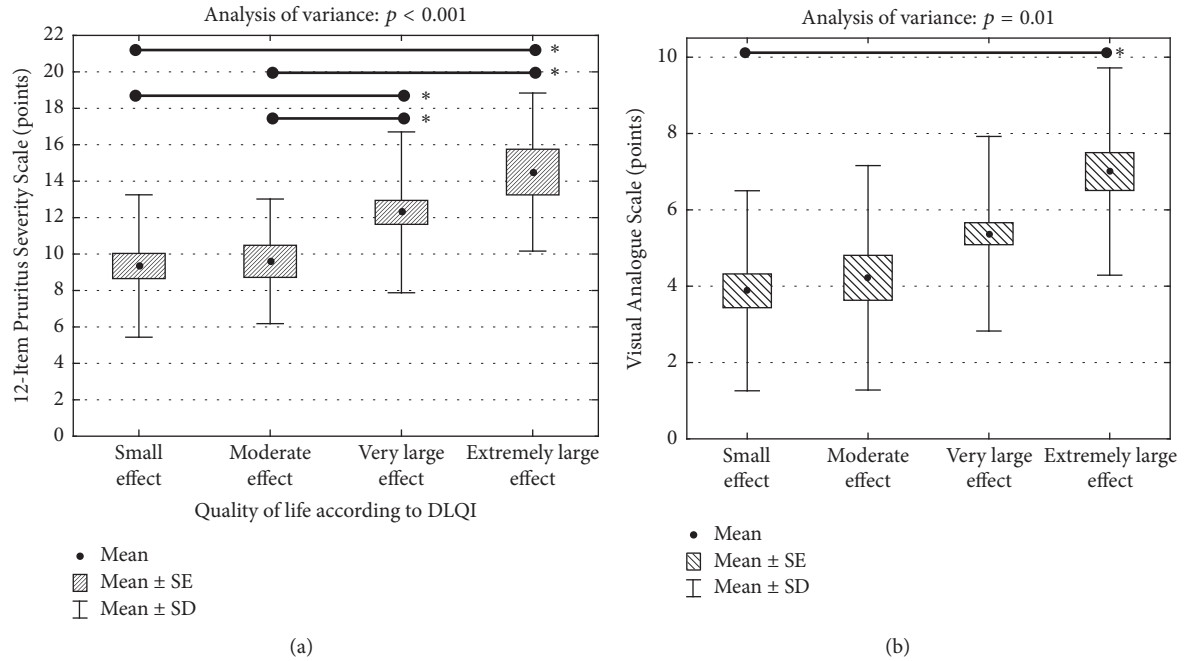

Figure 3: Comparison of pruritus severity assessed according to 12-PSS in patients with various impairments of health-related quality of life (DLQI: Dermatology Life Quality Index, SE: standard error of mean, SD: standard deviation, $^*p < 0.01$ acc. to Scheffé post hoc test). (b) Comparison of pruritus severity assessed according to VAS in patients with various impairments of health-related quality of life (DLQI: Dermatology Life Quality Index, SE: standard error of mean, SD: standard deviation, $^*p = 0.05$ acc. to Scheffé post hoc test).

Table 2: Spearman's rank correlation coefficients (ρ) for the each item (Q) score and the total score of the 12-PSS.

	N	ρ	p
Q1 and total score	148	0.76	<0.0001
Q2 and total score	148	0.62	<0.0001
Q3 and total score	148	0.62	<0.0001
Q4 and total score	148	0.49	<0.0001
Q5 and total score	148	0.68	<0.0001
Q6 and total score	148	0.32	<0.0001
Q7 and total score	148	0.2	0.01
Q8 and total score	148	0.53	<0.0001
Q9 and total score	148	0.72	<0.0001
Q10 and total score	148	0.8	<0.0001
Q11 and total score	148	0.66	<0.0001
Q12 and total score	148	0.5	<0.0001

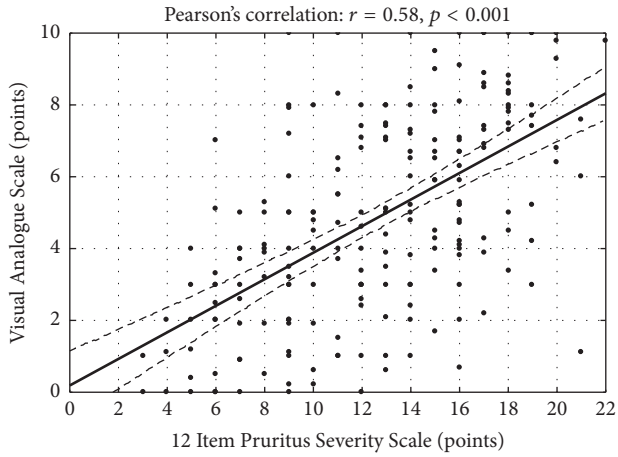

Figure 4: Correlation between the 12-PSS and the VAS scoring.

correlation with the VAS, DLQI, and anxiety and depression level assessed with HADS. The correlation between the 12-PSS and the VAS was strong ($r = 0.58$, $p < 0.001$) (Figure 4). The 12-PSS also showed significant correlation between the impairment of QoL ($r = 0.53$, $p < 0.001$) (Figure 5) and HADS scoring (for anxiety: $r = 0.37$, $p = 0.001$; for depression: $r = 0.28$, $p = 0.01$). These latter correlations could be assessed as weak to moderate, suggesting that 12-PSS reflected influence of pruritus on patients but provided slightly different information than the scales used as comparators. Interestingly, the VAS, which solely assesses pruritus intensity, showed only moderate correlation with DLQI ($r = 0.46$, $p < 0.001$) and no significant correlation with HADS components (anxiety domain: $r = 0.16$, $p = 0.16$; depression domain: $r = 0.16$, $p = 0.17$). Based on these observations, it could be concluded that the 12-PSS is able to catch a more complex influence of pruritus on patient well-being than the VAS. In addition, 12-PSS also correlated with pruritus duration ($r = 0.39$, $p < 0.001$). The mean 12-PSS scoring for patients with pruritus lasting <1 year was 10.3 ± 4.2 points and for those with pruritus lasting ≥1 year 12.6 ± 4.4 points ($p = 0.001$).

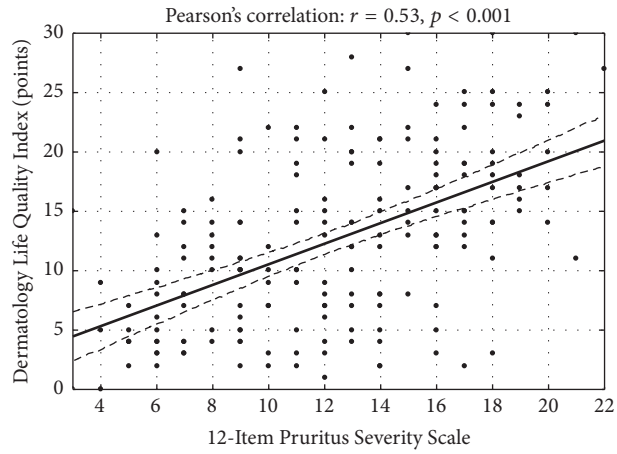

Figure 5: Correlation between the 12-PSS and the DLQI scoring.

3.5. Test-Retest Comparison. The reproducibility of the 12-PSS in the group of 102 subjects was high. The intraclass correlation coefficient (ICC) between the 12-PSS scores obtained in two assessments (I and II) was 0.72. Significant differences were observed only in three questions, where the second assessment demonstrated significantly lower values which might represent some variations in pruritus intensity (Table 3). However, we also cannot exclude the possibility that some patients applied treatments during this time leading to some improvement of skin condition and lowering of pruritus intensity.

4. Discussion

The new pruritus severity questionnaire (12-PSS) has been developed as a simple, multidimensional method for assessing pruritus intensity. The evaluation of the psychometric properties of the questionnaire has revealed that the measure demonstrates high internal consistency and convergent validity, a significant correlation with the VAS and quality of life level, and a high reproducibility. This indicates that the questionnaire is a reliable and valid measure of pruritus severity.

The test-retest reliability of the pruritus severity questionnaire was high. However, over a 3–5-day interval, the scores of some questions demonstrated lower values in the second assessment. This can be explained by spontaneous pruritus intensity fluctuations within few days. However, this interval is necessary for the patient not to remember the previous answers. It is also possible that within this period of time patients might apply some treatment modalities, even unintentionally, that decreased pruritus intensity, which might influence the achieved results. Taking this into consideration, it could be assumed that the questionnaire has a satisfactory sensitivity to change, but this requires further research.

The 12-PSS is easy to understand and to complete for subjects and is rather short and quick to be completed (usually less than 3 minutes). The questionnaire contains questions regarding different aspects of pruritus. It delivers data about localization, duration, frequency and intensity of pruritus, scratch response, disability, and quality of life

Table 3: Reproducibility of results achieved with pruritus severity questionnaire in 102 patients (based on paired Student's t-test, results demonstrated as means ± standard deviations).

	First assessment	Second assessment	p
Question 1	2.0 ± 0.7	1.8 ± 0.8	0.02
Question 2	0.5 ± 0.5	0.5 ± 0.5	0.66
Question 3	0.8 ± 0.4	0.8 ± 0.4	0.57
Question 4	0.6 ± 0.5	0.6 ± 0.5	1.0
Question 5	0.5 ± 0.5	0.6 ± 0.5	0.32
Question 6	0.9 ± 0.2	0.9 ± 0.3	0.32
Question 7	0.3 ± 0.5	0.3 ± 0.5	0.57
Question 8	0.7 ± 0.5	0.6 ± 0.5	0.42
Question 9	1.3 ± 1.1	1.0 ± 0.9	<0.05
Question 10	3.4 ± 1.1	2.9 ± 1.2	0.01
Question 11	2.1 ± 0.7	2.0 ± 0.8	0.17
Question 12	0.7 ± 0.5	0.6 ± 0.5	0.32
Total score	13.8 ± 4.1	11.3 ± 4.5	<0.001

impairment in patients with pruritus. It provides important information about relevant characteristics of pruritus and discriminates between different types of pruritus. It may be able to detect changes in pruritus over time. According to the Special Interest Group, our pruritus questionnaire considers the patient's perspective, the physician's perspective, and needs of various measurements in clinical trials [8].

The VAS is the most reliable scale to quantify pruritus currently. However, relying on a single measure is not sufficient for evaluation of pruritus. The VAS is adequate in assessing the intensity of symptoms but does not provide information about other aspects of pruritus, like the impact of pruritus on the QoL. However, it is of importance as chronic pruritus can significantly reduce patients QoL. Therefore, additional instruments assessing the psychiatric comorbidities, impact on patient's QoL and patient satisfaction should also be integrated into the routine care of chronic pruritus. For this reason, there are a variety of tools available that assess the QoL of affected patients. The DLQI is a widely used instrument which has already been validated [15]. However, the use of additional scale assessing the impact of pruritus on patient's QoL is time-consuming and sometimes impossible to implement in everyday practice. The data from our study has demonstrated that our pruritus severity questionnaire significantly correlates with the DLQI. Furthermore, it contains questions regarding the influence of pruritus on patient's daily life, mood, and concentration. The developed pruritus severity questionnaire can be successfully used as an appropriate tool to evaluate the severity of pruritus and the impact of pruritus on the QoL at the same time.

In conclusion, the developed pruritus severity questionnaire is a reliable measure that has been validated in patients with chronic pruritus. It may be a useful tool both in clinical trials and routine daily practice to qualify patients for the antipruritic treatment and to assess the efficacy of therapy.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

Results of this study have been presented as a meeting abstract on the 9th World Congress on Itch in Wrocław (Poland, 15-17.10.2017).

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Research Article

Prevalence and Relevance of Pruritus in Pregnancy

Justyna Szczęch,[1,2] Artur Wiatrowski,[3] Lidia Hirnle,[4] and Adam Reich[1,2]

[1]*Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland*
[2]*Department of Dermatology, University of Rzeszów, Rzeszów, Poland*
[3]*1st Department and Clinic of Gynecology and Obstetrics, Wroclaw Medical University, Wroclaw, Poland*
[4]*2nd Department and Clinic of Gynecology and Obstetrics, Wroclaw Medical University, Wroclaw, Poland*

Correspondence should be addressed to Adam Reich; adam.reich@umed.wroc.pl

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Pregnant women are at greater risk to suffer from chronic pruritus, but data on this symptom in this group is very limited. The aim of this study was to investigate the prevalence, clinical characteristics, and the importance of pruritus in pregnant women. A total of 292 consecutive pregnant women at the 33.0 ± 6.1 weeks of gestation (WoG) were recruited into this prospective, cross-sectional study. All patients underwent thorough anamnesis and detailed physical examination with the special emphasis on pruritus. Pruritus was assessed according to Visual Analogue Scale (VAS). Quality of life was measured with the Dermatology Life Quality Index (DLQI). The point prevalence of pruritus was 20.2% ($n = 59$), while pruritus prevalence during the entire pregnancy was 38.0% ($n = 111$). Pruritus started on average at the 27.2 ± 7.6 WoG; it was significantly more common among women in third trimester. The mean VAS was 4.8 (±2.4) points. The DLQI scoring significantly correlated with VAS ($r = 0.52$, $p < 0.001$). Based on the results of our study about one-third of women suffer from pruritus during pregnancy. Many of them find it a very distressing and disturbing symptom.

1. Introduction

Data on pruritus in pregnancy is rather limited, and physicians treating pregnant women may underestimate its frequency and clinical meaningfulness. Most published papers concerning this symptom during pregnancy focused mainly on itch occurring in intrahepatic cholestasis of pregnancy (ICP) and other pregnancy-specific dermatoses, leaving the problem of idiopathic itch in pregnant women without proper investigation.

Pregnancy is a state that leads to various hormonal, metabolic, and immunologic changes, which may influence the functioning and structure of the skin and mucous membranes. Almost 90% of the pregnant women will present with the signs of hyperpigmentation, mainly visible in physiologically highly pigmented areas, for example, genitals, perineum, periumbilical skin, and areolae [1, 2]. Equally often, on the abdomen may occur the striae gravidarum, or "stretch marks," which are the result of skin stretching combined with genetic and hormonal changes [1, 3]. In nearly 75% of pregnancy cases physicians will observe gray-brown patches located on the face, previously termed as "mask of pregnancy," namely, melasma [1]. Besides the above described skin changes pregnant women also present with some physiological hair, nail, and vascular changes, which need to be differentiated from pathological symptoms to avoid unnecessary treatment [1]. Moreover, there is a group of specific dermatoses of pregnancy, in which we can distinguish atopic eruption of pregnancy (AEP), polymorphic eruption of pregnancy (PEP), pemphigoid gestationis (PG), and ICP [4]. The endocrinology of pregnancy involves increased activity of maternal adrenal and pituitary glands, along with physiological development of fetal endocrine glands. Progesterone and estrogen, among other hormones (e.g., increased cortisone levels), are major factors influencing skin during pregnancy [5]. It is possible that these changes may alter the pruritus pathway and contribute to itch in susceptible individuals [6].

In 2007, the International Forum for the Study of Itch (IFSI) established a new classification of chronic itch which allows physicians to assign all patients with pruritus to one of three groups including subjects with pruritus on

diseased (inflamed) skin (group I), those having pruritus on nondiseased (noninflamed) skin (group II), and individuals with chronic secondary lesions (group III). After assigning all patients with pruritus to one group, they are further subdivided based on pruritus etiology, including dermatological, systemic, neurological, and psychogenic pruritus. If more etiologies are evident, then the patient is considered as having mixed category of pruritus, and in those subjects where the underlying cause cannot be identified pruritus is considered as being of unknown origin [7].

According to recent studies, the point prevalence of pruritus (both acute and chronic) in the general population is estimated at about 8% to 10% based on different sources [8]. Its frequency may differ in specific groups, affecting more commonly elderly people and some specific populations, like patients on dialysis [9]. Despite the growing interest in pruritus, our knowledge about pruritus in pregnancy is quite limited and is mostly based on outdated studies [10]. As the current classification of itch has changed the approach to this symptom, we performed a cross-sectional observational study to better evaluate the prevalence and characteristics of pruritus among pregnant women.

2. Materials and Methods

A total of 292 consecutive pregnant women were recruited into this prospective, cross-sectional study. They were at the mean age of 30.2 ± 5.3 years and in 32.9 ± 6.4 weeks of gestation (WoG). Among the pregnant women, 184 (63.0%) were primiparas and 108 (37.0%) multiparas. About 12% of participating women had a multiple pregnancy.

The indicated parameters, age and WoG, were similar among the women with pruritus and those who did not report this symptom. All patients underwent thorough anamnesis and detailed physical examination with the special emphasis on pruritus. In addition, all women with pruritus assessed its severity according to the Visual Analogue Scale (VAS), the Verbal Rating Scale (VRS), and the 12-Item Itch Questionnaire (12-IQ). The VAS is a 10-cm long horizontal line on which the patient indicates the point corresponding to her pruritus intensity, ranging from "no pruritus" to "worst pruritus imaginable" [11]. VAS was initially used to assess the severity of pain, but it is now widely used as a tool to measure itch intensity. Finally, it was validated by our group for itch assessment in 2012 [11]. In clinical studies, it is highly recommended to use at least two methods of assessment of the intensity of pruritus [11]. Keeping this in mind, all participants also classified their pruritus with the 5-point VRS, scoring this symptom verbally as "no pruritus," "mild pruritus," "moderate pruritus," "severe pruritus," and "very severe pruritus." All pregnant women with pruritus were asked to indicate the most severe pruritus experienced within the period of previous three days [12]. The 12-IQ consists of 12 questions about various aspects of pruritus giving the final score ranging from 0 (no pruritus) to 22 points (the most severe pruritus). In addition, the patients completed the Dermatology Life Quality Index (DLQI) to assess the quality of life impairment related to cutaneous symptoms. In order to establish the probable cause of pruritus we have followed the European Guideline on Chronic Pruritus [13]. All patients underwent basic laboratory examination and if needed, additional examination and medical consultation were performed [13]. The study was performed in accordance with the Declaration of Helsinki and was approved by Ethic Committee of Wroclaw Medical University (decision 406/2015).

2.1. Statistical Analysis. All results were analyzed using the software package Statistica® 12.0 (Statsoft, Krakow, Poland). Descriptive statistics included frequencies, median, and minimal and maximal values. The significance of the observed differences between groups has been determined by Mann–Whitney U test and χ^2 test with Yates correction, if necessary. Correlations between tested parameters were verified with Spearman rank correlation test. A p value lower than 0.05 was considered as statistically significant.

3. Results

3.1. Prevalence of Itch. The prevalence of pruritus in all recruited women (entire pregnancy prevalence) was 38.0% ($n = 111$), although at the time of examination (point prevalence) it was only reported by 20.2% ($n = 59$) of patients. Twenty-two (6.7%) women experiencing pruritus suffered from this sensation before the pregnancy. Among the women with itch, 78% ($n = 46$) had a singleton gestation and 22% ($n = 13$) had a multiple pregnancy. Pruritus was more frequently connected with multiple pregnancy (multiple pregnancy: 37.1% versus singleton pregnancy: 17.9%, $p = 0.01$); however, its prevalence was unrelated to the number of previous pregnancies and number of live births. Detailed data is demonstrated in Table 1. According to current classification of itch, 7 (11.8%) out of 59 women with pruritus had dermatologic itch connected with specific dermatoses of pregnancy (AEP, PEP, and PG). The second subgroup, where systemic itch was diagnosed, consisted of 16 (27.1%) patients. In this group itch was attributed to ICP ($n = 10$), hypothyroidism ($n = 3$), gestational diabetes ($n = 2$), and chronic hepatitis C virus infection ($n = 1$), as all these diseases are known to be related to chronic itch. However, we cannot exclude the possibility that at least in some women in this group the systemic disease was not causative but just coincidental to chronic pruritus. In the remaining participants with pruritus ($n = 36$, 61.0%), the underlying cause of pruritus could not be established and it was classified as pruritus of unknown origin (Figure 1).

3.2. Characteristic of Pruritus. Pruritus on average started at 27.2 ± 7.6 WoG. In most pregnant women, it started after the 25th WoG, although at the latest this symptom appeared at 38th WoG (Figure 2). Most commonly pruritus affected the abdomen and chest ($n = 52$ in both locations altogether, 88.1%), hands ($n = 25$, 42.4%), and feet and lower legs ($n = 24$ in each location, 40.7%) (Table 2). Surprisingly, only 3 (5.1%) women suffered from itch affecting the anogenital area. Almost one-third (32.2%) of women with pruritus presented with secondary lesions. Approximately 70% of women (69.5%) suffered from pruritus on a daily basis, whereas

Table 1: Characteristic of a group of patients.

	Without pruritus	With pruritus	p
Age	30.2 ± 5.3	30.3 ± 5.9	0.93
Number of previous pregnancies	0.9 ± 1.3	0.9 ± 1.0	0.97
Number of previous births given	0.5 ± 1.0	0.6 ± 0.7	0.84
WoG	32.9 ± 6.4	33.1 ± 4.6	0.82
Singleton pregnancy	211 (82.1%)	46 (17.9%)	0.01
Multiple pregnancy	22 (62.9%)	13 (37.1%)	

WoG: week of gestation.

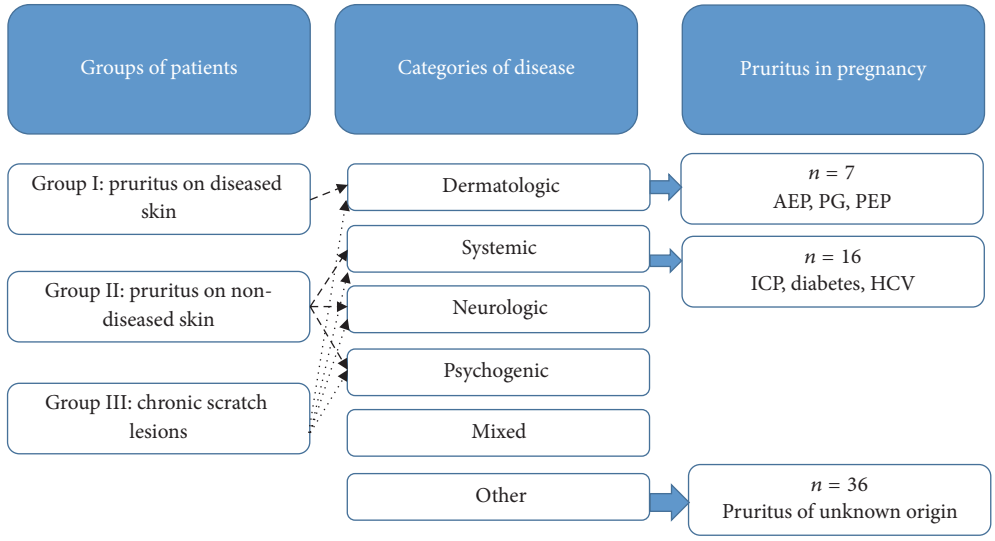

Figure 1: Classification on pruritus in pregnant women based on the itch classification proposed by IFSI. AEP: atopic eruption of pregnancy, PG: pemphigoid gestationis, PEP: polymorphic eruption of pregnancy, ICP: intrahepatic cholestasis of pregnancy, and HCV: chronic hepatitis C virus infection.

Table 2: Localization of pruritus.

Body area	Number of patients	Percent [%]
Abdomen	52	88.1
Chest	52	88.1
Hands	25	42.4
Shanks	24	40.7
Feet	24	40.7
Forearms	22	37.3
Thighs	21	35.6
Back	20	33.9
Shoulders and arms	19	32.2
Breasts	19	32.2
Scalp	7	11.9

the remaining 30.5% reported it as appearing a few times a week. Most frequently pregnant women described itch-related sensations as tickling (52.5%, $n = 31$) and burning (44.1%, $n = 26$), followed by tingling (23.7%, $n = 14$), pinching (18.6%, $n = 11$), prickling (15.5%, $n = 9$), numbness (1.7%, $n = 1$), and pain (1,7%, $n = 1$). Moreover, the patients who suffered from pruritus reported this symptom as being predominantly annoying (59.3%, $n = 35$), burdensome (49.2%, $n = 29$), unbearable (27.1%, $n = 16$), and worrisome (15.3%, $n = 9$). Although the itch sensation appeared most frequently in the evening, more than 50% of women also reported pruritus in other times of the day or at night (Table 3). About half of pruritic participants had troubles in falling asleep (almost always: 28.8%, occasionally: 20.3%) and 42.3% (almost always: 18.6%, occasionally: 23.7%) reported awakenings because of this symptom. In addition, 3 (5.1%) pregnant women used medication for insomnia due to pruritus. Heat, dry air, and sweat were the most important factors exacerbating pruritus (Figure 3).

3.3. Pruritus Severity and Quality of Life Impairment. The mean intensity of pruritus measured with VAS was 4.8 ± 2.4 points ranging from 0.6 to 10 points; 8 (13.6%) described it as very mild, 17 (28.8%) as mild, 26 (44.1%) as of moderate

Table 3: Occurrence of pruritus during different times of the day.

Time of the day/frequency	Not at all	Rarely	Often	All the time
Morning	9 (15.3%)	30 (50.8%)	10 (16.9%)	10 (16.9%)
Afternoon	17 (28.8%)	18 (30.5%)	17 (28.8%)	7 (11.9%)
Evening	7 (11.9%)	14 (23.7%)	21 (35.6%)	17 (28.8%)
Night	22 (37.3%)	12 (20.3%)	12 (20.3%)	12 (20.3%)

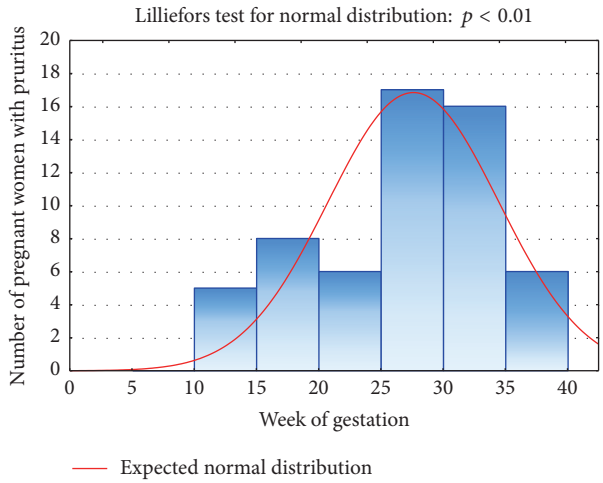

Figure 2: Pruritus onset depending on week of gestation.

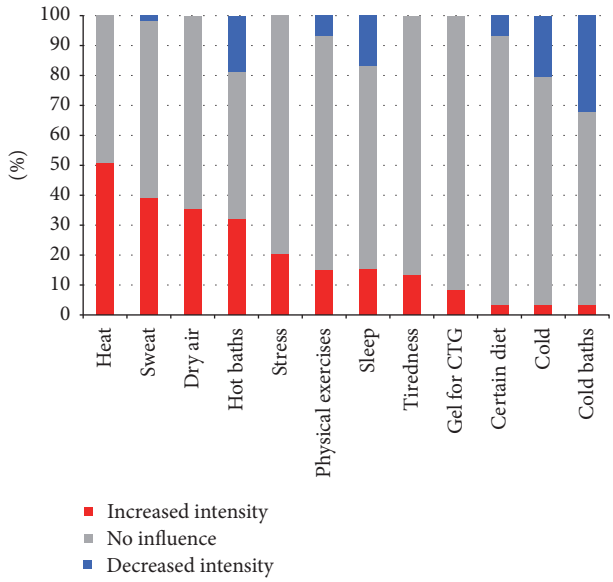

Figure 3: Factor exacerbating and relieving pruritus in pregnant women (CTG: cardiotocography).

intensity, 7 (11.9%) as severe, and 1 (1.7%) person as very severe. Regarding the 12-IQ the mean score was 10.5 ± 2.9 points (range: 5–17 which reflected 22.7% to 77.3% of the maximal itch scoring according to 12-IQ). A significant correlation between VAS and 12-IQ scores was observed (ρ = 0.52, $p < 0.001$) (Figure 4).

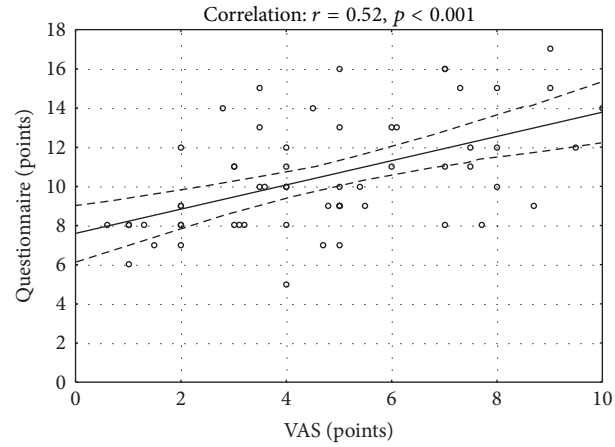

Figure 4: Correlation between 12-Item Itch Questionnaire scoring and VAS.

The mean DLQI scoring in patients with pruritus was 5.5 ± 5.8 points ranging from 1 to 30 points. A significant correlation was noted between DLQI scoring and pruritus intensity as assessed by the VAS (ρ = 0.41, p = 0.001) and the 12-IQ (ρ = 0.5, $p < 0.001$). According to DLQI 13 (22.0%) pregnant women with pruritus had normal QoL, 26 (44.1%) had slightly impaired QoL, 13 (22.0%) had moderately impaired QoL, 5 (8.5%) had severely impaired QoL, and 2 (3.4%) had extremely impaired QoL. As expected, pruritus was more frequent among women with ICP ($p <$ 0.001). The higher prevalence of pruritus was also observed in women diagnosed with systemic disorders, for example, diabetes or arterial hypertension.

4. Discussion

Pruritus is an unpleasant sensation that provokes the desire to scratch. The itch during pregnancy may have numerous causes connected mainly with infections, infestations, particular systemic disorders (e.g., liver or kidney dysfunction), pregnancy-specific dermatoses, and exacerbation of preexisting dermatologic conditions, like atopic dermatitis [14]. This is the first study evaluating the pruritus occurring during pregnancy based on the new classification of itch as proposed in 2007 and evaluating the associated quality of life impairment connected with this symptom [7]. Pruritus gravidarum might be both localized, affecting mainly breasts and abdomen, and generalized. It may accompany the specific dermatoses of pregnancy, although it can also occur without any underlying disease. Pregnancy, a unique physiological

state, brings with it endocrine and immunologic changes which may contribute to pruritus. As previously outlined, the true prevalence of pruritus among pregnant women is unknown. Our study showed that the frequency of itch during pregnancy is higher than previously suspected. Result of the study by Kenyon et al. [15] showed that the overall prevalence of itch during pregnancy was approximately 23%. According to our results, at certain periods of pregnancy, almost 40% of pregnant women may suffer from pruritus. Its occurrence seems to be most common in the third trimester. The finding is consistent with previously published observations [16, 17]. Interestingly, the majority of pregnant women in our study suffered from pruritus of unknown origin. Although all of our patients underwent detailed gynecological and dermatological examination, only 40% had an underlying cause for their pruritus. Usually the intensity of pregnancy-related pruritus was of moderate intensity. However, physicians should remember that generalized itch of greater severity (with a mean VAS = 6.6 points) commonly affecting hands and feet with deterioration during the night is frequently connected with ICP [15, 18]. Therefore, some authors classify pruritus gravidarum as with or without cholestasis [19].

The cause of itch accompanying pregnancy dermatoses is still poorly understood. Although infrequent, pregnancy dermatoses can not only cause pruritus but can also carry the risk of adverse fetal and maternal outcomes [20]. The connection between progesterone and pruritus was initially taken under consideration with regard to the pathophysiology of ICP [21]. However, recent experimental studies have suggested the role of autotaxin, and its product, lysophosphatidic acid, as possible mediators of cholestatic itch in ICP [22].

Indubitably, striae gravidarum (stretch marks) are one of the most common physiologic skin changes in pregnancy, visible in up to 90% of pregnant white women [20]. Their etiology remains unknown. Interestingly, pregnancy-associated striae may occasionally be the primary localization of PEP, a condition that typically affects primigravidas [20].

In our study, the most common location of itch, occurring in almost 90% of women reporting this symptom, was the abdomen. Similar results were observed by Kenyon et al. [15]. Abdominal pruritus in pregnancy is most related to pregnancy-induced stretching of the abdominal skin [13]. Stretching may activate dermal nerve endings leading to pruritus; however, the exact mechanism is poorly understood. In addition, damage to the collagen may induce an allergic type response contributing to the development of PEP lesions. This suggestion is supported by the fact that women with multiple pregnancies experience PEP more often.

It should be emphasized that itching appears to be a significant problem during night hours causing significant sleep disturbances in one-fifth of the pregnant women with pruritus. Some studies suggest that sleeping less than 8 hours per day during the 1st and 2nd trimester is a risk factor for miscarriage, so managing nighttime pruritus is important [23, 24].

In conclusion, pruritus during pregnancy is a complex symptom. Physicians taking care of the pregnant women affected with itch should undertake proper clinical management (for details see [13]), as it is essential for the well-being not only of the expectant mother, but also of the fetus. Additional laboratory findings and careful anamnesis with an emphasis on the location and timing of the pruritus often reveal important clues that can facilitate diagnosis and efficacious treatment. However, as many pregnant women may also suffer from pruritus of unknown origin, as in our group, further studies are needed to better characterize this subset of patients and determine the best treatment options.

Disclosure

Preliminary data of this study has been previously presented as a meeting abstract on the 8th World Congress on Itch in Nara (Japan, 27–29.09.2015) (Acta Derm Venereol 2015; 95: 892).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Review Article

Aprepitant for the Treatment of Chronic Refractory Pruritus

Alice He,[1] Jihad M. Alhariri,[1] Ronald J. Sweren,[1] Madan M. Kwatra,[2] and Shawn G. Kwatra[1]

[1]*Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[2]*Department of Anesthesiology, Duke University Medical Center, Durham, NC, USA*

Correspondence should be addressed to Shawn G. Kwatra; kwatra.shawn@gmail.com

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Chronic pruritus is a difficult condition to treat and is associated with several comorbidities, including insomnia, depression, and decreased quality of life. Treatment for chronic itch includes corticosteroids, antihistamines, and systemic therapies such as naltrexone, gabapentin, UV light therapy, and immunomodulatory treatments, including azathioprine, methotrexate, and cellcept. However, some patients still remain refractory to conventional therapy. Aprepitant is a neurokinin-1 receptor antagonist approved for the prevention of chemotherapy-induced and postoperative nausea and vomiting (CINV, PONV). Recently, aprepitant has demonstrated effectiveness in several case series and open label trials in relieving pruritus for patients refractory to other treatments. Patients with pruritus associated with Sézary syndrome, mycosis fungoides, lung adenocarcinoma, breast carcinoma, sarcomas, metastatic solid tumors, chronic kidney disease, hyperuricemia, iron deficiency, brachioradial pruritus, and Hodgkin's lymphoma have experienced considerable symptom relief with short-term use of aprepitant (up to two weeks). Due to differences in reporting and evaluation of drug effects, the mechanism of aprepitant's role is difficult to understand based on the current literature. Herein, we evaluate aprepitant's antipruritic effects and discuss its mechanism of action and adverse effects. We propose that aprepitant is an alternative for patients suffering from pruritus who do not obtain enough symptom relief from conventional therapy.

1. Introduction

Chronic itch is a distressing condition for patients with a significant effect on quality of life. If a patient is nonresponsive to topical therapy, there are limited systemic options available. Current options include corticosteroids, antihistamines, capsaicin, naltrexone, gabapentin, UV light therapy, and immunomodulatory treatments such as azathioprine, methotrexate, and cellcept. The purpose of this review is to make dermatologists aware of aprepitant as a medication that is effective for treating subsets of patients with chronic refractory pruritus.

Aprepitant was first approved in the United States in March 2003 to prevent chemotherapy-induced nausea and vomiting (CINV) [1]. The drug was originally developed to treat depression, but clinical trials failed to demonstrate an effect in a nontoxic dosage range [2]. Aprepitant is a neurokinin-1 (NK1) receptor antagonist and is the first of its class to be approved for use [3]. Aprepitant exerts its effects by blocking substance P (SP), an endogenous ligand of the NK1 receptor. Substance P mediates several physiologic processes, including pain, depression, nausea, vomiting, and pruritus [3]. As such, there is much excitement over the potential for developing NK1 receptor antagonists as a therapy for many disease states.

Recently clinicians have discovered an off-label use for aprepitant to treat chronic refractory pruritus. Concerns for aprepitant use include its high cost and potential interactions with multiple other drugs. Herein we review aprepitant's efficacy as an antipruritic agent, mechanisms of action, and adverse effects.

2. Materials and Methods

In December 2015 through April 2017, we conducted a literature search of PubMed, Ovid MEDLINE, clinicaltrials.gov, and Google Scholar for key word combinations of "aprepitant" coupled with "pruritus," "itch," and "antipruritic." All results were checked for relevance.

3. Results and Discussion

Our search yielded a total of 143 results (with redundancy) from 2001 to 2017 containing the aforementioned key words. Ultimately, 16 clinical articles were included in this review as they focused specifically on chronic refractory pruritus in humans. Only reports published in English were included.

4. Clinical Antipruritic Therapy of Aprepitant

There have been several case series and open label trials reported in literature about the efficacy of aprepitant to treat refractory chronic pruritus. A total of 73 patients were included in the reports reviewed here [4–18].

4.1. Pruritus Associated with Malignant Conditions. The first reported use of aprepitant for refractory pruritus was by Duval and Dubertret in 2009 [4]. Duval and Dubertret reported on three patients with Sézary syndrome who were all hospitalized for pruritus refractory to conventional therapy [4]. The visual analogue scale (VAS) score was used to assess pruritus severity, with 0 indicating no pruritus and 10 representing the worst possible case of pruritus imaginable. Quality of life was assessed using the Dermatology Life Quality Index (DLQI) questionnaire out of 30, with higher scores representing worse quality of life. After just one dose of 80 mg aprepitant, average VAS score for itch dropped from 8 to 2.33, and after one week the mean DLQI score improved from 19.5 to 6 [4]. All patients reported diminished insomnia and better quality of sleep [4]. However, the treatment had no effect on erythroderma [4]. The ability of aprepitant to treat refractory chronic pruritus associated with cutaneous T-cell lymphomas was further confirmed by several subsequent case reports in a total of 17 patients (nine with Sézary syndrome, seven with mycosis fungoides, and one with cutaneous anaplastic large cell lymphoma) [9, 10, 12, 14, 18]. Aprepitant regimens for these patients included either a 3-day course of 125 mg/80 mg/80 mg repeated every two weeks or daily 80 mg aprepitant. All patients showed symptom improvement within as early as three hours to two weeks, except for one patient who failed to respond to aprepitant at all. Average VAS score dropped from 9.53 to 3.03, and average DLQI score improved from 22.57 to 8. In this cohort, only one patient experienced a self-limited headache on the first day of aprepitant therapy [14], and one patient relapsed with substantial worsening of pruritus on the 12th day of treatment after an initial good response to aprepitant [16], but this patient's reaction was believed to be due to underlying disease progression; no other adverse reactions were reported.

Aprepitant has also been reported to treat chronic pruritus associated with solid tumors. Several case series have reported on a total of 29 patients with a variety of solid tumors, including lung adenocarcinoma, breast carcinoma, and soft tissue sarcomas [6–8, 11]. Most patients underwent anticancer treatment with erlotinib [6, 8, 11]. All patients failed conventional therapy for pruritus and were given aprepitant regimens of 125 mg/80 mg/80 mg for three consecutive days, 125 mg/80 mg/80 mg every other day for five days, or 80 mg daily. Average VAS scores dropped from 6.96 to 0.93, before and after aprepitant therapy. No adverse reactions were reported for any patients.

4.2. Pruritus Associated with a Variety of Nonmalignant Conditions. In 2010, Ständer et al. treated a cohort of 20 patients with chronic refractory pruritus associated with chronic kidney disease, hyperuricemia, and iron deficiency [5]. Majority of the patients also had severe prurigo nodularis. Patients were given 80 mg aprepitant daily for 3–13 days (mean 6.6 days). Mean VAS score improved from 8.4 to 4.9 for all patients, which included four patients who did not respond to aprepitant therapy at all. Interestingly, the authors found that patients with atopic diathesis and/or prurigo nodularis experienced greater reduction of pruritus (mean VAS score reduction of 50.9%) with clinical improvement of scratch lesions, as compared to patients without dermatological diseases (mean VAS score reduction of 26.3%). Three patients experienced adverse reactions of nausea, vertigo, and drowsiness, but none required cessation of aprepitant therapy.

One case in literature reports aprepitant's efficacy in treating refractory brachioradial pruritus [13]. The patient experienced vast improvement of pruritus and scratch lesions with just two days of 80 mg aprepitant daily for seven days. However, relapse occurred just 48 hours after the last dose of aprepitant. In contrast, aprepitant's antipruritic effects lasted for six weeks in a report of a man with pruritus of unknown origin with superficial psoriasiform dermatitis treated with 125 mg/80 mg/80 mg/80 mg aprepitant for 4 days [17]. He experienced significant symptom relief (VAS score 8 to 1 and DLQI 24 to 8, before and after treatment) with no adverse effects [17]. There is one report on treating chronic pruritus associated with Hodgkin's lymphoma with aprepitant [15]. Treatment with 80 mg aprepitant daily for two weeks dropped the patient's VAS score from 9 to 5 and allowed the patient to lead a better quality of life. Finally, one case reports on aprepitant treating refractory pruritus of unclear origin [17]. An aprepitant regimen of 125 mg on day 1 and then 80 mg on days 2–4 resulted in VAS score improvement of 8/10 to 4/10 after 24 hours, and it improved to 1/10 after six weeks [17]. The patient experienced no adverse effects and greatly improved insomnia and cutaneous lesions [17].

4.3. Summary of Clinical Effects. In summary, a total of 73 patients were included in this review who were treated with aprepitant for chronic pruritus associated with cutaneous T-cell lymphomas (27%), solid tumors (40%), and a variety of other conditions (33%). Several patients suffered from a decreased quality of life due to pruritus-related side effects, including insomnia (8 reported patients) and scratch lesions (27 reported patients). All patients previously failed conventional therapy, often consisting of oral antihistamines and topical steroids. Aprepitant treatment regimens varied by underlying disease (see Table 1). Initial mean VAS score for 71 patients was 8.1 (VAS score not reported for 2 patients). After initiation of aprepitant therapy, mean VAS score improved to 2.7. Time to improvement ranged from three hours to two weeks. Nearly all patients experienced symptomatic relief from pruritus with aprepitant, including reduction of scratch

Table 1: Aprepitant dosing by pruritus-associated disease based on prior studies.

Sézary syndrome	80 mg daily for 10–15 days and then 80 mg on alternate days for 1.5–23 weeks [4, 10, 16] OR 125 mg/80 mg/80 mg for 3 days, in 2-week repetitions for 6–24 weeks [9]
Mycosis fungoides	80 mg daily for 4 months or longer for prophylaxis [12] OR 125 mg/80 mg/80 mg for 3 days, in 2-week repetitions for 6–24 weeks [9, 14]
Cutaneous anaplastic large cell lymphoma	125 mg/80 mg/80 mg for 3 days [18]
Lung adenocarcinoma	80 mg daily continuously for prophylaxis [8] OR 125 mg/80 mg/80 mg for 3 days, then alternating days of 125 mg and 80 mg for 2 months or longer for prophylaxis [11]
Breast carcinoma	Day 1: 125 mg, day 3: 80 mg, day 5: 80 mg [7]
Metastatic solid tumors	Day 1: 125 mg, day 3: 80 mg, day 5: 80 mg [11]
Soft tissue sarcoma	Day 1: 125 mg, day 3: 80 mg, day 5: 80 mg [7]
Hodgkin's lymphoma	80 mg daily for 2 weeks [15]
Chronic kidney disease	80 mg daily for 3–13 days [5]
Hyperuricemia	80 mg daily for 3–13 days [5]
Iron deficiency	80 mg daily for 3–13 days [5]
Pruritus of unclear origin	125 mg on day 1, 80 mg on days 2–4 [17]
Brachioradial pruritus	80 mg daily for 7 days; repeat if relapse [13]

lesions (63% of those reported) and reduced insomnia. Four patients (5.6%) did not respond to aprepitant therapy at all. Mild adverse reactions were reported in only four patients (5.6%), and one patient experienced substantial worsening of pruritus during treatment after an initial good response due to underlying disease progression and required cessation of aprepitant. No patients required cessation of aprepitant therapy due to drug-related adverse effects. Relapse trends were variable; nine patients were reported to have pruritus symptom relapse 48–72 hours after last aprepitant dose, while six patients were reported to have stable symptom control over two weeks after last aprepitant dose. Five patients continued with aprepitant prophylaxis at last follow-up with good symptom control.

The shared conclusion from the reviewed reports is that SP is indeed an important mediator of pruritus in many diseases and that aprepitant exhibits antipruritic activity as a NK1 receptor and SP antagonist. The authors agree that there is enough convincing evidence to warrant multicenter randomized, controlled, clinical trials to truly assess the efficacy of aprepitant's antipruritic effect. Additional trials will be necessary not only to delineate the optimal dosage and therapeutic interval for aprepitant's antipruritic effects, but also to understand the pruritic disease states that will benefit most from aprepitant, as pruritic pathomechanisms differ among various underlying diseases.

5. Pharmacology

Aprepitant is a selective, high-affinity antagonist of NK1 receptors, with little to no affinity for serotonin, dopamine, and corticosteroid receptors [19]. The oral bioavailability of aprepitant is approximately 60–65% at the recommended dose range of 80–125 mg and achieves peak plasma concentrations (T_{max}) in 4 hours [3, 19]. The mean apparent volume of distribution at steady-state is 66 L in humans, where the drug is highly bound to plasma proteins (>95%) [3]. Aprepitant is able to cross the blood-brain barrier in humans into the central nervous system (CNS) [3]. Aprepitant undergoes extensive metabolism in the body and is eliminated primarily by metabolism; it is not renally excreted [19]. Aprepitant is metabolized largely by cytochrome P450 3A4 isoform (CYP3A4), which occurs mainly by oxidation at its morpholine ring and its side chains [19]. Aprepitant has a plasma clearance of approximately 62–90 ml/min, and its terminal half-life ranges from 9 to 13 hours [19].

6. Side Effects

Aprepitant does not have acute adverse events [19]. The side effects of aprepitant therapy have been monitored in clinical trials in patients using aprepitant for depression and prevention of CINV and PONV.

Kramer et al. and Keller et al. reported on a total of 2739 patients taking up to 300 mg oral aprepitant for up to eight weeks for depression. Both reports found no significant differences in adverse events between aprepitant versus placebo and concluded that aprepitant is generally well tolerated over a long period (up to eight weeks) [1, 20, 21].

In two active-controlled, double-blind, clinical trials that compared aprepitant in combination with ondansetron and dexamethasone (aprepitant regimen; $n = 1412$) to

Table 2: Aprepitant side effects reported in ≥3% of patients by organ system for adults and pediatric patients [5, 14, 19].

Adult population	
Neurologic	Fatigue, vertigo, drowsiness, headache
Gastrointestinal and hepatic	Diarrhea, constipation, dyspepsia, abdominal pain, increased alanine aminotransferase, nausea
Neuromuscular and musculoskeletal	Asthenia, hiccups
Hematologic	Decreased WBC count
Endocrine and metabolic	Dehydration
Cardiovascular	Hypotension
Pediatric population	
Neurologic	Headache, fatigue, dizziness
Gastrointestinal	Diarrhea, decreased appetite
Neuromuscular and musculoskeletal	Cough, hiccups
Hematologic	Neutropenia, decreased hemoglobin

ondansetron and dexamethasone alone (standard therapy; $n = 1396$) for prevention of CINV, the most common adverse reactions that occurred in >3% of adults in both regimens included fatigue, diarrhea, asthenia, dyspepsia, abdominal pain, hiccups, decreased white blood cell count, dehydration, constipation, hypotension, and increased alanine aminotransferase (see Table 2) [19]. The type of adverse reactions was similar for patients in both groups, but the incidence of each adverse reaction was consistently 1-2% higher in the aprepitant regimen group as compared to those on standard therapy [19].

Two active-controlled, double-blind, clinical studies compared 40 mg oral aprepitant ($N = 564$) to 4 mg intravenous ondansetron ($N = 538$) for the prevention of PONV [19]. Common adverse reactions experienced by >3% of adults included constipation and hypotension, with a 1% higher incidence of both in those treated with aprepitant as compared to ondansetron [19].

Aprepitant is approved for use in children > 12 years of age or in children < 12 years who weigh 30 kg [19]. Two active-controlled clinical trials in pediatric patients compared aprepitant and ondansetron (aprepitant regimen; $n = 184$) to ondansetron with or without dexamethasone (control regimen; $n = 168$) for CINV [19]. Common adverse events experienced in >3% of the pediatric population for the prevention of CINV include neutropenia, headache, diarrhea, decreased appetite, cough, fatigue, decreased hemoglobin, dizziness, and hiccups [19]. The incidence of each adverse event was consistently 1–4% higher in the aprepitant regimen than in the control regimen [19].

7. Contraindications and Warnings

There are two strict contraindications to aprepitant therapy according to aprepitant's pharmaceutical drug label package: (1) known hypersensitivity to any component of the drug and (2) concurrent use with pimozide [19]. Aprepitant is a substrate, moderate inhibitor, and inducer of CYP3A4 [19]. As such, there are risks of many drug-drug pharmacokinetic interactions. Pimozide is a CYP3A4 substrate, thereby inhibition of CYP3A4 by aprepitant could increase plasma levels of pimozide, increasing risk of serious adverse reactions such as QT prolongation, a known adverse effect of pimozide [19].

Coadministration of other CYP3A4 substrates with aprepitant also requires caution and careful monitoring. Concurrent use of aprepitant with warfarin yields a risk of decreased INR [19]. Likewise, efficacy of hormonal contraceptives may be reduced with concurrent use with aprepitant and up to 28 days after the last dose of aprepitant [19]. Erlotinib is a commonly used anticancer therapy that is primarily metabolized and cleared by CYP3A4 [22]. Aprepitant has been shown to significantly decrease erlotinib clearance and increase its plasma concentration [8]. Strict monitoring and surveillance of drug plasma concentrations are necessary when administering aprepitant with erlotinib and other chemotherapy agents metabolized by CYP3A4.

Since aprepitant is also a CYP3A4 substrate, its plasma concentration needs to be carefully monitored when coadministered with other CYP3A4 inhibitors, which may increase risk of adverse reactions, or inducers, which may reduce the drug's efficacy (see Table 3) [19].

8. Mechanism of the Antipruritic Effect

The main antipruritic effect of aprepitant is via substance P (SP) antagonism. SP plays a major role in the induction and maintenance of pruritus in the skin [1, 23–26]. SP is a short neuropeptide that preferentially binds to the NK1 receptor expressed in the CNS and on immune cells, cutaneous keratinocytes, and mast cells [27]. An increase in NK1 receptor expression has been reported on keratinocytes in pruritic skin conditions [28, 29]. Upon binding to its receptor on keratinocytes, fibroblasts, and mast cells in the skin, SP stimulates the secretion of a variety of inflammatory factors, including interferon-γ, IL-1β, IL-8, histamine, leukotriene B4, prostaglandin D2, and vascular endothelial growth factor (VEGF) [27]. This leads to vasodilation of vessels and neurogenic inflammation, which clinically presents as erythema, edema, and pruritus [27].

Aprepitant is a highly selective NK1 receptor antagonist with little to no affinity for other neurokinin receptors [10, 11]. By blocking mast cell degranulation, aprepitant is able to inhibit SP-mediated inflammation and pruritus [28, 30]. This conclusion is further supported by reports that aprepitant is more effective at relieving pruritus in patients with prurigo nodularis, as prior studies have found that patients with prurigo nodularis have an increased number of nerve fibers positive for SP [5, 31].

Another hypothesis is that oral aprepitant acts on the CNS [32]. Wallengren reported that pruritus failed to respond to local treatment with 5% topical aprepitant despite correct cutaneous absorption [32]. While this author agrees that aprepitant's antipruritic effect is via SP antagonism, she suggests that the effect is in the CNS and not the skin [32].

Table 3: Drugs that may interact with aprepitant if used concurrently, based on CYP3A4 interactions.

CYP3A4 interaction	CYP3A4 substrates	CYP3A4 inducers	CYP3A4 inhibitors
Risk	Risk of increased or decreased plasma levels with concurrent aprepitant use	Risk of decreased aprepitant plasma levels	Risk of increased aprepitant plasma levels
Drugs	Pimozide	Rifampin	Ketoconazole
	Erlotinib		Diltiazem
	Warfarin		
	Hormonal contraceptives		
	Ifosfamide		
	Methylprednisolone		
	Dexamethasone		

9. Conclusions

In the studies reviewed here, aprepitant has successfully treated chronic refractory pruritus associated with cutaneous T-cell lymphomas, solid tumors, chronic kidney disease, and Hodgkin's lymphoma, among others. These patients experienced considerable pruritic symptom relief and improvement in pruritus-induced comorbidities, such as insomnia, depression, and significant reductions in quality of life. Few patients experienced adverse effects. Collectively, these reports demonstrate the potential for oral aprepitant to be an alternative antipruritic treatment for patients who are insufficiently relieved by conventional therapy. However, these conclusions must be taken in the context of aprepitant's high cost and potential interaction with multiple other drugs [33]. The high cost of aprepitant prevents its wide use and more economical antipruritic therapies should be attempted first. Even though aprepitant has been shown in these case series to produce a dramatic improvement in pruritus symptoms, unfortunately it may have to be used as a last resort due to high economic barriers. Additional studies are needed to clarify the optimal dosage for aprepitant's antipruritic effects and to determine in which disease states aprepitant will be most effective and applicable.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Research Article

Prevalence and Clinical Characteristics of Itch in Vitiligo and Its Clinical Significance

Vasanop Vachiramon, Woranit Onprasert, Sarawin Harnchoowong, and Kumutnart Chanprapaph

Division of Dermatology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Correspondence should be addressed to Vasanop Vachiramon; vasanop@gmail.com

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Objective. Vitiligo usually presented as asymptomatic depigmented macules and patches. Little is known regarding itch in vitiligo. This study aimed to evaluate the prevalence and characteristics of itch in vitiligo patients. *Patients and Methods*. A cross-sectional study was conducted on vitiligo patients. Itch character and intensity were determined through questionnaires. Evaluation was also made by dermatologists to define vitiligo subtype, body surface area, Koebner phenomenon (KP), and so on. Data were assessed by computer software. Results were considered statistically significant if $p < 0.05$. *Results*. Among 402 patients, itch on vitiliginous lesion presented in 20.2%. Prevalence of itch was most common in focal vitiligo (29.4%), followed by segmental vitiligo (20.3%) and nonsegmental vitiligo (19.6%), respectively. Tingling sensation was the most common itch-related symptom (82.7%). The median itch intensity is 5 by 10-point visual analog scale. Daily activity and sleep disturbance were observed in 60.5% and 39.5% of patients who experience itch. Itch occurred approximately 3 days prior to the development of lesions in 48.1% of patients. Thirty-two patients (78.1%) with both itch and KP type IIb had active disease. *Conclusions*. Itch in vitiligo is not uncommon. The presence of itch with KP type IIb may warrant the active vitiligo.

1. Introduction

Vitiligo is a common acquired hypopigmentary disorder, affecting up to 2% of the general population [1]. The pathogenesis of vitiligo is still not fully elucidated. However, it is postulated that vitiligo is a multifactorial, polygenic disorder, with a complex pathogenesis. Several theories on the etiology of vitiligo have emerged, for example, genetic hypothesis, autoimmune hypothesis, defects of melanocyte adhesion, neurogenic damage, and biochemical damage [2–7].

Classically vitiligo is manifested as well-defined, irregular-shaped, depigmented macules or patches. The lesions enlarge centrifugally over time, and the rate may be slow or rapid. Erythematous border is occasionally observed at the vitiliginous lesions, which is referred to as inflammatory vitiligo or vitiligo with raised inflammatory borders.

Vitiligo is usually considered as an asymptomatic dermatosis. However, itch was occasionally mentioned in some vitiligo patients. According to a study by Levai, vitiligo affected patients, with or without the presence of irritated skin lesions, can suffer from itch prior to the appearance of depigmented patches [8]. Furthermore, published data on the prevalence and characteristics of itch in vitiligo are very limited. The objective of this study was to determine the prevalence and factors influencing itch in patients with vitiligo.

2. Materials and Methods

2.1. Study Design and Patient Eligibility. This questionnaire-based cross-sectional study was conducted from January 2016 to December 2016 at university-based hospital (Ramathibodi Hospital, Mahidol University, Bangkok, Thailand). Patients over 18 years of age affected with all types of vitiligo attending the dermatology outpatient department were enrolled in this study. They were excluded if they refused to participate in the study. Patients unable to read or understand the questionnaire were also excluded. The study was approved by

institutional review board of Faculty of Medicine Ramathibodi Hospital, Mahidol University (protocol number 125813). The study protocol followed the guidelines of the 1964 Helsinki declaration. All patients had obtained the inform consent prior to enrollment.

2.2. Questionnaire Details. The questionnaire was divided into 2 parts. The first was self-reported information from patients, namely, demographic data (e.g., age, gender, weight, height, and income), family history of vitiligo, age of onset of vitiligo, initial location of the lesion, factors influencing the disease, Koebner phenomenon (KP) type 1, disease activity, and dermatology life quality index (DLQI). "True itch" refers to pruritus occurring before or after development of vitiliginous lesion but not related to treatment (e.g., topical medications, phototherapy). If it is present, patients then would be questioned about the different dimensions of itch including characteristic, aggravating and alleviating factors, the relationship of itch and the development of lesion, disease activity during the past 6 months, and sleep and activity disturbance. A 10-point visual analog scale (VAS) was used to grade itch intensity. Patients were also asked to compare the magnitude of itch to their past itch experience from a common itch-related condition, namely, insect bite. The VAS scale was categorized into the terms "mild itch" (VAS > 0 to <3.0), "moderate itch" (VAS ≥ 3.0 to <7.0), and "severe itch" (VAS ≥ 7.0 to 10).

The second part of the questionnaire was physician-reported information regarding physical examination and laboratory data of the participants, for example, Fitzpatrick skin type, other skin and systemic diseases, percentage of body surface area (BSA) involvement using the rule of nines as in burn assessment, type of vitiligo, leukotrichia, KP, anti-microsomal, anti-thyroglobulin, and anti-nuclear antibody (ANA), thyroid-stimulating hormone (TSH), free triiodothyronine (free T3), and free thyroxine (free T4).

KP was classified into 3 types based on the Vitiligo European Task Force group [9]. Type 1 KP is defined as the diagnosis of KP based on history (i.e., depigmentation after skin trauma). Type 2A KP is classified as patients having vitiligo localized to areas of repeated pressure or friction (e.g., elbows, knee, and knuckle) and type 2B KP is characterized by depigmented lesions clearly induced by trauma (i.e., artefactual lesions, punctiform, and crenate). Type 3 KP is defined as experimentally induced KP.

2.3. Assessment and Statistical Analyses. Statistical analyses were performed using computer software (Stata version 14, StataCorp., College Station, Texas) for Windows. Categorical variables were expressed as percentages. Continuous variables (e.g., age, BSA involvement, and VAS) were expressed in terms of mean ± standard deviation or median (range). Comparison of categorical variables was performed using the chi-squared test. The paired t-test or Wilcoxon signed-rank test was used to compare continuous data between two dependent samples. A p value of 0.05 or less was considered statistically significant.

3. Results

3.1. Patients' Demographic Data. A total of 402 patients were enrolled. There were 144 male and 258 female participants in the study. The mean age of patients was 45.43 (±16.19). The median duration of vitiligo was 7 years (0.8–59). Most patients had less than 20% of BSA involvement. Regarding type of vitiligo, nonsegmental vitiligo was the most common in this study ($N = 321$, 79.9%) followed by segmental vitiligo and focal vitiligo, 64 (15.9%) and 17 (4.2%), respectively. The demographic data and baseline characteristics of patients affected by vitiligo with and without itch are shown in Table 1. There were no significant differences in demographic characteristics between the two groups.

3.2. Prevalence of Itch and Itch Characteristics. Overall, itch was found in 81 patients with vitiligo (20.2%). Among vitiligo subtypes, itch was most commonly presented in focal vitiligo (29.4%), followed by segmental vitiligo (20.3%) and non-segmental vitiligo (19.6%), respectively. The presence of itch significantly correlated with initial lesion located on the trunk ($p < 0.001$) (Table 1). Patients described the sensory qualities of itch as tingling (82.7%), crawling (18.5%), and burning (18.5%). Other itch sensations (e.g., pinching, electric discharge, and tickling) were rarely reported (<3%). Approximately 21% of patients who suffered from itch reported having at least two sensory qualities (Table 2). Among them, women were reported to have crawling sensation more frequently than men (7.4% in men versus 24.1% in women, $p = 0.069$) (Table 3).

3.3. Severity of Itch. The median intensity of itch on 10-point VAS was 5 (1–10), a magnitude equivalent to pruritus caused by insect bite reaction through the patients' experiences. Severe itch was reported in 23 patients (28.4%). Itch of moderate and mild intensity was documented in 35 (43.2%) and 23 (28.4%) of patients, respectively (Table 2). Itch was described to be more intense in females when compared to the male counterpart (33.3% versus 18.6%, $p = 0.291$) (Table 3).

As for the burden of itch among affected patients, the median DLQI score in the itch group was significantly higher than those without it (7 versus 5, $p < 0.001$) (Table 1). Daily activity disturbance was found in 49 patients (60.5%) and sleep disturbance was found in 32 patients (39.5%). Thirty patients (37%) reported moderate to severe activity disturbance. This was significantly more among female patients ($p = 0.033$) (Table 3). The magnitude of activity disturbance correlated significantly with itch intensity ($p = 0.002$) (Figure 1).

3.4. Relationship of Itch and the Development of Lesions. Itch preceded the onset of vitiliginous lesions in 39 patients (48.1%) with the median of 3 days (1–60) prior to the development of the lesion. Thirty-seven patients (45.7%) reported that itch occurred after the appearance of vitiliginous lesion, with the median of 1 day after the onset (0.5–30) (Table 2). In 5 out of 81 patients who had itch (6.2%), the relationship

Table 1: Demographic data and clinical characteristics of vitiligo patients with and without itch.

Characteristics	Itch	Nonitch	p
Age, mean ± SD (years)	46.5 ± 16.0	45.2 ± 16.2	0.519
Gender, *n* (%)			0.601
(i) Male	27 (33.3)	117 (36.4)	
(ii) Female	54 (66.7)	204 (63.6)	
Onset (years), median (range)	37 (0–72)	36 (1–75)	0.438
Duration of vitiligo (years), median (range)	6 (0–59)	7 (0.83–51)	0.456
Family history of vitiligo, *n* (%)	17 (21.0)	73 (22.7)	0.735
Family history of thyroid and autoimmune disease, *n* (%)	10 (12.4)	40 (12.5)	0.978
Leukotrichia, *n* (%)	38 (46.9)	151 (47.0)	0.984
Body surface area involvement (%), median (range)	3 (0.2–50)	2 (0.1–90)	0.458
Fitzpatrick skin types, *n* (%)			0.521
(i) Type III	13 (16.0)	57 (17.8)	
(ii) Type IV	57 (70.4)	234 (72.9)	
(iii) Type V	11 (13.6)	30 (9.3)	
Type of vitiligo, *n* (%)			0.618
(i) Nonsegmental	63 (77.8)	258 (80.4)	
(ii) Segmental	13 (16.0)	51 (15.9)	
(iii) Focal	5 (6.2)	12 (3.7)	
Initial location, *n* (%)			
(i) Head and neck	37 (45.7)	143 (44.6)	0.855
(ii) Trunk	13 (16.1)	17 (5.3)	0.001
(iii) Arms	4 (4.9)	38 (11.8)	0.070
(iv) Hands	17 (21.0)	103 (32.1)	0.051
(v) Legs	9 (11.1)	23 (7.2)	0.241
(vi) Feet	5 (6.2)	12 (3.7)	0.354
Associated diseases, *n* (%)	28 (34.6)	110 (34.3)	0.959
(i) Hyperthyroidism	1 (2.6)	15 (9.6)	0.560
(ii) Hypothyroidism	1 (2.6)	11 (6.7)	0.560
(iii) Diabetes mellitus	3 (3.7)	14 (4.4)	1.000
(iv) Allergic rhinitis/asthma	6 (7.4)	22 (6.9)	0.861
(v) Alopecia areata	1 (1.2)	9 (2.8)	0.368
(vi) Halo nevi	3 (3.7)	19 (5.9)	0.319
Positive results for anti-microsomal antibody	16 (25.4)	75 (30.0)	0.472
Positive results for anti-thyroglobulin antibody	12 (19.5)	49 (19.8)	0.888
Positive results for ANA	30 (45.5)	117 (45.2)	0.967
TSH level			0.216
(i) Low	2 (3.23)	16 (7.31)	
(ii) Normal	60 (96.77)	195 (89.04)	
(iii) High	0 (0)	8 (3.65)	
DLQI, median (range)	7 (0–26)	5 (0–26)	0.001

between onset of itch and the lesion development could not be determined.

3.5. Aggravating Factors and Alleviating Factors. Common aggravating factors of itch were skin dryness (58.0%), hot environment (49.4%), and sunlight (24.7%). Topical corticosteroids (55.6%) were the most common itch-alleviating factor followed by shower (38.2%). Oral antihistamine improved itch in some patients (9.9%). Cold environment was found to both aggravate and alleviate itch in 16.1% and 25.9% of patients, respectively. Factors that aggravated and relieved itch were shown in Table 2.

3.6. Itch and the Disease Activity. In this study, KP was found in 56% of patients. The presence of KP types I and II tends to be more common in vitiligo patients with itch compared to those without. This is especially true for KP type IIb (p = 0.056) (Table 4). Among 32 patients with itch and KP type IIb,

Table 2: Characteristics of itch in vitiliginous lesions.

Characteristics	*n* (%)
Prevalence of itch	81 (20.2), 95% CI (16.3–24.4)
Intensity of itch in vitiligo (VAS), median (range)	5 (1–10)
Intensity of itch in insect bite (VAS), median (range)	5 (0–10)
Frequency of itch	
(i) Always	4 (4.9)
(ii) Often	77 (95.1)
Aggravating factors	
(i) Hot environment	40 (49.4)
(ii) Dry skin	47 (58.0)
(iii) Sunlight	20 (24.7)
(iv) Cold environment	13 (16.1)
(v) Seafood	7 (8.6)
Alleviating factors	
(i) Topical corticosteroids	45 (55.6)
(ii) Shower	31 (38.2)
(iii) Cold environment	21 (25.9)
(iv) Oral antihistamines	8 (9.9)
(v) Phototherapy	5 (6.2)
Relationship of itch and onset of lesion(s)	
(i) Itch before onset	39 (48.1)
Day, median (range)	3 (1–60)
(ii) Itch after onset	37 (45.7)
Day, median (range)	1 (0.5–30)
(iii) Uncertain	5 (6.2)
Itch sensory qualities	
(i) Tingling	51 (63.0)
(ii) Crawling	5 (6.2)
(iii) Burning	7 (8.7)
(iv) Pinching	1 (1.2)
(v) Tingling + crawling	5 (6.2)
(vi) Tingling + burning	4 (4.9)
(vii) Tingling + electric discharge	1 (1.2)
(viii) Tingling + tickling	2 (2.5)
(ix) Tingling + crawling + burning	4 (4.9)
(x) Crawling + electric discharge	1 (1.2)
Severity of itch	
(i) Mild itch (VAS > 0 to <3.0)	23 (28.4)
(ii) Moderate itch (VAS ≥ 3.0 to <7.0)	35 (43.2)
(iii) Severe itch (VAS ≥ 7.0 to 10).	23 (28.4)

78.1% had active disease (i.e., lesion progression and/or newly developed lesion), while 21.9% had stable disease within the past 6 months ($p = 0.001$) (Figure 2).

4. Discussion

Itch is a common symptom of many dermatological diseases. It may originate in the skin or nervous system. Clinically, itch can be classified into itch associated with skin disorders (e.g., xerosis, atopic dermatitis, urticaria, psoriasis, and arthropod bite), itch associated with systemic diseases (e.g., chronic liver disease, end stage renal failure), neuropathic itch (e.g., notalgia paresthetica, postherpes zoster neuropathy), and psychogenic itch. However, itch associated with vitiligo is rarely mentioned in the literature.

In this study, the prevalence of itch in vitiligo patients is up to 29.4% depending on vitiligo subtype. The prevalence of itch in this study is higher than a previous report. According to a study by Levai, 44% of vitiligo patients had a history of prior skin disease in an area of depigmentation, 15% had depigmentation in areas of constant pressure or irritation, and 10% complained of itching without prior history of skin

Table 3: Intensity, sensation of pruritus, and activity and sleep disturbance between males and females.

Characteristics	Male, *n* (%)	Female, *n* (%)	*p*
Intensity of pruritus in vitiliginous lesion by VAS			0.291
(i) Mild (1–3)	10 (37.0)	13 (24.1)	
(ii) Moderate (4–6)	12 (44.4)	23 (42.6)	
(iii) Severe (7–10)	5 (18.6)	18 (33.3)	
Itch sensory qualities			
(i) Tingling	24 (88.9)	43 (79.6)	0.365
(ii) Crawling	2 (7.4)	13 (24.1)	0.069
(iii) Burning	6 (22.2)	9 (16.7)	0.544
(iv) Pinching	0	1 (1.9)	1.000
(v) Electric discharge	1 (3.7)	1 (1.9)	1.000
(vi) Tickling	1 (3.7)	1 (1.9)	1.000
Activity disturbance			0.033
(i) No	15 (55.6)	17 (31.4)	
(ii) Mild	8 (29.6)	11 (20.4)	
(iii) Moderate	2 (7.4)	15 (27.8)	
(iv) Severe	2 (7.4)	11 (20.4)	
Sleep disturbance			0.152
(i) No	21 (77.8)	28 (51.9)	
(ii) Mild	4 (14.8)	14 (25.9)	
(iii) Moderate	1 (3.7)	6 (11.1)	
(iv) Severe	1 (3.7)	6 (11.1)	

Table 4: Koebner phenomenon (KP) between itch and nonitch groups.

Koebner phenomenon	Itch ($n = 81$)	Nonitch ($n = 321$)	*p*
KP, *n* (%)	50 (67.9)	175 (54.52)	0.243
KP type I	35 (43.2)	110 (34.3)	0.134
(i) Cutting/scratching	28 (34.6)	86 (26.8)	0.165
(ii) Rubbing	35 (8.7)	24 (7.5)	0.082
(iii) Chemical/heat/cold	5 (6.2)	16 (5.0)	0.588
(iv) Pressure	5 (6.2)	8 (2.5)	0.094
(v) Previous skin disease	4 (4.9)	11 (3.4)	0.521
KP type II	43 (53.1)	141 (43.9)	0.139
(i) KP type IIa	19 (23.46)	76 (23.8)	0.967
(ii) KP type IIb	32 (39.5)	92 (28.9)	0.059
KP type III	1 (1.23)	4 (1.25)	1.000

disease or trauma [8]. The higher prevalence of itch in our study could be due to the differences in the study population. Itch in several patients with depigmented lesions described by Levai, in fact, could possibly be from chemical leukoderma and postinflammatory depigmentation and, thereby, may not represent the exact prevalence of itch in true vitiligo patients.

Itch can occur as a consequence of treatment, for example, topical mediation and phototherapy. We have excluded this group from the study. Moreover, certain systemic disease associated with vitiligo could potentiate itch such as hyperthyroidism, hypothyroidism, diabetes mellitus, allergic rhinitis, or asthma. According to our study, there were no significant differences regarding the prevalence of these conditions among patients with and without itch. Therefore, we postulate that itch in vitiliginous lesion is a manifestation of vitiligo itself.

The pathogenesis of itch in vitiligo remains unclear. However, the possible concept of itch in many dermatological diseases is focused on neurogenic inflammation and mediators such as neuropeptides released from dermal nerve endings induced by various stimuli. There are many evidences to support the hypothesis of inflammation in vitiliginous lesion. According to recent studies, cell-mediated immunity in vitiligo was demonstrated by the presence of CD8+ T cells in suction blistering skin, perilesional skin, and the blood of vitiligo patients. Moreover, vitiliginous lesion demonstrated

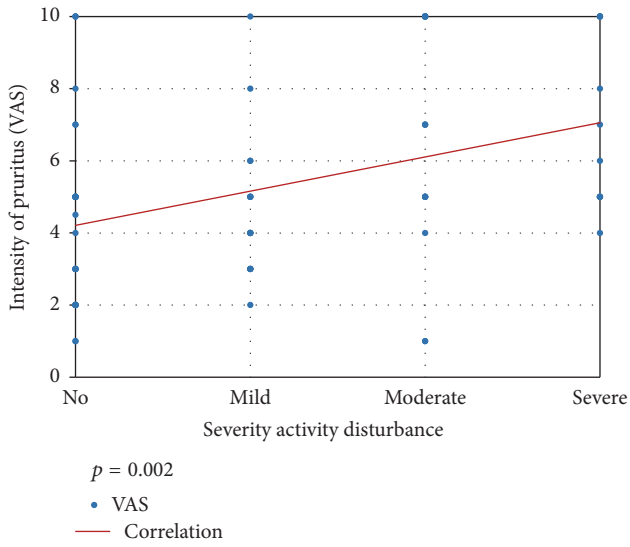

Figure 1: Correlation of intensity of pruritus and degree of activity disturbance.

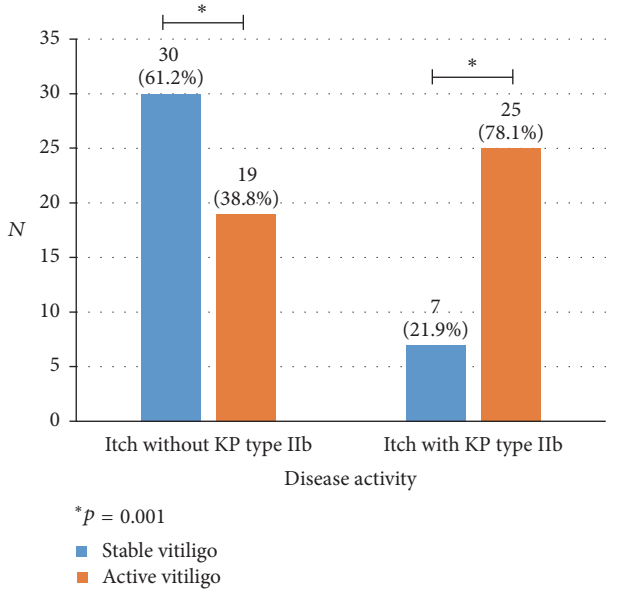

Figure 2: Disease activity among patients with itch and Koebner phenomenon (KP) type IIb.

lower CD4+ to CD8+ lymphocytes ratio compared to non-lesional skin [10–13]. Other parameters such as cytokines and regulatory T cells may also play major roles in vitiligo pathogenesis [14]. An increase in tumor necrosis factor alpha (TNF-α), interferon-gamma (IFN-γ), and interleukin-(IL-) 1 compared to healthy skin suggests that vitiligo is mediated by cytotoxic T cells and T helper cell-1 (Th1) response [15–18]. In segmental vitiligo, dysfunction of the sympathetic nervous system can restrain melanin production and lead to depigmentation [19]. All these findings may illustrate neurogenic inflammatory mechanism of itch in vitiligo. However, it is unclear whether primary immune response targets normal melanocytes or if immune activation is triggered by damaged melanocytes through exogenous or endogenous insult. Further studies are needed to explain the complex mechanisms of itch in vitiligo.

There are several methods to assess the intensity of itch. In this study, the ratings were based on patients' 10-point VAS self-evaluation scale. According to our data, the median intensity of itch in was 5 (median VAS = 5). Our patients rated this equivalent to the severity of itch caused by arthropod bite. However, the comparison itch intensity in different types of dermatoses is very difficult and no direct assessment has been performed. Based on previous studies, using a similar VAS score, the intensity of itch in atopic dermatitis, psoriasis, and lichen planus was 4.8, 6.3, and 6.9, respectively [20–22]. In this study, 71.6% of patients with itch reported moderate or severe intensity. Approximately 60% of vitiligo patients with itch had daily activity disturbance and 39.5% had sleep disturbance. This may result in psychological distress and potentiate the severity of several dermatoses including vitiligo. Therefore, we emphasized the importance of itch in vitiligo which remains underrecognized.

Among the clinical variants of vitiligo, pruritus was more common in focal vitiligo and significantly correlated with initial truncal distribution. Our finding supports previous evidence on the variations in area-specific innervation density and pruritic mediator release in different anatomical sites of the body [23, 24]. In addition, the nerves which supply sensation to the upper trunk emerge from the 2nd to 6th thoracic segments of spinal cord. They run a long course up through the thick muscles of the back and make a right-angled turn before reaching the skin. These nerves appear to be vulnerable to compression or traction and lead to the symptom of itch [25]. Although our data indicates that the presence of initial lesion on trunk is highly associated with itch ($p = 0.001$), the numbers are too small to make a convincing support that the location is the key issue for itch. When compared to other itchy dermatosis, pruritus in lichen planus tends to be more prominent on the extremities, while psoriatic patients experience itch on both the trunk and lower extremities [22, 26].

Regarding factor influencing itch, skin dryness was identified as an aggravating factor of pruritus by 58% of the patients. However, the presence of skin dryness did not correlate with the degree of itch which is consistent with other pruritic dermatoses [27–29]. Several factors such as alteration stratum corneum surface lipid, water metabolism, pH, and cytokine levels may contribute to the sensation of itch [30, 31].

Hot environment and sunlight were identified as an important aggravating factor of itch in our vitiligo patients, possibly from high temperatures in our tropical climate. It was suggested that heat can increase itch sensation by its direct effect on dermal nerve endings or by indirect effect on neuroautonomic mechanism via sweating, as both itch and sweating are mediated by C nerve fibers [32, 33]. According to recent data, heat stimulated itch through the activation of transient receptor potential cation channel subfamily vanilloid type 1 (TRPV1), the calcitonin gene-related peptide, the vesicular glutamate transporter 2, and accumulation of artemin [34]. Further investigations are needed to validate

whether these receptors are involved in the pathogenesis of itch in vitiligo.

The most common antipruritic treatment used was topical steroids. Due to the evidence of inflammatory cell infiltration and certain cytokines in vitiliginous lesion, anti-inflammatory therapies may result in cessation of itch. Moisturizers in topical medication may have a contributing benefit in reducing the itch. In addition, cold environment and shower were found to alleviate itch in vitiligo. These observations support a role for the cold-sensitive transient receptor potential melastatin-8 (TRPM8) ion channel, the major receptor for sensing cold environmental, in the modulation of pruritus [35]. In contrast to other pruritic dermatoses, the role of antihistamines in relieving itch is questionable in vitiligo. Only a few of our patients responded to oral antihistamines.

According to a study by Van Geel et al., higher disease activity was found in KP1-positive and KP2B-positive vitiligo patients [9]. In our study, there is a tendency towards itch being more prevalent in patients presenting with KP type 2B (Table 4). Therefore, it could be implied that the presence of itch may warrant active stage of vitiligo especially with the presence of KP type IIb. A possible explanation to this phenomenon is that the inflammatory process of active vitiligo promotes pruritogenic cytokines and induces itch.

There are some limitations in our study. Firstly, recall bias associated with self-responded questionnaire may influence the results. Secondly, as patients were gathered from university-based hospital, there is a possibility of subject selection election bias. Thirdly, our study involved patient subjected evaluation; an objective assessment was not performed. Finally, further studies regarding the neurophysiology of itch including mechanism of itch in vitiligo are necessary.

In conclusion, this is the first step towards enhancing comprehensive knowledge regarding itch in vitiligo. As dermatologists, it is prudent to acknowledge that pruritus is an important aspect of vitiligo. Prompt detection to provide early treatment is mandatory in patients with active vitiligo.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Research Article

The Role of Intereukin-31 in Pathogenesis of Itch and Its Intensity in a Course of Bullous Pemphigoid and Dermatitis Herpetiformis

Lilianna Kulczycka-Siennicka, Anna Cynkier, Elżbieta Waszczykowska, Anna Woźniacka, and Agnieszka Żebrowska

Department of Dermatology and Venereology, Medical University of Lodz, Poland Hallera Square No. 1, 90-647 Lodz, Poland

Correspondence should be addressed to Lilianna Kulczycka-Siennicka; lilakulczycka@wp.pl

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Itch which is one of the major, subjective symptoms in a course of bullous pemphigoid and dermatitis herpetiformis makes those two diseases totally different than other autoimmune blistering diseases. Its pathogenesis is still not fully known. The aim of this research was to assess the role of IL-31 in development of itch as well as to measure its intensity. Obtained results, as well as literature data, show that lower concentration of IL-31 in patients' serum may be correlated with its role in JAK/STAT signaling pathway which is involved in development of autoimmune blistering disease. Intensity of itch is surprisingly huge problem for the patients and the obtained results are comparable with results presented by atopic patients.

1. Introduction

Itch which occurs in a course of bullous pemphigoid (BP) and dermatitis herpetiformis (Duhring disease, DH) is a symptom which differentiates those two autoimmune blistering diseases among others. The reasons for which itch is present are still unknown.

Although the first definition of itch (unpleasant sensation leading to scratching) was made in 1660, its exact pathogenesis is still unknown. It is known that histamine, proteases, neuropeptides, acetylcholine, and bradykinin as well as receptors: opioid, cannabinoid, TRVP1 (transient receptor potential cation channel subfamily V member 1), and PAR2 (protease activated receptor 2) play an important role in the pathogenesis [1]. Moreover interleukins: IL-2, IL-8, and IL-31 are part of this response. In particular IL-31 is a subject of scientific interests in recent years. In most cases researches were made in patients with allergic diseases or atopy, particularly atopic dermatitis and prurigo [2–4]. Single reports present involvement of IL-31 in pathogenesis of itch in a course of other diseases [5–7]. So far there are no data connected with the role of IL-31 in development of itch in a course of autoimmune blistering diseases as well as itch intensity in a course of dermatitis herpetiformis. Moreover there are scarce data connected with itch intensity in a course of bullous pemphigoid [8, 9].

Interleukin-31 belongs to the family of IL-6 and is produced by Th2 lymphocytes. It works by activation of heterodimeric receptor which consists of two subunits: alpha (IL-31RA) and receptor for oncostatin M [2, 3]. Lymphocytes T (Th1, Th2, CD4+, and CD8+) as well as monocytes, macrophages, dendritic cells, mastocytes, eosinophils, and fibroblasts are the source of IL-31. In turn subunit A is localized on monocytes, eosinophils, dendritic cells, and keratinocytes.

Bullous pemphigoid is the most common autoimmune blistering disease which usually occurs among elderly patients [10, 11]. Pathogenesis of the disease is connected with presence of autoantibodies against antigens present in basement membrane: bullous pemphigoid antigen 2 (BPAG2, collagen XVII) whose molecular weight is 180 kD and bullous pemphigoid antigen 1 (BPAG1) with molecular weight 230 kD which are part of hemidesmosomes. It is also known that

mediators excreted by mast cell play a role in development of the disease.

First symptoms of the disease may be unspecific. But itch is dominating symptom which is bothering patients. In a course of the disease many different clinical symptoms may be present: urticarial lesions, erythematous edema, papules, and eczematous lesions. Classic clinical picture of bullous pemphigoid is presence of tense blisters localized on normal-looking skin or on erythematous basis with coexistence of papules or erythema. Usually mucous membranes are not involved.

Dermatitis herpetiformis is more often present in young adult people but it is also the most common autoimmune blistering disease among children. Together with autoimmunological process against transglutaminases (TG) in the skin there is a silent or oligosymptomatic, gluten sensitive enteropathy. The reason for development of clinical symptoms in a course of the disease is still not fully understand process of formation of granular deposits of IgA in dermal papillae, as well as deposits of other immunoglobulins and complement components [12].

As in BP in a course of dermatitis herpetiformis polymorphic symptoms as papules, erythema, wheals and vesicles with herpetiform pattern, and rarely tense blisters are present. Moreover also secondary lesions which are result of scratching are possible. Typical localization on elbows, knees, buttocks, and scalp is characteristic. Skin symptoms are accompanied by very severe itch.

The aim of this paper was to evaluate role of IL-31 in development of itch in a course of bullous pemphigoid and dermatitis herpetiformis. Also intensity of itch was measured using proper questionnaires. Research was performed after acceptance of Bioethics Committee of Medical University of Lodz, Poland (RNN/145/09/KB-17.02.2009r).

2. Materials and Methods

2.1. Clinical Characteristic. The study was performed on 52 patients: 28 with bullous pemphigoid and 24 with dermatitis herpetiformis. Group of BP patients was composed of 21 women and 7 men, at the age of 49–91, mean 74.5. In turn group of patients with dermatitis herpetiformis was formed by 14 women and 10 men, at the age of 21–79, mean 41.9. The diagnosis of both diseases was made based on clinical pictures and positive results of direct immunofluorescence (DIF). Also indirect immunofluorescence (IIF) and skin biopsy were performed. In a group with pemphigoid additional test using salt split technique was made to exclude epidermolysis bullosa acquisita. At the time of examination all patients were in an active phase of the disease; survey questionnaires as well as blood samples were taken before treatment. Control group consisted of 13 healthy volunteers which are age and sex matched.

2.2. Measurement of IL-31 Concentration. To measure concentration of IL-31, 5 mL of blood was taken from both patients and control group. It was centrifuged for 10 minutes at 2500 rpm and frozen at −20°C. Concentration of IL-31 was measured in serum using ELISA and presented as mg/dL. Commercial BioLegend Kit was used. The assessment was made according to the producer's instruction. To get results calibration curves were established.

2.3. Measurement of Itch Intensity. Measurement of itch intensity was made in both groups: BP and DH. According to current rules two independent scales were used: four-item itch questionnaire and numeric rating scale (NRS).

The questionnaire prepared by Reich et al. [13] contains four questions which measure different aspects of itch: extent, intensity, frequency, and sleep disturbances. It is possible to get from 3 to 19 points where 3 means little intensity of itch and 19 means very severe intensity of itch. If there is no itch patient gets 0. Patients were asked to take into consideration only the latest 72 hours because the intensity of itch may be variable in a course of the disease.

The second tool is eleven-step rating scale. As an answer the patient gives the right number responding to the intensity of itch in a course of the disease. Zero means "no itch" and 10 means "the most intense itch ever." According to the literature data proposed interpretation of obtained results by Polish population was made: 0: no itch, 1–3: mild itch, 3–7: moderate itch, 7–9: severe itch, and 9-10: very severe itch [14–16]. Because of ambiguous character of interpretation of extreme values we decided that patients who matched 3 were qualified as those with mild itch not moderate, those who matched 7 were qualified to be in the group "severe itch" not very severe, and those who matched 9 were qualified to be in the group "very severe itch." Zero means no presence of itch. Similarly as in case of the questionnaire patients were asked to give answers taking into consideration only the latest 72 hours. Numeric rating scale is a variant of VAS (Visual Analogue Scale).

2.4. Statistical Methods. Results of IL-31 concentrations were analyzed taken into consideration differences among mean results obtained by BP, DH, and control group. Analysis of variance and NIR test as post hoc test were made. Differences at $p < 0.05$ were considered statistically significant.

Results obtained by using the questionnaire and NRS were analyzed using the nonparametric Mann–Whitney test and the χ^2 test. Moreover to analyze differences between obtained results also the Pearson correlation (r) was used and its significance was checked by the Student t-test making for statistically important correlation linear regression equation.

All calculations were made using Statistica®10.

3. Results

3.1. IL-31 Concentration. It was revealed that concentration of IL-31 was statistically significantly lower in both BP (41.2 ± 13.22; $p < 0.01$) and DH (53.4 ± 6.04; $p < 0.05$) patients in comparison with control group (84.9 ± 5.59) (Figure 1).

Nevertheless differences between patients' groups were statistically insignificant. Obtained results are shown in Table 1.

3.2. Itch Intensity. Results achieved using itch intensity questionnaire showed that, for both groups of patients, with BP

Table 1: Results of variance analysis and NIR test as post hoc test for IL-31 in different groups.

	Control group	DH	BP
Control group		0.030925 ($p < 0.05$)	0.001662 ($p < 0.01$)
DH	0.030925 ($p < 0.05$)		0.358572 ($p > 0.05$)
BP	0.001662 ($p < 0.01$)	0.358572 ($p > 0.05$)	

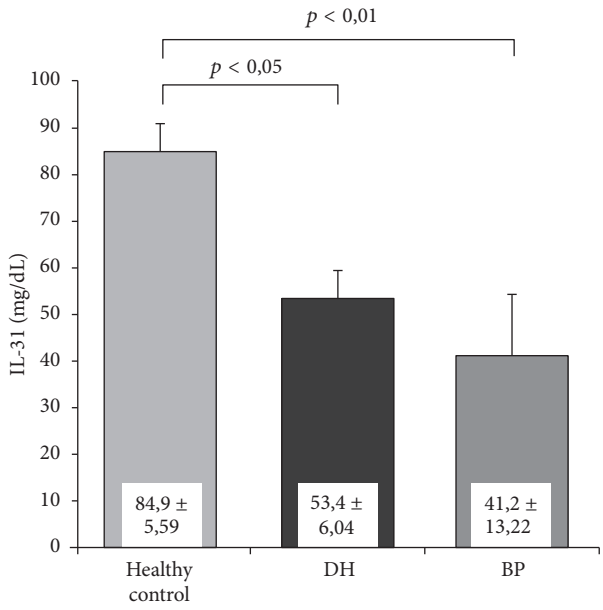

Figure 1: Mean IL-31 concentrations.

and DH, itch was similarly important problem. Patients with BP got from 5 to 19 points, mean 11.4. Women's results ranged from 5 to 19 points, mean 11.7. Men achieved from 6 to 18 points, mean 10.4. Presented differences were statistically insignificant ($p > 0.05$). Results obtained by DH patients were between 4 and 19 points, mean 12.4. Taking into consideration sex, women got from 5 to 19 points, mean 13.4, while men got from 4 to 19 points, mean 11.0. Presented differences were also statistically insignificant ($p > 0.05$). Figure 2 shows distribution of answers given by both groups of patients.

In group with BP the most popular scores (for every score 4 out of 28 patients, which made 14.3%) were 7 and 16. In case of DH group most patients (5 out of 24, 20.8%) got 14 points. Answers given by patients with BP were more differentiated.

Careful analysis of questions from itch intensity questionnaire showed that 75% of BP patients pointed that presence of itch is connected with a few localizations what means presence of skin lesions in particular area. Rest of the group pointed that their itch was generalized. Results obtained by DH patients were similar: 79.2% and 20.8%, respectively. Figure 3 presents obtained results.

Taking into consideration intensity of itch 25% of DH patients showed general irritation because of that feeling. Similar percentage of patients revealed itch which provoked scratching with presence of excoriations as well as itch without relief after scratching, without presence of excoriations. Moreover, 12.5% of DH patients showed both: itch which needs scratching, without presence of excoriations, and presence of itch without need to scratch.

28.6% of patients with BP showed that their itch needed scratching without presence of excoriations. Next 28.6% of patients revealed that scratching is not helpful. In case of 14.3% of interviewees itch needed scratching with presence of excoriations and next 14.3% of patients showed that presence of itch is not connected with scratching. Figure 4 presents the obtained results.

Most of the patients with DH (54%) reported itch as a constant feeling. 30% of patients with DH had episodes which last longer than 10 minutes and 16% shorter than 10 minutes. Only 35.7% of patients with BP reported itch as a constant problem, and not much more (39.3%) reported presence of episodes longer than 10 minutes. 25% of BP patients experienced itch which lasts no longer than 10 minutes. All results are presented on Figure 5.

Most of both DH patients (66.7%) and BP patients (67.9%) confirmed sleep disturbances provoked by presence of itch. In DH group 33.3% reported that they woke up many times during the night because of itching. Nevertheless the same amount of patients did not wake up at all. The rest of the interviewees woke up only once during night (12.5%) or twice (20.8%). By contrast patients with BP woke up twice during night (32.1%) or once (21.4%). Obtained results are presented on Figure 6.

Results obtained using four-item questionnaire are presented in Table 2.

3.3. Numeric Scale. It was shown that both groups of patients got similar results using numeric scale to assess itch intensity. The maximal number was 10 and it was pointed out by 25% of patients with BP and 20.83% of patients with DH. The minimal number was 4 and it was pointed out by 7.14% and 8.33%, respectively. Mean result was 7.7 in group with BP and 8.0 in group with DH.

Taking into consideration sex, women with BP marked from 4 to 10, mean 7.9, while men marked from 6 to 10, mean 7.3. In a group with DH obtained results according to sex were as follows: women from 7 to 10, mean 8.6, and men from 4 to 10, mean 7.3.

Also correlations between itch intensity questionnaire and results of NRS were assessed. In group of patients with BP statistically significant correlations ($p < 0.0001$) between results of NRS and general results of questionnaire (the whole results) and itch intensity and sleep disturbances were shown. In group of patients with DH statistically important correlations between NRS results and general intensity of itch ($p < 0.001$) and intensity of itch (one item from questionnaire) ($p < 0.05$) and sleep disturbances ($p < 0.0001$)

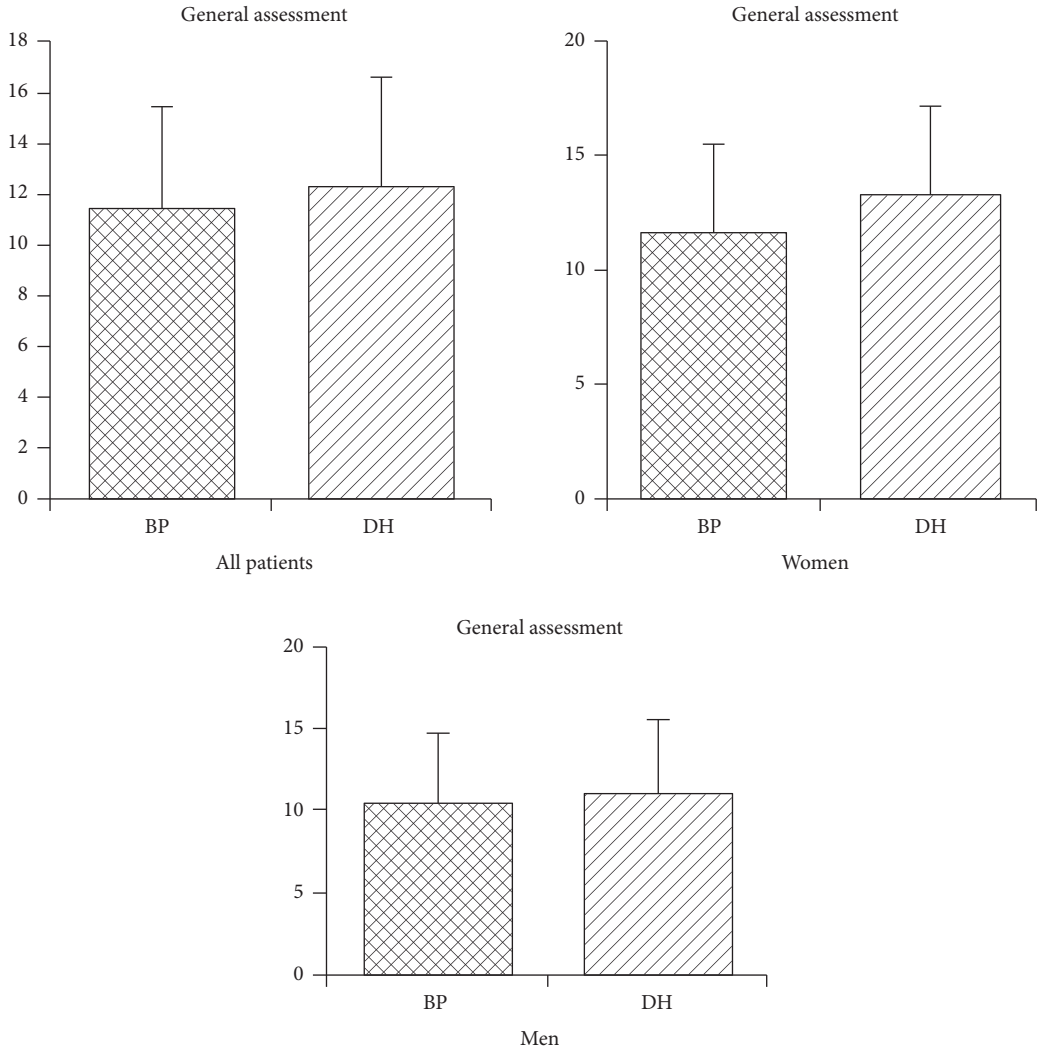

Figure 2: Itch intensity questionnaire, distribution of given answers.

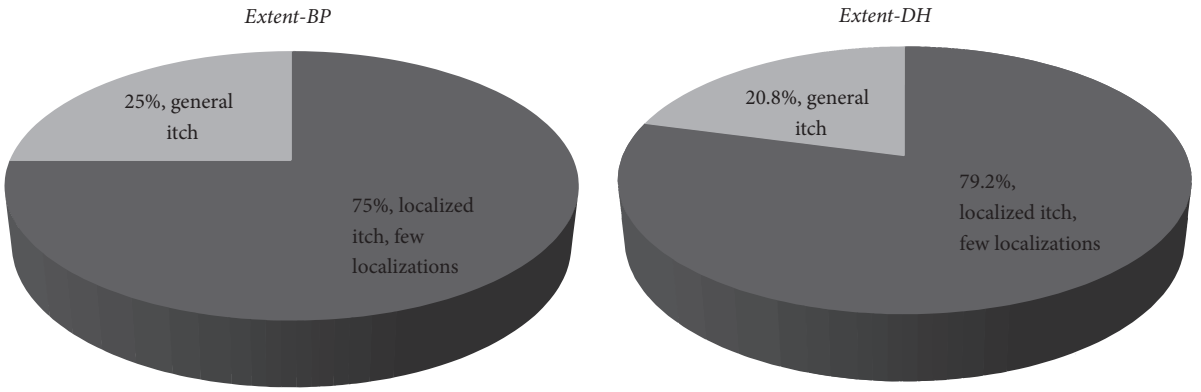

Figure 3: Itch extent, percentage of given answers.

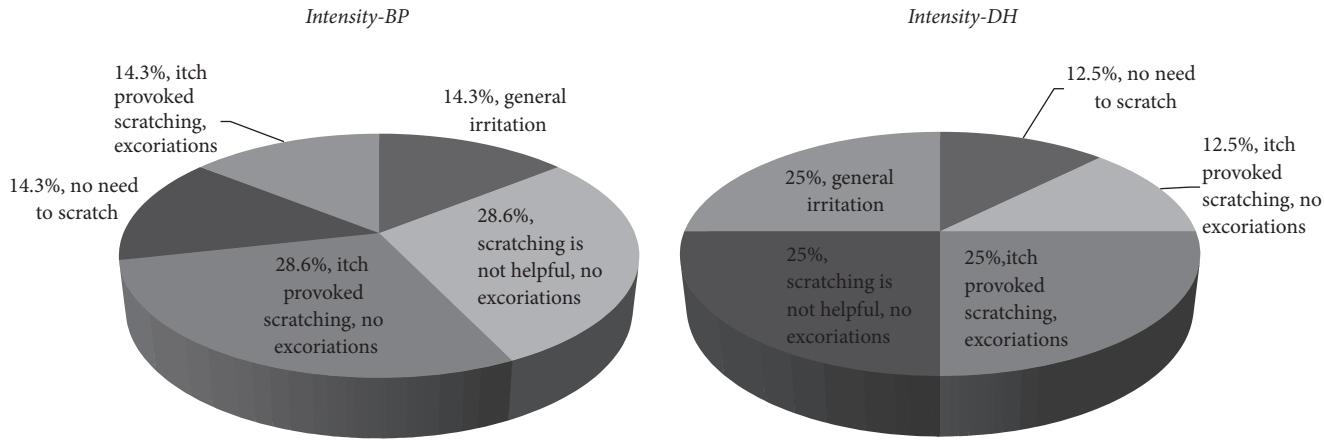

Figure 4: Itch intensity, percentage of given answers.

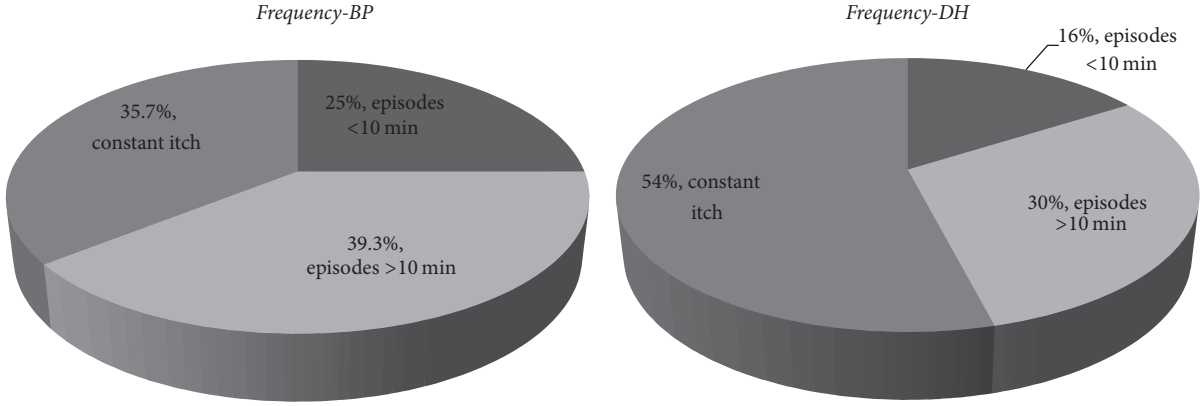

Figure 5: Itch frequency, percentage of given answers.

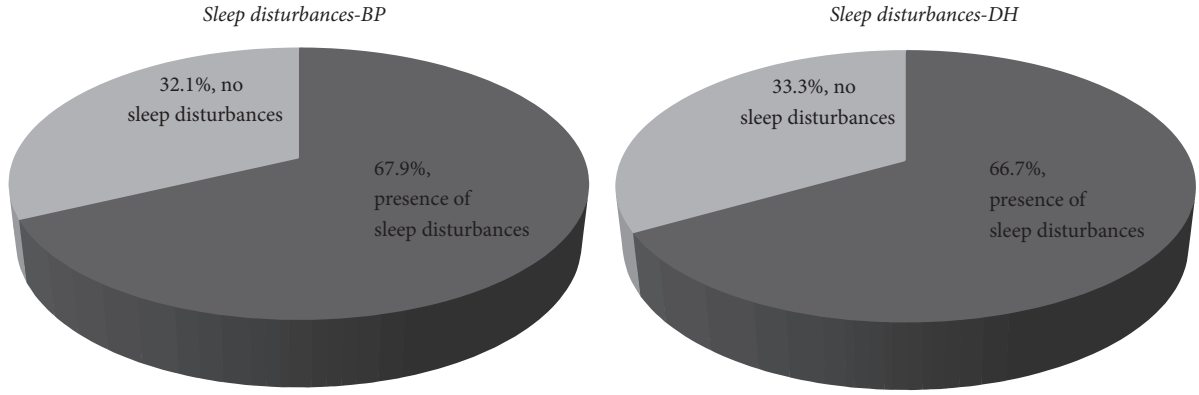

Figure 6: Sleep disturbances provoked by itch, percentage of answers.

were shown. In both investigated groups correlations between NRS results and itch extent as well as frequency were statistically insignificant ($p > 0.05$).

In group of patients with DH statistically significant correlations between general intensity of itch and particular items from questionnaire ($p < 0.0001$ for itch intensity and sleep disturbances, $p < 0.001$ for itch extent and frequency) were shown. In group of BP patients correlation between general itch intensity and itch extent was statistically insignificant ($p > 0.05$), while general itch intensity and other items from questionnaire revealed correlations were statistically significant ($p < 0.0001$). No statistically significant correlations between age of patients from both groups and general intensity of itch as well as particular items from the questionnaire and NRS results were shown. Also correlation between sex of patients from both groups and general

Table 2: Results of itch intensity questionnaire.

	General assessment		Extent		Intensity		Frequency		Sleep disturbances	
	BP	DH	BP	DH	BP	DH	BP	DH	BP	DH
Mean	11.4	12.4	2.3	2.3	2.9	3.4	3.7	3.7	2.6	3.1
SD	4.1	4.3	0.4	0.4	1.2	1.3	1.4	1.7	2.1	2.5
SEM	0.77	0.88	0.08	0.08	0.23	0.27	0.26	0.35	0.40	0.51
MAX	19	19	3	3	5	5	5	5	6	6
Median	11	14	2	2	3	4	4	5	2	4
MIN	5	4	2	2	1	1	1	1	0	0
n	28	24	28	24	28	24	28	24	28	24

SD: standard deviation; SEM: standard error of the mean; *n*: number of patients.

intensity of itch as well as particular items of questionnaire and results of NRS were statistically insignificant ($p > 0.05$).

4. Discussion

Results of investigations conducted during past years, mainly among patients with atopic dermatitis, prurigo, chronic urticaria, and psoriasis, confirmed important role of IL-31 in pathogenesis of itch [2, 17]. No data are available about its role in autoimmune blistering diseases in course of which itch is also present as bullous pemphigoid and dermatitis herpetiformis.

We confirmed that concentration of IL-31 in serum from BP and DH patients is importantly lower than in a control group. This result is opposite to outcomes from research conducted in other diseases with presence of itch [2, 17]. Raap et al. showed higher concentration of IL-31 in serum from patients with atopic dermatitis [18] as well as spontaneous chronic urticaria [5]. In turn Narbutt et al. showed intensified expression of IL-31 in serum from patients with psoriasis [6]. After UVBNB exposure it becomes lower but did not achieve values as in a control group.

It is known that both bullous pemphigoid and dermatitis herpetiformis present in active phases Th2 cytokine profiles [19, 20]. Similar profile is in atopic dermatitis [21]. Our result suggests that IL-31 is a component of signal path responsible for itch development but dependsing on the disease paths may be different as well as the role of IL-31.

It is known that activated mastocytes contribute to higher expression of mRNA for IL-31 receptors [2, 3]. It is possible that hyperactivation of mastocytes which causes degranulation may be also responsible for higher expression of mRNA for IL-31 receptors, which may be the reason for low concentration of IL-31 in serum. Literature data show also that IL-31A receptors present on typical, human keratinocytes have different variants which depend on progress of cell division but also on impact of proinflammatory cytokines as INFγ [3]. Maybe in a course of bullous pemphigoid and dermatitis herpetiformis there is deposition of IL-31 in changed areas. The obtained result suggests the need to continue research especially taking into consideration assessment of IL-31 mRNA expression in skin biopsies from patients. That kind of research was conducted in a group of patients with atopic dermatitis, psoriasis, prurigo [22], and lichen planus [7]. Sonkoly et al. showed increased mRNA for IL-31 expression in more than half of the investigated patients with atopic dermatitis but not in case of psoriasis [22]. Similar observations were true for prurigo. Unfortunately they did not assess concentration of IL-31 in patients' serum. Also higher expression of IL-31 in skin biopsies from lichen planus patients was confirmed by Welz-Kubiak et al. without assessment of IL-31 concentration in patients' serum [7]. However intensity of itch was measured using two, independent scales—VAS and questionnaire containing twelve questions. It was shown that maximal intensity of itch was assessed by patients as medium (VAS max 6.5 ± 2.7) and at the time of assessment as mild (VAS 2.2 ± 1.8). Results obtained using questionnaire showed that patients got 6.9 ± 2.8 points. There was no correlation between IL-31 expression and itch intensity.

It is known that IL-31 acts also through JAK/STAT signaling pathway and activates JAK-1 and JAK-2 but also STAT-1, STAT-3, and STAT-5 [2]. Thus low concentration of IL-31 in patients' serum may be connected with involvement of IL-31 into the mentioned signaling pathway. Its involvement in pathogenesis of bullous pemphigoid and dermatitis herpetiformis needs future researches. Nevertheless literature data showed that IL-31 is rather responsible for itch induction compared to development of inflammatory skin lesions [17].

Assessment of itch intensity is difficult because of its subjective nature. There are many available methods but none is accepted as adequately objective and reliable. That is why two different, independent methods are accepted to assess intensity of itch.

We decided to use the questionnaire to assess intensity of itch because it was available and validated in Polish population and previously results were accessible [13]. On the other hand NRS, which is variant of VAS, is very easy to use and needs short time to fill. Literature data show that both scales may be used to assess itch intensity in clinical trials and the obtained results are comparable [23]. On this basis it is possible to accept equivalence of those two tools in assessment of pain intensity, which can be referring to evaluation of itch intensity. Nevertheless it is worth remembering that NRS is not free of defects and some of the patients have difficulties with understanding this type of tool. Moreover numeric scale does not give opportunity to statistical comparison with other, more descriptive tools.

It may be due to different interpretation of particular terms and they may not be constant with those used by patients. Our results show that intensity of itch which is present in a course of BP and DH is from moderate to severe. Detection of positive correlation between results obtained using two different tools suggests their similar statistical value.

As it was mentioned before there are scarce data connected with itch intensity in a course of bullous pemphigoid [8, 9]. Bardazzi et al. showed that patients with BP suffered from moderate to severe pruritus [9]. To measure it they use 5-point Verbal Rating Scale (VRS), which is little bit different than scale used by us. That is why it is difficult to easily compare obtained results. Nevertheless in both cases itch is a serious problem for patients. Moreover Bardazzi et al. revealed a strong positive correlation between BP180 ELISA and VRS. Authors explained the result that BP180 ELISA is a monitoring instrument for BP, particularly in the assessment of itch. Also Kalinska-Bienias et al. showed that pruritus is an important problem for patients with BP [8]. Authors did not measure this symptom using separate tool but one of the questions from quality of life questionnaire takes into consideration this symptom.

Comparison of our results and literature data shows that itch in a course of BP and DH is only little bit weaker than in a course of atopic dermatitis. Chrostowska-Plak et al. showed that patients with atopic dermatitis got from 5 to 19 points, mean 14 [24]. In turn, intensity of itch assessed using VAS was 7.9 during last 2 weeks and 3.1 at the time of measurement. Mean value obtained by our patients with BP was 7.7 and with DH 8.0. Of course we are aware that our research has some limitations. First of all number of participating patients, especially with DH, is small. It is due to relatively rare occurrence of autoimmune blistering diseases. Moreover, we did not confirm relationship between patients' age and sex and obtained results. This is also consequence of small number of participating patients.

Mean results of NRS show that for our patients itch is an important problem. Comparison of the results with literature data demonstrates that more than one-third (37%) of atopic dermatitis patients also experience itch as a severe problem while only 8.1% as a very severe symptom [23]. It is quite surprising. It may be explained by subjectivity of the used method. Literature data confirm that age and sex as well as antihistamines (which are not effective in a course of autoimmune blistering diseases) have no influence on the obtained results.

5. Conclusion

To summarize, the role of IL-31 in pathogenesis of autoimmune blistering diseases is not fully known and that is why it needs future researches. Increasing knowledge in that field will be for sure helpful in development of new therapeutic methods, maybe less excessive than those available now. It is important especially for patients with bullous pemphigoid.

The consciousness that intensity of itch present in a course of both blistering diseases is comparable with symptoms reported by patients with atopic dermatitis, which is a model pruritic disease, gives us opportunity to develop right attitude to the patient. Furthermore it gives also opportunity to choose the right therapeutic strategy which takes into consideration not only skin improvement but also symptoms bothering patients. This is worth remembering as patient mental state stays in a strict relationship with compliance and effectiveness of treatment.

Conflicts of Interest

Authors have no conflicts of interest to declare.

Acknowledgments

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