Pruritus

67

Magda Blessmann Weber,
Fernanda Oliveira Camozzato,
and Júlia Kanaan Recuero

Itch is an unpleasant sensation which evokes the desire to scratch

Samuel Hafenreffer (1660)

Abbreviations

Ach	Acetylcholine
AD	Atopic dermatitis
AhR	Aryl hydrocarbon receptor agonists
ATX	Autotaxin
BEACH	Bettering the evaluation and care of health
CB	Cannabinoid receptors
CGRP	Calcitonin gene-related peptide
CRH	Corticotropin-releasing hormone
CRH-R	CRH receptor
CTCL	Cutaneous T-cell lymphoma
GPCRs	G protein-coupled receptors
IBAT	Ileal bile acid transporter inhibitors
IFSI	International forum for the study of itch
IL-2	Interleukin 2
JAKs	Janus kinase inhibitors
LPA	Lysophosphatidic acid
MF	Mycosis fungoides
NGF	Neurotrophins and nerve growth factor
SCG	Sodium cromoglycate
SP	Substance P
SS	Sézary syndrome
STT	Spinothalamic tract
TNF-α	Tumor necrosis factor alpha
TrkA	Tropomyosin-receptor kinase A inhibitors
TRP	Transient receptor potential channels
TRPM8	Transient receptor potential cation channel subfamily M member 8

Key Points

- Pruritus is the most common dermatological symptom. It is the main symptom of several dermatoses and frequently occurs in systemic diseases. In some cases, it is the first symptom of malignant systemic diseases.
- Several etiopathological mechanisms may cause pruritus with peripheral or central origin.

M. B. Weber (✉)
Dermatology, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil

F. O. Camozzato · J. K. Recuero
Sociedade Brasileira de Dermatologia, Porto Alegre, Brazil

R. Rangel Bonamigo (ed.), *Dermatology in Public Health Environments*,
https://doi.org/10.1007/978-3-031-13505-7_67

- Patient assessment includes complete clinical history, detailed history of pruritus, and additional tests.
- Patient management requires treatment of symptoms and underlying diseases.
- Providing follow-up and orientation is essential in the management of patients with chronic pruritus.
- Psychological assessment is required for these patients.

Concepts

Pruritus was defined by Samuel Hafenreffer in 1660 as an unpleasant sensation that causes the desire or reflex to scratch [1]. This condition is the most frequent symptom in dermatologic diseases and it's also the one that better defines these diseases; additionally, it may be present in several systemic diseases [2]. It is associated with a considerable reduction in quality of life and may be as debilitating as chronic pain [3].

Pruritus may be disseminated or localized, acute or chronic and affect skin surface, squamous epithelium of the conjunctiva, mouth, nose, pharynx, and anogenital region, as well as the ciliated epithelium of the trachea [4, 5]. This symptom may be intense, even when patients have no visible skin changes. Pruritic areas around the primarily stimulated site and that itch even after very weak stimuli are defined as areas of alloknesis [6].

By definition, chronic pruritus occurs when the symptom lasts for 6 months or more [7]. Chronic pruritus is difficult to ignore, leading to difficulties in concentrating, sleep disorders, absence from school or work, and sometimes suicide attempts in patients with more severe symptoms [5, 8]. In the other side, when occurring with less than 6 months, it is classified as acute pruritus. It has been associated with pain and protective mechanisms against external harmful agents, as insect bites for example [9].

Besides biological pruritus, triggered by several chemical mediators, itch may be also a psychosocial manifestation resulting from mechanisms of frustration, similarly to what happens in non-human social animals (grooming) [10].

Epidemiology

Statistical data on the epidemiology of pruritus are scarce, possibly leading to an underestimation of its prevalence. This is due to the fact that many studies, especially those outside the field of dermatology, do not collect data on pruritus, even when the symptom is considered as relevant by patients.

Pruritus is more common in women than in men and it is more frequently diagnosed in Asians than in Caucasians [11–13]. The prevalence of pruritus increases with age because elderly population not only usually presents with xeroderma but also have a higher prevalence of systemic problems that cause pruritus [14, 15]. Pruritus is more prevalent among individuals with low socioeconomic status and limited income [11].

A cross-sectional study with almost 19,000 adults found a prevalence of 8 to 9% of acute pruritus in this study population [13] and an association between pruritus and chronic pain [16]. Recent research shows that the prevalence of chronic pruritus is around 13.5% in the general adult population [12] and around 16.8% in a sample of company employees attending a routine medical appointment [14]. In a study of 18.137 individuals with skin diseases, 42% reported having pruritus [17].

Few studies evaluated the frequency of pruritus in the primary health care setting. According to data from the Bettering the Evaluation and Care of Health (BEACH) Program for the Australian population, pruritus is the main complaint at 0.6% of medical visits, excluding perianal, periorbital, or auricular pruritus [18]. The Fourth National Study of Morbidity Statistics from General Practice [19], conducted in Britain with 502,493 patients, found that pruritus and related conditions are reported in 1.04% of appointments (0.73% for men and 1.33% for women).

The origin of pruritus, whether dermatologic or systemic, could not be established in 8 to 15% of patients [15]. However, in systemic diseases that cause pruritus, its prevalence may be very high, as is the case with hemodialysis patients, who may present with pruritus in up to 90% of cases [20]. This symptom may be present in up to 50% of patients with cholestasis, in 80 to 100% of those with primary biliary cirrhosis, in up to 80% of those with cutaneous T-cell lymphoma, in up to 50% of those with polycythemia vera, and in up to 30% of those with Hodgkin's lymphoma [8]. In dermatologic diseases, the frequency of pruritus is relevant and depends on the underlying disease, being present, for example, in all patients with urticaria and atopic dermatitis [21].

Classification

Pruritus may have its origin from peripheral or central neurological pathways, and the perception of this symptom depends on the neurophysiological and psychological changes that it causes. Patients may report different sensations to define pruritus, such as itch, bite, tingle, perforation, pinch, burn [8].

A neurophysiological classification of the type of pruritus was proposed and is important both for patient management and for understanding of disease mechanisms. More than one form of pruritus may coexist in the same patient, e.g., atopic individuals, who present with neurogenic and pruritoceptive pruritus. In 2003, some articles initiated some classification that consider the neurological origin of this symptom [5]. Recently, Song et al have also proposed a similar classification, and a combination of these two ideas is summarize below [22]:

- Skin-derived pruritus with skin origin may be caused by inflammatory mechanisms, xeroderma, or direct skin damages. It is present in scabies, urticaria, and insect bites, induced by stimulation of C-nerve fibers by different pruritogens.
- Neuropathic pruritus: resulting from lesions at any point of the afferent nervous pathway, such as what occurs in postherpetic neuralgia, multiple sclerosis, and brain tumors.
- Neurogenic pruritus: has central origin, but there are no lesions to nervous fibers. It results from the increase in the concentration of endogenous opioids, like in cholestasis and after the administration of exogenous opioids.
- Psychogenic pruritus: triggered by psychiatric diseases such as parasitophobia or by psychological factors such as anxiety disorders.
- Mixed pruritus: caused by more than one factor above described.

The International Forum for the Study of Itch (IFSI) has his own classification [7], divided into two parts, and gives priority to the clinical manifestations of pruritus, distinguishing between disorders with or without skin lesions, whether these lesions are primary or secondary.

In the first part of classification, three groups of conditions are defined according to history and symptoms in the skin of patients with pruritus.

- First group includes pruritus in primary skin diseases represented by pruritic dermatoses (inflammatory, infectious, and autoimmune diseases, genodermatosis, reaction to drugs, dermatoses of pregnancy, and skin lymphomas), all of which leading to specific skin changes.
- Second group includes pruritus in normal skin resulting from systemic diseases (endocrine, hematologic and metabolic disorders, infections, lymphoproliferative diseases, solid neoplasms, neurological diseases, psychiatric diseases, and drug-induced pruritus).
- Third group includes chronic lesions secondary to scratching, such as prurigo nodularis or simple chronic lichen.

In the second part of classification, patients were categorized according to their underlying disease, which was divided into several categories:

1. Dermatologic disease: pruritus caused by "skin diseases" such as psoriasis, atopic dermatitis, dry skin, scabies, or urticaria.

2. Systemic disease: pruritus caused by "systemic diseases" other than those affecting the skin, such as hepatic diseases (primary biliary cirrhosis), renal diseases (chronic kidney disease), hematologic diseases (Hodgkin's disease), and multifactorial causes like metabolic or drug-induced.
3. Neurological disease: pruritus caused by "diseases of the central or peripheral nervous system," such as nerve compression, nerve damage, or nerve irritation.
4. Psychogenic or psychosomatic disease: pruritus caused by "psychiatric or psychosomatic disease."
5. Mixed: pruritus caused by the overlap and coexistence of several diseases.
6. Pruritus of undetermined origin.

This classification aims to avoid unnecessary laboratory and imaging studies, as is the case in patients with typical clinical history suggestive of dermatosis-induced pruritus, when usually there is no need of further investigation.

Neurophysiology

The neuronal basis of the mechanisms underlying pruritus is complex and has been elucidated by new discoveries in this field. Skin, conjunctiva, and mucosa are the peripheral tissues that may produce a sensation of pruritus. In the skin, sensory nerves innervate epidermis, dermis, and subcutaneous adipose tissue. Free nerve endings for pruritus are located mainly at the dermoepidermal junction [23].

The introduction of a pruritogen is the trigger for the physiological itch starts. Electrophysiology studies of peripheral nerves in humans and in animal models show that the chemical mediators of pruritus elicit action potentials in a subset of nociceptors, the pruriceptive nociceptive neurons (or pruriceptors), which are mainly amyelinic C fibers with cell bodies in the dorsal root ganglia are activated by these pruritogens [24, 25].

Most of pruritoceptors are G protein-coupled receptors (GPCRs) which promote the opening of ion channels and carry impulses towards the dorsal horn of the spinal cord, where they make a synapse with the secondary neuron [25]. The axons of this neuron cross to the contralateral spinothalamic tract (STT) through the anterolateral funiculus and continue into the thalamus to terminate in the somatosensory cortex, reaching areas involved in the processes of evolution, sensation, emotion, reward, and memory, which are superposed to the areas activated by painful stimuli [26]. The transection of this ascending pathway impairs itch as well as pain and temperature sensations [27].

There are two types of neurons that can be sensitive to itch. They are independent from each other and classified as histaminergic and non-histaminergic. Acute itch is linked to the histaminergic system. Conversely, the non-histaminergic is connected to chronic symptoms. These neurons are activated in different locals on the central nervous system and each one reaches the brain through distinct spinal tracts [25].

Neurons of the STT in animal models show that nearly two-thirds of the nociceptive neurons of this tract are not pruritogen and the other third is. Non-pruritogen neurons of the STT are activated by mechanical stimuli, heat, or capsaicin, and pruritogen neurons are activated both by painful stimuli such as heat or capsaicin and by pruritic stimuli such as histamine. It is still unclear whether there are specific pruritogen neurons, i.e., that transmit only the sensation of pruritus [28, 29]. However, a recent study found that, in a genetically engineered mouse with restricted expression of the capsaicin receptor, selective activation of a class of pruriceptors by capsaicin elicits itch-like and not pain-like behavior, showing that there may be a neurological distinction between nerve cells that cause pain and cells that cause itching [30].

As a hypothesis, itch may result from activity in the pruriceptive neurons in the absence of sufficient activity in non-pruriceptive neurons. The neural circuitry hypothesized to evaluate the relative activity in pruriceptive and non-pruriceptive neuronal populations and to decode itch from pain is unknown, but it is likely to reside in supra-segmental regions of the brain [24].

Mediators of Pruritus

A large number of pruritogens have been discovered over the years. These pruritogens may be located both peripherally and centrally, and many of them act synergistically through a myriad of mechanisms.

The main mediators of pruritus and their respective antagonists are represented in Table 67.1.

Histamine is the main peripheral mediator of pruritus, having been acknowledged for more than 60 years and in experimental studies is the best known to induce itch after skin application [31]. Secreted by degranulated mast cells and circulating basophils, this substance causes pruritus by directly stimulating nerve endings and by interacting with H_1 receptors present in C fibers, leading to vasodilation and edema [32]. The involvement of H2 receptors in the induction of itching is less convincing, being considered a marginal mechanism in this process [31]. Unlike other receptors, H3 seems to act in an antagonistic manner, having a role in controlling itching instead of its induction.

Histamine type 4 receptor (H4), present in dendritic cells, mast cells, and eosinophils, is involved in allergic inflammation and also may be involved in the mediation of pruritus, making this receptor a possible new target in the management of pruritus, especially in atopic dermatitis [33]. The role of histamine in pruritic diseases such as urticaria, reactions to insect bites, skin mastocytosis, and some drug eruptions has already been established [4, 5]. However, this substance is not the main pruritogenic agent in systemic diseases, which is evident with the low response of patients with these diseases to antihistamine therapy [34].

Serotonin is a less potent pruritogenic agent than histamine. According to the literature, serotonin evokes itching through the histamine pathway. However, antihistamines fail to reduce the pruritus mediated by this pruritogen when administered to humans. Because of this, the exact mechanism of this route remains unclear [23, 35]. Its central action probably involves the neurotransmitter system of opioids and the activation of $5HT_3$ receptors, which are not found in the skin. Serotonin is also found in great amounts in platelets, a fact that may explain the presence of pruritus in hematologic diseases with platelet involvement [5].

Substance P is synthesized by C-type neurons and transported through peripheral nerve endings. Substance P binds to NK1 receptor as well as to mas-related G protein-coupled receptor, also a class of receptors involved in pruritus signaling [36]. Intradermal injection of substance P causes pruritus, edema, and erythema, resulting in the release of tumor necrosis factor alpha (TNF-α), leukotriene B4, histamine, and prosta-

Table 67.1 Itch mediators and corresponding antipruritic agents

Mediators of pruritus	Antipruritic agent
Histamine	Antihistamines
Serotonin	Paroxetine, fluoxetine, mirtazapine, ondansetron
Substance P	Aprepitant
Prostaglandins	Nonsteroidal anti-inflammatory drugs, aspirin
Opioids	Naloxone, naltrexone, nalfurafine, butorphanol
TRPV1 receptor	Capsaicin
TRPM8 receptor	Menthol
Interferon-α	Thalidomide
GABA (γ-aminobutyric acid)	Gabapentin, pregabalin
Acetylcholine	Doxepin, oxybutynin
Leukotrienes	Zafirlukast, zileuton

glandin D2 [37]. In renal disease, atopic and contact dermatitis, serum levels of substance P are elevated and it can be correlated to disease severity in atopic patients [38, 39]. A study conducted by Costa et el. showed that aprepitant, the NK1 receptor antagonist, was tested as a potential antipruritic agent in Sézary syndrome [40]. Depletion of this substance by capsaicin is one of the mechanisms to control pruritus and pain [28, 41].

Prostaglandins: Considered in isolation, prostaglandins are not pruritogen agents, but may potentiate the effect of histamine and of other mediators of pruritus [42]. The use of cyclooxygenase inhibitors does not improve pruritus in the general patient population but appears to be useful in patients with HIV. The use of aspirin improves pruritus in patients with polycythemia vera, probably due to the action of this drug on platelet adhesiveness rather than on the formation of prostaglandins [43].

Cytokines: Interleukin 2 (IL-2): its involvement in the development of pruritus is based on the observation of generalized pruritus in patients using high doses of recombinant IL-2 for the treatment of cancer [44]. Patients with atopic dermatitis using cyclosporine, an IL-2 inhibitor, experience a considerable relief of pruritus. It is not clear whether this process is directly mediated by receptors or indirectly mediated by mast cells and endothelial cells.

Interleukin 31 (IL-31): Patients with pruritic symptoms had serum levels of IL-31 higher than those one without itch [45]. This substance is present in the skin of patients with atopic dermatitis and prurigo nodularis, indicating that it may be a possible cause of pruritus in patients with these conditions [46]. Studies in animals have found that administration of IL-31 (venous or dermal/cutaneous) prompts severe pruritus [47].

Opioid peptides: Opioid peptides may trigger pruritus by leading both to degranulation of mast cells and activation of opioid receptors, either central or peripheral. Intradermal morphine causes pruritus, which may be inhibited by topic pretreatment with doxepin (H1 antihistaminic agent) [48] but may be only partially inhibited by the μ-receptor antagonist (naloxone). Intraspinal μ-opioid agonists induce segmental pruritus, a condition that may be inhibited by μ-receptor antagonists but is not affected by antihistamines [49]. Additionally, it has been demonstrated that the stimulation of κ-opioid receptors blocks the effect of μ receptor agonists [50], suggesting that the imbalance between those opioid receptors in the skin and in the central nervous system can lead to the sensation of itching [25, 51]. Opioid peptide antagonists have been used in the treatment of pruritus associated diseases in chronic kidney disease and cholestasis.

Proteolytic enzymes: Human mast cells produce two proteases: tryptase and chymase. These enzymes act on G proteins coupled to PAR-2 receptors expressed in afferent C-fiber neurons [52]. When activated, these fibers secrete substance P, which will activate mast cells, thus closing the cycle that stimulates pruritus [6]. Tryptase serum in high levels has been described in patient with end stage renal disease submitted to hemodialysis, associated with the severity of itch, as well as in patients with atopic dermatitis [53]. Upregulation of PAR-2 receptors has been observed in patients with atopic dermatitis [52].

Transient receptor potential channels (TRP): Composed of 28 subtypes, TRPs can be subdivided into 6 families: TRPA, TRPC, TRPM, TRPML, and TRPV. They are involved in several sensory functions and in the last decades it has been discovered that the TRP channels are involved in the itchy sensation in physiological and pathological aspects [54]. These molecules are calcium-permeable channels which sense temperature, osmotic and mechanical changes. TRPV1 is present on nociceptive C-neurons and is activated by capsaicin and endogenous substances (endovanilloids). Other TRPVs (TRPV2, TRPV3, TRPV4, TRPM8) are activated at specific temperatures [55]. Evidence suggests that TRPV1 is a fundamental integrating element in pruritic and pain pathways. It has been seen that sensory neuronal activation by histamine and PAR2 receptor also involves the activation/sensitization of TRPV1, so that TRPV1 expression is amplified in keratinocytes of prurigo nodularis, and that stimulation of TRPV1 channels releases multiple pruritoceptive mediators like interleukins and neuropeptides [56]. It has been postulated that TRPV3 might be a regulator and/or co-transducer of TRPV1-mediated pruritus and

pain. A study by Stokes et al. [57] showed mast cell degranulation upon thermal and physical activation of TRPV2. In addition, mast cells also express TRPV1 and TRPV4. TRP melastatin 8 (TRPM8) is expressed selectively by C-type neurons. Menthol and its analogs as well as penicillin stimulate TRPM8 [58].

Neurotrophins and nerve growth factor (NGF): NGF-dependent primary afferent C fibers appear to be essential in mediating peripheral stimuli to the spinal cord and brain and consequently leading to itchy symptoms [59]. These mediators are overexpressed in prurigo nodularis, and its therapeutic administration is pruritogenic [60]. In atopic dermatitis, NGF is released by keratinocytes, mast cells, and fibroblasts, and plasma levels of NGF are also elevated and correlated with disease activity [61]. In addition, expression of neurotrophin 4 is elevated in the cutaneous lesions of patients having atopic dermatitis and prurigo nodularis [60, 61].

Endocannabinoids and cannabinoid receptors: Cannabinoid receptors CB1 and CB2 are present in both the skin and the central nervous system. These are GPCRs that cause an inhibiting effect when activated [25]. Cannabinoid receptors are expressed on skin nerve fibers and may have a role in pruritus. For instance, cannabinoid receptor (CB1) agonist HU210 diminishes histamine-induced excitation of nerve fibers and thereby reduces itching [62]. This suggests that CB1 signaling may be involved in initiation of itch.

Corticotropin-releasing hormone: Studies propose that the corticotropin-releasing hormone (CRH) and the CRH receptor (CRH-R) have activity similar to hypothalamic–pituitary–adrenal axis. This substance, in mice, is released by nerve endings and in humans, synthesized in the skin. In addition, mast cells have a large amount of CRH and its analog urocortin (Ucn) and both are secreted after an immunological stimulus. It is suggested that autocrine effects could be attributed to these peptides [63, 64]. CRH e Ucn lead to histamine release upon intradermal injection [51], and it is also involved in mast cell degranulation occurring during periods of acute stress.

Calcitonin gene-related peptide: Many neurons of the dorsal root ganglion co-express substance *P* (SP), CGRP, and PAR2. CGRP plays a modulatory role in inflammation and pruritus. PAR-2 causes release of SP and calcitonin gene-related peptide (CGRP), which, then, induce the secretion and activation of inflammatory mediators that have the ability of decreasing the threshold for itching [53]. The severity of chronic itching seems to be associated with the expression of PAR-2 in keratinocytes. It is important to highlight that histamine-responsive C fibers are involved in the generation of erythema reflex from the axon consequently to the liberation of vasoactive neuropeptides such as the CGRP peptide near to the vasculature located in the dermis [65].

It was realized that CGRP has an inhibitory effect on substance P-induced itching as it prolongs itch latency following injection, but increased levels of CGRP are seen in atopic dermatitis, nummular eczema, and prurigo nodularis [66]. Like substance P, CGRP-mediated itch may result from mast cell activation.

Acetylcholine: Acetylcholine (Ach) is a neurotransmitter which binds to both muscarinic and nicotinic receptors. In some patients, painful stimuli are perceived as itching, in this case mediated by Ach. This phenomenon has been described in atopic patients who perceive normally painful electrical stimuli as itching when applied to the injured skin [65, 67]. Histamine-sensitive as well as histamine-insensitive C-nerve fibers are stimulated by acetylcholine. Atopic dermatitis patients are more sensitive to acetylcholine and less sensitive to histamine than normal subjects [68].

Pruritus in Systemic Diseases

Cutaneous changes can be seen on the skin of patients with systemic diseases and itching, such as dry skin in hyperparathyroidism or candida infection in diabetics. However, in these patients with comorbidities, the most frequent is the absence of signs on physical examination, with the symptom manifesting in healthy-looking skin [69].

Therefore, in systemic diseases, the skin may appear normal or have skin lesions induced by scratching and a diagnosis may be difficult to

establish. In these cases, pruritus is usually symmetric and extensive and has an insidious onset. In addition, its intensity is not directly related to the severity of underlying disease. Moreover, localized forms may be transformed into generalized forms during disease progression. Only half of patients complaining of pruritus and without apparent dermatologic lesions at the time of the medical visit have its etiology identified [70], showing that pruritus may precede the diagnosis of the underlying disease by years. The estimate is that 10–50% of patients seeking medical help due to itching have some underlying systemic disease [69].

There are many etiological hypotheses for the several manifestations of pruritus in systemic diseases, some of which have not been confirmed yet. This is one of the main reasons why the treatment of this symptom is still difficult and often does not give a definite solution for the patient. Patient follow-up and good doctor–patient relationship are essential to manage this symptom, which in most cases is extremely debilitating and has no curative treatment. The main systemic diseases associated with pruritus are summarized in Table 67.2.

Table 67.2 Systemic diseases that can induce pruritus

Metabolic and endocrine diseases	Chronic renal insufficiency Liver diseases with or without cholestasis Hyperparathyroidism Hyper- and hypothyroidism Iron deficiency
Infective diseases	HIV and AIDS Parasitosis including helminthiasis
Hematological disorders	Polycythemia vera, myelodysplastic syndrome Lymphoma, e.g., Hodgkin's lymphoma
Neurological diseases	Multiple sclerosis Brain tumors Nostalgias paresthetica Brachioradial pruritus Postherpetic neuralgia
Psychiatric or psychosomatic diseases	Depression Affective disorders Hallucinosis Obsessive and compulsory disorders Schizophrenia Eating disorders

Pruritus in Chronic Kidney Diseases

The pathophysiology of pruritus associated with chronic kidney diseases is unknown. However, some mechanisms have been suggested, including skin conditions such as moderate to severe xeroderma, dialysis, medications taken by the patient, metabolic factors, dysfunction of peripheral or central nerves, involvement of opioid receptors (μ and κ), and microinflammation in uremia [71, 72]. Pruritus is not related to the etiology of renal failure nor to age, gender, skin color, or time on dialysis.

The number of mast cells is greater in uremic patients than in normal patients [73], and the skin of uremic patients produces several pruritogenic cytokines that stimulate the nerve endings of fibers carrying the sensation of pruritus. Additionally, an increase in the concentration of calcium, magnesium, phosphates, and mast cells was observed in hemodialysis patients with symptoms of pruritus [71]. Although plasma concentrations of histamine are higher in uremic patients than in non-uremic patients, these values are not related to the severity of pruritus and antihistamines did not resolve the symptoms. Serum serotonin is high in hemodialysis patients; however, randomized, placebo-controlled, double-blind trials did not observe an improvement in pruritus among patients treated with ondansetron, an antagonist of 5-HT3 receptors [74]. Studies obtained controversial results on the improvement of chronic kidney disease-associated pruritus with the use of opioid antagonists. UVB phototherapy has been used with good results. Systemic changes resulting from dialysis, such as decreased erythropoietin, and hyperparathyroidism were also related to pruritus and should be corrected in patients with these conditions.

A total of 22% to 90% of patients with severe renal failure complain of pruritus, especially those who are undergoing dialysis. This complaint has declined in recent years, probably due to the use of highly permeable membranes during dialysis. Patients with more intense pruritus have worse prognosis for renal disease and have higher mortality rates.

Pruritus in Liver Disease

Pruritus is a frequent symptom in patients with liver diseases caused by cholestasis, mechanical obstruction, metabolic disorders, or inflammatory diseases [75] and is less frequent in patients with infectious liver disease (hepatitis B or C) or alcoholic liver disease.

Pruritus is an initial symptom of cholestasis and affects 20% to 50% of patients with jaundice; additionally, its intensity is not related to the severity of cholestasis. The onset of this type of pruritus occurs in the palmoplantar region, but most patients present with the generalized form, with symptoms worsening at night [76]. In addition to pruritus, these patients show postinflammatory hyperpigmentation at their back, which spares the central region and the characteristic "butterfly" sign. Other clinical findings related to cholestasis may also be present, such as xanthelasma secondary to hypercholesterolemia, jaundice, ascites, and hepatomegaly. Sometimes, pruritus is so intense that leads the patient to think about suicide and becomes one of the indications for liver transplant [75].

Diseases causing intrahepatic cholestasis that may lead to pruritus are primary biliary cirrhosis, pruritus gravidarum, sclerosing cholangitis, viral hepatitis, and drug-induced cholestasis. In primary biliary cirrhosis, pruritus occurs in almost 100% of patients and is the initial symptom of disease in nearly 50% of the cases. The symptom may be severe and may precede the diagnosis of primary biliary cirrhosis by years [77]. In pruritus gravidarum, pruritus occurs in the third trimester of pregnancy, being more common in multiple pregnancies. The symptom disappears immediately after delivery and may recur in subsequent pregnancies and with the use of oral contraceptives. Drug-induced cholestasis may be very symptomatic and may be caused mainly by the following drugs: phenothiazine, estrogens, and tolbutamide. Extrahepatic bile duct obstruction may also cause pruritus [4, 75].

Several hypotheses have been suggested to explain the cause of cholestatic pruritus, such as the stimulation of skin fibers by toxic bile salts, pruritogens derived from destroyed hepatic cells, changes in the metabolism of bile salts in the intestine, steroid hormones, accumulation of endogenous opioids, and plasma accumulation of substances produced in the liver [78]. Recent studies showed that increased serum levels of autotaxin (ATX), the enzyme responsible for metabolizing lysophosphatidylcholine into lysophosphatidic acid (LPA) and increasing the levels of this acid, are a specific finding for cholestatic pruritus but not for other types of systemic pruritus [79]. Rifampicin significantly reduces the intensity of pruritus by decreasing ATX activity in patients with cholestatic pruritus. The therapeutic action of rifampicin may be partially explained by binding of this drug to the pregnane X receptor, which inhibits ATX expression [79].

The treatment of cholestasis recommended in guidelines includes anion-exchange resins (cholestyramine), pregnane X receptor agonists, opioid antagonists (naltrexone, naloxone), and serotonin reuptake inhibitors (sertraline). In patients with severe pruritus and unresponsive to standard therapy, experimental approaches should be considered, such as UVB phototherapy, extracorporeal albumin dialysis, nasobiliary drainage, and liver transplantation [78].

Pruritus in Hematologic Diseases

Several hematologic diseases evolve into symptoms of pruritus, which are often severe. Most of these diseases are malignant, including tumors, bone marrow diseases, and lymphoproliferative diseases. The mechanisms leading to pruritis in these diseases may consist of toxic products released by the tumor, allergic reactions to the released components, and direct damage to brain nerves, in the case of tumors located in this area [80, 81].

Iron Deficiency Anemia: The most common symptom is generalized pruritus, with no direct relationship to the severity of anemia. Some patients may present with localized pruritus, especially in the vulvar and perianal regions. Laboratory abnormalities may be observed only for ferritin levels, with normal levels of serum

iron. The causes of this deficiency should be investigated and corrected [82].

Polycythemia Vera: Around 50% of patient with polycythemia vera complain of pruritus [83] characterized by the sensation of "biting" and usually triggered by contact with water (aquagenic pruritus). Pruritus may precede clinical disease by years. Studies suggest that the mechanism of pruritus in polycythemia vera is related to platelet aggregation leading to the secretion of serotonin and other pruritogenic agents [83]. Other studies show that the release of high levels of histamine resulting from the increased number of basophil granulocytes may trigger pruritus [81]. Pruritus appears to be more pronounced in patients with the JAK2V617 mutation [84].

Hodgkin's Disease: Pruritus is present in up to 30% of patients with Hodgkin's disease and may precede the disease by up to 5 years [81, 82]. It is described as producing a burning sensation that usually becomes more severe at night, affects the lower half of the body, and tends to evolve into generalized pruritus. Dermatological lesions may be present and resemble ichthyosiform changes. Patients with more severe pruritus and exhibiting poor therapeutic response are those with the worst prognosis of disease progression [82]. Several factors, such as the secretion of leukopeptidases and bradykinin, histamine, and high IgE levels deposited in the skin, may contribute to pruritus in lymphomas [81, 82].

Leukemia: Pruritus is not a frequent complaint in patients with leukemia, but, when present, it is usually disseminated. Skin infiltrates may produce localized itch at the site of the lesion [82].

Systemic mastocytosis: Causative agents of degranulation of mast cells cause generalized pruritus in these patients [81].

Cutaneous T-cell lymphoma (CTCL): Encompasses a diverse group of diseases that are characterized by malignant T lymphocytes that initially home to the skin. The mycosis fungoides (MF) is the most common variant, and Sézary syndrome (SS) is the rarest [85]. A characteristic hallmark of CTCL, especially SS, is pruritus, the sensation of itch which is repeatedly observed in various CTCL types [86, 87]. In an outpatient setting, approximately one-third of the patients with the diagnosis of CTCL complain of itch that accompanies the disease, and, in some cases, pruritus was the only symptom in a patient leading to the diagnosis of a CTCL [86, 87]. Pruritus as a symptom is almost invariably present in CTCL progressing into generalized erythrodermic MF and Sézary syndrome. It may be speculated that T cells homing to the skin provoke the release of inflammatory cytokines, but the precise molecular mechanism is still unknow. Pruritus in CTCL seems to be both a blessing and a curse: a blessing in those patients in whom it may lead to early diagnosis, and a curse for those that are resistant to therapy. Further research is mandatory to unravel the molecular mechanisms to provide more specific treatment of pruritus in CTCL [88].

Pruritus in Endocrinological Diseases

Pruritis is present in several endocrinological diseases such as hyperthyroidism, hypothyroidism, diabetes mellitus, multiple endocrine neoplasia, carcinoid syndrome, hyperparathyroidism [82].

Hyperthyroidism: 4–11% of patients with thyrotoxicosis present with pruritus [89, 90]. Triggering mechanisms may include: (1) Activation of kinins in the skin; (2) decrease of itch threshold due to vasodilation; (3) changes of bile acids in the blood. The correction of disease improves pruritus, which may be the main complaint in some patients with hyperthyroidism.

Hypothyroidism: Pruritus is related to xeroderma, a characteristic symptom of patients with hypothyroidism. The use of emollients, as well as the correction of the underlying disease, improves the symptom [89].

Diabetes Mellitus: Nearly 3% of these patients present with pruritus. In this case, the mechanisms involved in the development of pruritus are peripheral neuropathy, uremia secondary to chronic renal failure, and anatomic dysfunction [91].

Carcinoid Syndrome: Patients with carcinoid syndrome may present with pruritus com-

bined with flushing, diarrhea, and cardiac symptoms [89].

Primary Hyperparathyroidism: A substantial number of patients with primary hyperparathyroidism complain of pruritus [90]. The pathophysiology of pruritus in this disease is not well known, although these patients usually present with deficiency of vitamin D and minerals like zinc, which may contribute to pruritus.

Pruritus in Psychiatric Diseases

Psychiatric diseases such as depression, anxiety, and some psychoses may include severe pruritus as one of their symptoms [8]. The accurate diagnosis of these patients is important because treatment requires a psychiatric approach. In this case, there are no primary skin lesions but rather lesions secondary to itching, ranging from superficial excoriations to major lichenifications. Currently, it is estimated that 1/3 of patients seeing a dermatologist have emotional and psychosocial factors involved in their disease; however, there is still great reluctance in including psychiatric treatment as part of the management of dermatoses [3, 5]. It is extremely important to raise awareness on these diseases and to provide appropriate guidance to patients, despite their reluctance.

Pruritus in Neurological Diseases

Neurological diseases such as multiple sclerosis, focal lesions, tumors, abscesses, and stroke may include pruritus as part of their clinical picture. Localized neurological lesions, such as tumors and brain abscesses, may result in unilateral pruritus.

Brachioradial Pruritus: Located in the dorsal and lateral regions of upper limbs, this type of pruritus especially affects patients in the sixth decade of life and is more common in summer months, being classified by several authors as a photodermatosis. An investigation for associated neuropathies should always be made because current studies show that up to 57% of these patients present with radiculopathies in the cervical region. Treatment with antihistamines, topical capsaicin, and topical corticosteroids may lead to an improvement in these patients. Therapy regimens for neuropathies may also relieve symptoms [92].

Pruritus in HIV Infection

Pruritus is a very common complaint in patients with HIV and is sometimes the first manifestation of disease. The intensity of pruritus may range from mild to very severe presentations. It is associated with most common dermatoses in patients with HIV but may be present even when there is no dermatological change. Pruritic dermatoses associated with HIV disease include pruritic papular eruption and eosinophilic folliculitis. These dermatoses may be easily diagnosed through skin inspection and physical examination and have a high positive predictive value for the diagnosis of HIV infection [93, 94].

In these patients, chronic pruritus may lead to skin changes such as excoriations, lichenification, prurigo nodularis, pigmentation changes, and secondary infection. Intense xeroderma is found in patients with AIDS and leads to a physicochemical action on the endings of C fibers in the skin. Additionally, systemic complications such as liver diseases and renal failure may also worsen pruritus in these patients. Finally, the drugs used in the specific treatment of this disease often trigger pruritus [93].

Treatment of these patients includes the treatment of xeroderma, with the daily use of emollients and basic care to avoid the worsening of skin dryness.

Pruritus in Dermatological Diseases

Dermatological diseases often evolve into pruritus, which may be located in the area of skin lesion or sometimes be generalized. Many dermatoses cause this symptom, such as atopic dermatitis, urticaria, irritative and allergic contact dermatitis, seborrheic dermatitis, stasis eczema,

pruritus, lichen planus, but analyzing the specific approaches for these diseases is not the focus of this chapter.

Pruritus Ani: Anal and perianal pruritus affects 1–5% of the general population in the proportion of four men to one woman [95]. Its symptoms have an insidious onset and may last for years before the patient seeks treatment. This type of pruritus may be primary, with no apparent dermatological lesion, or secondary to hemorrhoids, anal fistulas and fissures, psoriasis, contact eczema, lichen sclerosus, sexually transmitted diseases, parasitosis, neoplasms. Primary causes include dietary factors such increased intake of coffee, poor personal hygiene, and psychogenic diseases. Anxiety and depression increase pruritus ani. Patients with mild pruritus ani respond to general care such as hip baths and cold compresses, avoidance of abrasives and soaps in the area, and corticosteroid therapy with low-potency corticosteroids [95]. Patients with severe pruritus require high-potency corticosteroids and sometimes topical immunomodulators such as tacrolimus [82].

Genital Pruritus: The characteristics of vulvar and scrotal pruritus are very similar to those of perianal pruritus. However, less than 10% of patients with genital pruritus symptom present with psychogenic pruritus; thus, a detailed investigation should be conducted to find the triggering agent. The management of these patients is similar to that of patients with pruritus ani [82].

Scar Pruritus: During the time when scars are healing, which ranges from 6 months to 2 years, patients commonly present with pruritus triggered by nerve regeneration and chemical and physical stimuli. However, the formation of keloids and hypertrophic scars may prolong the duration of pruritus. The treatment is performed with emollients, topical and injectable corticosteroids, interferon, topical retinoids, gels, and silicone strips [82].

Drug-Induced Pruritus

Almost all drugs have the potential of inducing pruritus by several mechanisms; therefore, the use of medications should always be addressed in medical history taking [96]. Drugs may induce pruritus by causing skin lesions such as urticarial and morbilliform rash, by producing systemic changes such as hepatotoxicity or cholestasis, or by causing xeroma or phototoxicity [97]. Drugs that may induce or maintain chronic pruritus are listed in the Table 67.3.

Table 67.3 Drugs that may induce or maintain chronic pruritus (without a rash)

Class of drug	Substance (examples)
ACE inhibitors	Captopril, enalapril, lisinopril
Antiarrhythmic agents	Amiodarone, disopyramide, flecainide
Antibiotics	Amoxicillin, ampicillin, cefotaxime, ceftriaxone, chloramphenicol, ciprofloxacin, clarithromycin, clindamycin, cotrimoxazole, erythromycin, gentamycin, metronidazole, minocycline, ofloxacin, penicillin, tetracycline
Antidepressants	Amitriptyline, citalopram, clomipramine, desipramine, doxepin, fluoxetine, fluvoxamine, imipramine, lithium, maprotiline, mirtazapine, nortriptyline, paroxetine, sertraline
Antidiabetic drugs	Glimepiride, metformin, tolbutamide
Antihypertensive drugs	Clonidine, doxazosin, hydralazine, methyldopa, minoxidil, prazosin, reserpine
Anticonvulsants	Carbamazepine, clonazepam, gabapentin, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid
Anti-inflammatory drugs	Acetylsalicylic acid, celecoxib, diclofenac, ibuprofen, indometacin, ketoprofen, naproxen, piroxicam
AT II antagonists	Irbesartan, telmisartan, valsartan
Beta blockers	Acebutolol, atenolol, bisoprolol, metoprolol, nadolol, pindolol, propranolol
Bronchodilators, mucolytic agents, respiratory stimulants	Aminophylline, doxapram, ipratropium bromide, salmeterol, terbutaline

Table 67.3 (continued)

Class of drug	Substance (examples)
Calcium antagonists	Amlodipine, diltiazem, felodipine, isradipine, nifedipine, nimodipine, nisoldipine, verapamil
Diuretics	Amiloride, furosemide, hydrochlorothiazide, spironolactone, triamterene
Hormones	Clomifene, danazol, oral contraceptives, estrogens, progesterone, steroids, testosterone and derivates, tamoxifen
Immunosuppressive drugs	Cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus (up to 36%), thalidomide
Antilipids	Clofibrate, fenofibrate, fluvastatin, lovastatin, pravastatin, simvastatin
Neuroleptics	Chlorpromazine, haloperidol, risperidone
Plasma expanders, blood supplying drugs	Hydroxyethyl starch, pentoxifylline
Tranquilizers	Alprazolam, chlordiazepoxide, lorazepam, oxazepam, prazepam
Uricostatics	Allopurinol, colchicine, probenecid, tiopronin

Diagnosis

As in all good clinical practice, a well-done anamnesis is essential, as well as a lot of empathy with the patient. Pruritus, just like in pain, is a subjective symptom and some peculiarities of the history can help in the differential diagnosis. It is always necessary to remember to ask about the onset, location and triggers of symptoms, in addition to researching the use of drugs or the presence of psychiatric illness. Travel history, symptoms in family members, and the type of personal care of the patient when asked can also be useful for the diagnosis [98].

The first step in the therapeutic approach of pruritus is attempting to evaluate whether itch is attributed to a dermatological cause or to an underlying disease. In a practical management, patients with pruritus may be divided into the following groups: (1) patients with primary pruritic dermatological disease; (2) patients with dermatological lesions secondary to pruritus; (3) patients with pruritus and without dermatological lesions [99]. In most cases, no systemic diseases are found in patients with generalized pruritus, who are classified as patients with pruritus *sine materia* [99, 100].

In patients with pruritic dermatological disease, the diagnosis and management of pruritus aim to treat the dermatosis [99–104]. However, in individuals who have no dermatological lesions or in those whose lesions are secondary to scratching, a detailed assessment should be made, including patient's history, clinical characteristics of pruritus, thorough physical examination, laboratory screening, and imaging studies to investigate systemic diseases that cause pruritus [99–104].

Patient's clinical history: a detailed past and current medical history should be taken with the purpose of identifying symptoms of systemic diseases, and family history should be taken to identify factors that predispose to systemic diseases [99–104]. It is also important to investigate the use of drugs that may trigger pruritus, possible allergenic agents, infectious diseases such as scabies, parasitological diseases, patient's occupation and lifestyle, personal and family history of atopy and other allergic diseases. Personal and family psychiatric history of the patient should also be investigated.

Some factors also should be considered in pruritus evaluation [99]. When several family members are affected, scabies or other parasites should be considered. The relationship between pruritus and special physical activities are suggested of cholinergic pruritus. Pruritus provoked by skin cooling after bathing should prompt consideration of aquagenic pruritus and may be associated with polycythemia vera or myelodysplastic syndrome. Nocturnal generalized pruritus associated with chills, fatigue, tiredness, and "B" symptoms (weight loss, fever, and nocturnal sweating) raises the possibility of Hodgkin's disease.

Somatoform pruritus rarely disturbs sleep, but most other pruritic diseases cause nocturnal wakening. Seasonal pruritus frequently presents as "winter itch," which may also be the manifestation of pruritus in the elderly due to xerosis and asteatotic eczema (Box 67.1).

Box 67.1: Clinical evaluation of Patients with Pruritus

1. Patient's clinical history: including hygiene habits that may dry the skin, contact with animals, occupation, leisure activities, infectious and parasitic diseases.
2. Patient's history: allergies; renal, hepatic, hematologic, and psychiatric diseases.
3. Family history of allergic and systemic diseases.
4. Use of topic and systemic drugs.

History of pruritus: a detailed evaluation of pruritus may lead to the differential diagnosis of this condition. It is important to investigate how disease onset was, the period of the day when the disease worsens, whether pruritus is intermittent or continuous, the sensation that pruritus causes, as well as duration of symptoms, severity, location, relationship with daily activities, triggering factors, and patient's perception about the symptom (Box 67.2) [99, 100].

Box 67.2: Medical history Taking for the Assessment of Pruritus

1. Occurrence of progression of previous episodes.
2. Onset of current symptoms (acute, progressive).
3. Period of the day when the disease worsens (day/night).
4. Triggering agents (baths, clothes, room temperature).
5. Sensation caused by pruritus (bite, burn).
6. Frequency (continuous, intermittent).
7. Location (localized, generalized).
8. Association with daily activities (interference, triggering).
9. Patient's perception about pruritus (the extent to which it affects quality of life).

Measurement of Pruritus: Pruritus is a subjective symptom that can be fully assessed only by the individual suffering from this symptom. However, several methods of assessment and measurement of pruritus have been developed in order to enable a better investigation both on the etiology of pruritus and the results of therapeutic studies. Visual analog scales and measures of scratching activity have been used for this assessment. A questionnaire developed by Yosipovitch et al. [21] evaluates the intensity, affective and sensory dimensions of pruritus and may be extremely useful for the measurement of pruritus in systemic diseases.

Patient Physical Examination: Search for dermatologic lesions that characterize pruritic dermatosis, xeroderma, jaundice, weight loss, hematomas, and excoriations caused by scratching [99–101]. General physical examination also should include palpation of the liver, kidneys, spleen, and lymph nodes.

Laboratory Tests: An accurate investigation is required mainly in those patients who do not have changes in the dermatological examination and who do not respond to treatment. When this larger assessment is indicated, the following exams should be considered: complete blood count, platelet, ferritin, serum iron, fasting glucose, stool test, erythrocyte sedimentation rate, evaluation of renal, hepatic, thyroid and parathyroid function, hepatitis B and C markers, anti-HIV, qualitative urine test. Other tests may also be performed in case of clinical suspicion of a specific disease [98–100], such as immunoelectrophoresis.

Imaging Tests: Chest X-ray and full abdominal ultrasound. Other tests may be requested according to clinical suspicion or medical judgment [99].

Histopathological tests may sometimes elucidate the diagnosis but is not routinely performed [99].

Patients with generalized pruritus and those that have normal test results should be periodically monitored, because they present with malignant disease or other systemic diseases later in life, with pruritus being the initial symptom. In some cases, such as in patients with skin lymphoma, pruritus may persist for many years before the onset of clinical and laboratory manifestations of the disease and the possibility of diagnosis.

Management

Considering that pruritus has various causes, there is no standardized recommendation for treatment. Topical and systemic therapies should be individualized, taking into account the age, previous diseases, current medications, allergies, pruritus severity, and impact on quality of life [102, 103]. According to recent studies, the therapy should also address both cutaneous and central mechanisms of pruritus (Fig. 67.1).

The first step in pruritus treatment is focused on the diagnosis of an underlying disease and on how to control it. Depending on the underlying cause, the appropriate therapy may vary considerably, including treatment for a specific dermatosis, non-exposition to contact allergens,

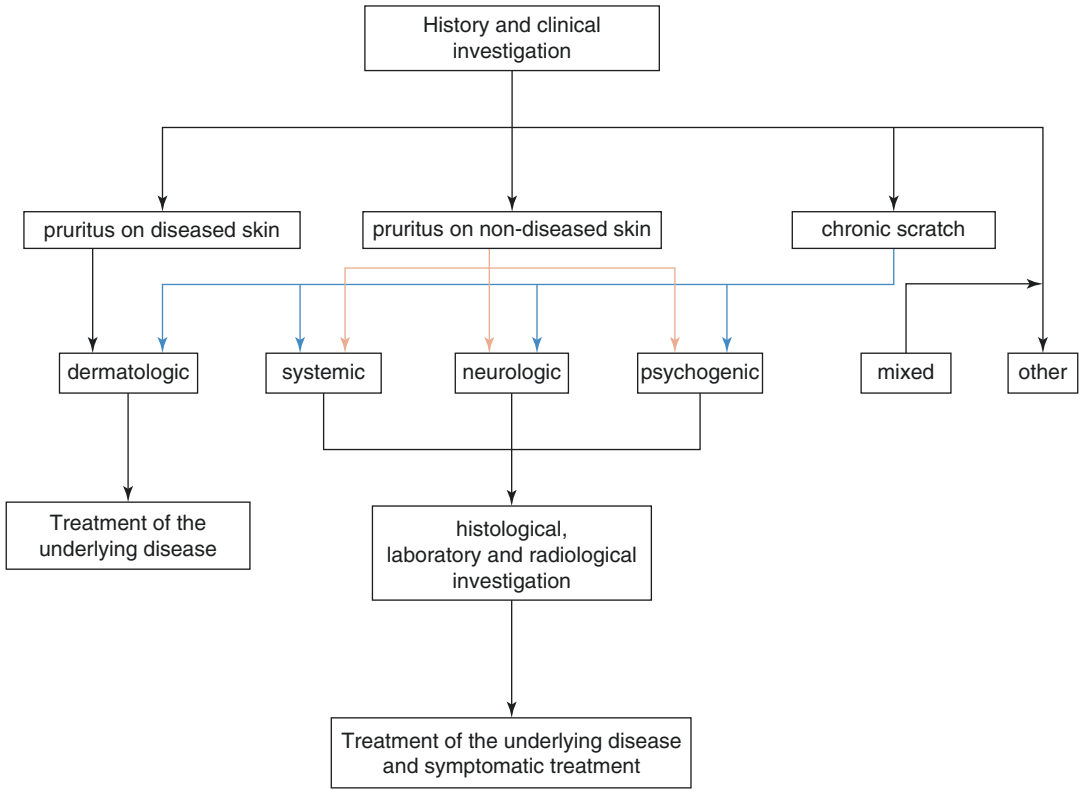

Fig. 67.1 Algorithm for the assessment of pruritus. (Adapted from Weisshaar et al. [102])

discontinuation of a medication, treatment of systemic, neurological, or psychiatric diseases, and even surgical treatments for removal of an underlying tumor [102, 103]. Pruritus caused, for example, by hyperthyroidism or cutaneous T-cell lymphoma resolves with an effective treatment for these diseases.

When the cause cannot be determined, knowing the characteristics of the pruritus, such as intense itching hours and triggering agents, is extremely important for the therapeutic approach [102]. We should keep in mind that, in some cases, there is no totally effective therapy for relieving itching. Therefore, patient counseling on measures for relieving pruritus is essential. Xeroderma occurs in a great number of these patients and should always be addressed with the use of emollients. Being careful with active substances that may cause skin irritation and increase pruritus is important as well. Itching causes traumatic skin lesions, which may be avoided by keeping fingernails trimmed. Elevated body temperature may increase pruritus. Measures such as wearing light clothes, staying in cooled areas, taking warm showers, and avoiding alcohol intake and spicy foods help alleviate the symptom [102, 103]. It should be considered that chronic pruritus is often caused by several factors and may be intensified by many cofactors, suggesting a multifactorial origin [104].

Care of patients, particularly those with chronic pruritus, may often extend for a long time, with periods of diagnostic uncertainty, therapeutic failures, and psychological stress. Physicians should discuss treatment duration and diagnostic investigation with patients in order to increase adherence to treatment and establish a good doctor–patient relationship. In all cases, however, early treatment and patient counseling may prevent nerve sensitization and, thus, pruritus chronification.

Topical Treatment

Topical treatment is considered first-line therapy for patients with mild symptoms and xerosis on physical examination. For those with localized or acute itching, they are the most suitable, particularly in cases where there is a contraindication for systemic treatment [65].

Emollients: Topical emollients are the first-line therapy for mild or localized pruritus and for xeroderma. In hemodialysis patients with intense xeroderma, the use of emollients associated with other therapies is indicated [99]. These agents are likely to reduce pruritus by softening the sharp edges of the outermost layer of dry skin (stratum corneum) and by improving skin barrier function. In inflammatory diseases, skin barrier function is insufficient, and repetitive itching intensifies this problem, facilitating the entry of irritating substances. “Wet wrap” therapy may be useful and soothing in cases of extensive inflammation, as in severe atopic dermatitis [105]. In that instance, the patient should first apply an emollient and a low-potency topical glucocorticoid on the affected area, and then wear water-soaked cotton pajamas at night. This treatment should be limited to short periods (<1 week at a time) because of the associated risks of infection and absorption of topical glucocorticoids in excess. High pH solutions, such as alkaline soaps, may increase the secretion of serine proteases, which intensify itching, and should be avoided in those patients. Conversely, moisturizers and skin care products with low pH (4.5–6.0) can be used [106].

Corticosteroids are not antipruritic agents, acting only in situations in which the pruritus is caused by inflammatory skin reaction. In randomized clinical trials, moderate- to high-potency glucocorticoids have proven to be an effective treatment for inflammatory skin diseases, such as atopic eczema, psoriasis, lichen planus, and genital lichen sclerosus et atrophicus [99]. High-potency glucocorticoids have also been used in medical practice in cutaneous manifestations secondary to chronic pruritus, such as prurigo nodularis and lichen simplex chronicus.

Capsaicin acts locally by desensitizing peripheral nerve fibers through depletion of substance P [107]. Usually its concentration varies from 0.025 to 0.075%. However, irritation on the injection site is a side effect, limiting its utilization greatly. Topical capsaicin has proven to be

an effective treatment for notalgia paresthetica and for hemodialysis patients with localized pruritus, as well as for patients with brachioradial pruritus [92].

Menthol: Topical menthol relieves itching by activating cold-sensitive A-delta fibers, which are responsible for transmitting a cool sensation through the activation of a transient receptor potential cation channel subfamily M member 8 (TRPM8) [58]. Clinical experience has suggested that this substance may be effective in skin care creams with concentrations varying from 1 to 5%, applied several times a day. Higher concentrations tend to cause skin irritation [108].

Calamine: Oil-based lotions and aqueous creams are effective in relieving pruritus. Patients often refuse to use it because of its pinkish color, and some formulations may cause skin dryness with water evaporation [5].

Topical anesthetics: preparations such as pramoxine 1% or 2.5% cream and lidocaine 2.5% and prilocaine 2.5% cream were effective in alleviating neuropathic, facial, and anogenital pruritus in several cases. In a randomized clinical trial with chronic kidney disease-associated pruritus, pramoxine 1% cream significantly reduced pruritus when compared to the isolated vehicle [109]. Long-term safety of these agents is still unknown.

Calcineurin Inhibitors: Relieve itching in inflammatory diseases, such as psoriasis, eczema, seborrheic dermatitis, and anogenital pruritus [110]. However, a common adverse effect of these agents is a burning sensation that begins a few days after repeated application of the product.

Doxepin: Doxepin 5% cream, a tricyclic antidepressant with H1-receptor inhibitory properties, was effective in reducing the sensation of itching in patients with atopic eczema and contact dermatitis [111]. Potential adverse events include sleepiness and allergic contact dermatitis.

Topical Antihistamines: The real effect of the treatment of skin pruritus with topical antihistamines is controversial, and studies in the literature are often limited or inconsistent [112].

Phosphodiesterase Inhibitors: Currently, the example is crisaborole, which acts in the inhibition of cytokines promoters of itching through phosphodiesterase 4. This medication has proven benefits in improving symptoms in patients with atopic dermatitis. Stinging and/or burning at the application site may be some of the side effects of this topical drug [113–115].

Topical Cannabinoids: Cannabinoids are lipophilic and easily absorbed by the skin. A high safety profile has been noted, in addition to being applied directly to the areas involved, there is no report of systemic absorption by topical use. Many of the antipruritic effects have been demonstrated with the use of non-THC cannabinoids, which lessens the concern with psychoactive effects [116]. Some scientists consider that topical cannabinoids promote an antipruritic effect as a consequence of the activation of cannabinoid receptors in the skin or an increase in the activity of endocannabinoids. It has also been suggested that the descending inhibitory serotonergic pathways are not involved in the antipruritic effect, being these substances totally independent. Atopic dermatitis, nodular prurigo, lichen sclerosis, postherpetic neuralgia, or aquagenic pruritus are some of the examples that have a good result to the use of topical cannabinoid receptor agonists [25].

Topical Prostanoid Inhibitors: Cyclooxygenase inhibitors, such as acetylsalicylic acid, have been reported to have antipruritic effects, most likely explained by their inhibitory effects on prostanoids and their action on prostaglandin E2 [65, 117].

Janus Kinase Inhibitors (JAKs) belong to the group of cytoplasmic tyrosine kinases. JAKs phosphorylate signal transducer of transcription factors affecting the expression of specific genes associated with inflammatory cytokines and growth factors [118]. These products are potential antipruritic agents, and a large number have been developed to combat itching. (Table 67.5) Topical tofacitinib, ruxolitinib, and delgocitinib are some examples [25, 146, 147]. Through topical administration, the known side effects of systemic exposure have no manifestation, in addition to allowing greater inhibition of cytokines in the local tissue and due to this, greater possibility of more immediate relief [148].

Tropomyosin-Receptor Kinase A Inhibitors (TrkA): The inhibition of this transmembrane receptor blocks the NGF response and consequently the histamine secretion from mast cells [149]. Pegcantratinib and cucurbitacins (topical TrKA inhibitors) revealed a clinical improvement in psoriatic lesions [149, 150].

Aryl Hydrocarbon Receptor Agonists (AhR): AhR maintains skin barrier, regulates innate and adaptive immune responses, and impacts the balance of Th17 and T-regulatory cells [151, 152]. The AhR pathway is linked to pruritic as AD and psoriasis [153]. Topical tapinarof, an agent that activates AhR, showed potential for alleviating symptoms of AD [152].

Systemic Treatment

Antihistamines: Antihistamines are among the most used drugs for itch's treatment, but there is no indication in chronic symptoms [53] Currently, four types of receptors are described (H1R, H2R, H3R, and H4R). The sedating ones, which are H1-receptor antagonists, are widely prescribed in medical practice as a first-line therapy for pruritus, despite the shortage of clinical trials proving their efficacy for pruritic diseases. The benefit observed in medical practice may result from the sedative action of these medications in the central nervous system, which can help patients with sleeping problems and relieve the symptoms. The use of second-generation antihistamines, with less sedative effect, is directed to the treatment of urticaria and mastocytosis [25]. Non-sedating histamine H1- and H2-receptor antagonists have limited efficacy in the treatment of chronic pruritus [99, 154]. Antihistamines have little effect on hemodialysis patients and patients with cholestatic disease [71, 73].

Neuroactive Drugs: Anticonvulsants, especially gabapentin and pregabalin, are being used not only for chronic pain but also in various itchy conditions. Possibly, its mechanism of action is the decrease of hypersensitization in the central nervous system [155].

Structural analogs to the neurotransmitter γ-aminobutyric acid, gabapentinoids are an effective treatment for some types of pruritus. In randomized clinical trials in patients with chronic kidney disease, low-dose gabapentin (100–300 mg administered three times a week) was effective in controlling pruritus when compared to placebo [156]. Case reports show that these drugs may also be used in the treatment of postherpetic neuralgia, brachioradial pruritus, and prurigo nodularis [100]. The most common adverse events are constipation, weight gain, sleepiness, ataxia, and blurred vision.

Oral Corticosteroids: Similarly to topical corticosteroids, there is no direct antipruritic action on these medications. In situations of itching due to inflammation, such as urticaria, cutaneous lymphoma, and bullous pemphigoid, corticosteroids have the power to decrease the secretion of the cytokine IL-31 and, consequently, the itching derived from this mechanism. They should be used in short treatments or avoided, not only because of the lack of evidence of effectiveness, but since the potential for adverse effects is very large.

Tricyclic Antidepressants: Serotonin reuptake inhibitors (paroxetine, sertraline, fluvoxamine, fluoxetine) have been used to reduce psychogenic pruritus and various types of generalized pruritus [157]. A double-blind study demonstrated the efficacy of sertraline (daily dose of 100 mg) for the treatment of cholestatic pruritus [158]. Studies have suggested that the antidepressant mirtazapine (daily dose of 15 mg) may relieve nocturnal itching related to some types of cancer [159]. In several cases of intractable pruritus related to cutaneous T-cell lymphoma, patients treated with a combination of low-dose mirtazapine and gabapentin or pregabalin showed improvement of the symptom [160]. Tricyclic antidepressants, such as amitriptyline, have also been used in the treatment of chronic pruritus (neuropathic and psychogenic forms, for instance) [99]. Paroxetine, a selective serotonin reuptake inhibitor, seems to have positive effects in low doses (5–10 mg a day). However, these effects tend to decrease after 4–6 weeks of use [5]. Doxepin has an antihistaminergic, antiserotonergic, and antiadrenergic effect, and the use of 10–100 mg per day, with a gradual increase in the

dose every 10 mg, is a strategy that has been established. Proved to be a very safe drug and to have an effect on various forms of itching [161].

Sodium cromoglycate: Sodium cromoglycate (SCG), a product developed as an inhalator for asthma treatment, is considered a mast cell stabilizer. Topical SCG has shown action to reduce the severity of itching when applied to individuals with atopic dermatitis [162]. Has effects on the improvement of pruritus in patients with Hodgkin's lymphoma [163].

Rifampicin: Indicated for the treatment of severe pruritus in patients with primary biliary cirrhosis and patients with cholestasis. Recent reports of drug-induced hepatitis caused by this medication reduce its therapeutic indication [164].

Cholestyramine: Reduces the levels of bile salts through chelation in the intestinal lumen. It is indicated in the treatment of cholestatic pruritus, but it does not work when there is bile duct obstruction. It may be used in hemodialysis patients as well [165].

Activated Charcoal: In hemodialysis patients with pruritus, it has shown positive results in relieving pruritus. Daily dose is 6 g [165].

Immunosuppressants: Immunosuppressive drugs such as dapsone, thalidomide, methotrexate, cyclosporine, and azathioprine previously used as antipruritic therapy are effective in their purpose of reducing symptoms. However, treatment with these drugs should be carried out for a limited time, due to the potential for serious long-term adverse effects. Thalidomide is used for pruritus treatment in several pruritic diseases, such as eczema, psoriasis, senile pruritus, and liver diseases, and has an effect on hemodialysis patients, who have shown an improvement of more than 50% [166, 167].

Opioid agonist-antagonists: Throughout the years, drugs targeting μ and kappa-opioid receptors have revealed antipruritic properties. In patients with chronic urticaria, atopic eczema and cholestasis, μ-opioid antagonists (naltrexone, nalmefene, and naloxone) have shown antipruritic effects [168]. Naltrexone and naloxone were effective for resistant itching associated with uremia and cholestasis. In randomized controlled trials conducted in Japan, nalfurafine hydrochloride (a kappa-opioid agonist) significantly reduced itching in hemodialysis patients with chronic kidney disease [169, 170]. However, some studies involving patients with chronic kidney disease have shown inconsistent results [171, 172]. According to reports, butorphanol (a μ-opioid antagonist and kappa-opioid agonist) administered via intravenous reduced intractable pruritus associated with non-Hodgkin's lymphoma, cholestasis, and the use of opioids [173]. In another series of cases, the use of butorphanol intranasally was effective in the treatment of patients with chronic itching due to systemic conditions and inflammatory skin diseases [168]. In a recent study, nalbuphine (μ -opioid antagonist and kappa-opioid agonist) demonstrated relief of itching in patients with uremic pruritus [174]. Another drug, difelikefalin (a kappa-opioid peripheral agonist) is currently receiving growing interest in relief uremic pruritus after hemodialysis session [175]. Initial adverse effects of these agents, such as nausea, loss of appetite, abdominal colic, diarrhea, and insomnia, limit their utilization.

NK-1 inhibitors: Due to the fact that SP is directly linked to acute and chronic itching, inhibitors of the NK-1 receptor, primary receptors of this substance, are effective in reducing the perception of pruritus. Aprepitant has shown to be effective in treating itchy nodular prurigo, Sézary syndrome, and paraneoplastic syndromes. Despite its proven effectiveness, it has many drug interactions and therefore may be restricted in some patients. On the other hand, serlopitant, with minimal adverse effects, significantly reduced itching in patients with chronic itching from different origins. However, there was no clinical response when used in patients with atopic dermatitis [25, 53]. Tradipitant, another NK-1 inhibitor drug is in study for management of atopic pruritus, revealing promising results [176].

Biologic drugs: In recent years, targeted therapies with biologics for several chronic inflammatory dermatoses have been considered, substantiating of proof regarding cytokines playing a role in pruritus. The mechanisms of action and indications of recent biologic drugs are summarized in Table 67.4 [219].

Table 67.4 Emerging biologic drugs for chronic pruritus

Drug	Mechanism of action	Administration	Indications	Reference
Dupilumab	IL-4 and IL-13 antagonist	Subcutaneous	AD, urticaria, chronic prurigo, BP, chronic refractory pruritus	[79–97, 177–195]
Lebrikizumab	IL-13 antagonist	Subcutaneous	AD	[100, 101, 196, 197]
Tralokinumab	IL-13 antagonist	Subcutaneous	AD	[198]
Secukinumab	IL-17A antagonist	Subcutaneous	Psoriasis, AD	[111–114, 199–203]
Ixekizumab	IL-17A antagonist	Subcutaneous	Psoriasis	[204–210
Brodalumab	IL-17A receptor antagonist	Subcutaneous	Psoriasis	[147, 211]
Ustekinumab	IL-12 and IL-23 antagonist	Subcutaneous	Psoriasis	[207, 212]
Risankizumab	IL-23 antagonist subcutaneous	Subcutaneous	Psoriasis, AD	[151, 212]
Guselkumab	IL-23 antagonist	Subcutaneous	Psoriasis	[156, 210, 213, 214]
Tildrakizumab	IL-23 antagonist	Subcutaneous	Psoriasis	[159–163, 203]
Nemolizumab	IL-31RA antagonist	Subcutaneous	AD, chronic prurigo	[215, 216]
Vixarelimab	(KPL-716) OSMRβ antagonist	Subcutaneous	AD	[217]
Ligelizumab IgE	IgE antagonist (targets free IgE, FcεRI, and surface IgE)	Subcutaneous	Chronic spontaneous urticaria	[172, 218]

AD atopic dermatitis

Table 67.5 Emerging JAK inhibitors for chronic pruritus

Name	Administration	Indications	Reference
Ruxolitinib	Topical, oral	AD, polycythemia vera, essential thrombocytosis, primary myelofibrosis, LP, cGVHD	[119–124]
Baricitinib	Oral	AD, psoriasis	[125–129]
Tofacitinib	Oral, topical	Psoriasis, AD	[130–138]
Abrocitinib	Oral	AD	[139, 140]
Upadacitinib	Oral	AD	[140, 141]
Delgocitinib	Topical	Chronic hand eczema, AD	[142–145]

Janus Kinase Inhibitors: There is growing evidence regarding the safety and efficacy of the use of oral JAKs inhibitors in psoriasis, atopic dermatitis, alopecia areata, and vitiligo [220] (Table 67.5).

Ileal Bile Acid Transporter Inhibitors (IBAT): IBAT inhibitors decrease reabsorption of bile acids in the ileum reducing enterohepatic recirculation and stimulating fecal excretion of bile acids improving chronic pruritus in patients with primary biliary cholangitis, primary sclerosing cholangitis, or Alagille syndrome [221, 222]. IBAT drugs as linerixibat, odevixibat, and maralixibat are in study showing promising results in alleviation of pruritus [221–224].

Phototherapy: The antipruritic effect of phototherapy is related to the direct action of ultraviolet radiation on sensory cutaneous nerve fibers or, indirectly through the release of skin cell mediators, which modulate the transmission of the itch to the central nervous system [225]. Observational studies have suggested that narrowband ultraviolet B (NB-UVB) phototherapy,

either isolated or in combination with ultraviolet A (UVA) radiation, reduces pruritus caused by chronic kidney disease and alleviates itching in diseases such as psoriasis, atopic eczema, and cutaneous T-cell lymphoma [125, 226]. In a randomized clinical trial involving patients with refractory itch secondary to chronic kidney disease [126], there was no significant difference in terms of efficacy between NB-UVB radiation and UVA radiation.

Liver Transplantation and Kidney Transplantation: Both are indicated in patients with extremely serious pruritus who do not respond to any therapeutic modality [165].

Psychotherapeutic Treatments: In cases of psychogenic pruritus, some patients with pruritus that is difficult to control have depressive symptoms and may benefit from psychotherapeutic treatment as well.

References

1. Hafenreffer S. De pruritu, Nosodochium in quo cutis, eique adharetium partuim, affectus omnes, singulari methodo, et cognoscendi et curandi fidelissime traduntur. Ulm: B Kühn; 1660. p. 98–102.
2. Carstens E, Follansbee T, Iodi CM. The challenge of basic itch research. Acta Derm Venereol. 2020;100(2):adv00023.
3. Yamamoto Y, Yamazaki S, Hayashino Y, et al. Association between frequency of pruritic symptoms and perceived psychological stress: a Japanese population based study. Arch Dermatol. 2009;145:1384–8.
4. Etter L, Myers SA. Pruritus in systemic disease: mechanisms and management. Dermatol Clin. 2002;20(3):459–72.
5. Twycross R, Greaves MW, Handwerker H, Jones EA, Libretto SE, Szepietowski JC, et al. Itch: scratching more than the surface. QJM. 2003;96(1):7–26.
6. LaMotte RH. Subpopulations of "nocifensor neurons" contributing to pain and allodynia, itch and alloknesis. Am Pain Soc J. 1992;1:115–26.
7. Ständer S, Weisshaar E, Mettang T, Szepietowski JC, Carstens E, Ikoma A, et al. Clinical classification of itch: a position paper of the international forum for the study of itch. Acta Derm Venereol. 2007;87:291–4.
8. Yosipovitch G, Greaves M, Schmelz M. Itch. Lancet. 2003;361:690–4.
9. Han L, Dong X. Itch mechanisms and circuits. Annu Rev Biophys. 2014;43:331–55. https://doi.org/10.1146/annurev-biophys-051013-022826.
10. Adler HM. Might a psychosocial approach improve our understanding of itching and scratching? Int J Dermatol. 2003;42:160–3.
11. Dalgard F, Svensson A, Holm JO, Sundby J. Self-reported skin morbidity in Oslo. Associations with sociodemographic factors among adults in a cross-sectional study. Br J Dermatol. 2004;151:452–7.
12. Matterne U, Apfelbacher CJ, Loerbroks A, et al. Prevalence, correlates and characteristics of chronic pruritus: a population based cross-sectional study. Acta Derm Venereol. 2011;91:674–9.
13. Stander S, Stumpf A, Osada N, Wilp S, Chatzigeorgakidis E, Pfeiderer B. Gender differences in chronic pruritus: women present different morbidity, more scratch lesions and higher burden. Br J Dermatol. 2013;168(6):1273–80.
14. Stander S, Schäfer I, Phan NQ, et al. Prevalence of chronic pruritus in Germany: results of a cross-sectional study in a sample working population of 11,730. Dermatology. 2010;221:229–35.
15. Weisshaar E, Dalgard F. Epidemiology of itch: adding to the burden of skin morbidity. Acta Derm Venereol. 2009;89:339–50.
16. Dalgard F, Dawn AG, Yosipovitch G. Are itch and chronic pain associated in adults? Results of a large population survey in Norway. Dermatology. 2007;214:305–9.
17. Wolkenstein P, Grob JJ, Bastuji-Garin S, Ruszczynski S, Roujeau JC, Revuz J. French people and skin diseases: results of a survey using a representative sample. Arch Dermatol. 2003;139:1614–9.
18. Britt H, Pan Y, Miller GC, Valenti L, Charles J, Knox S, et al. Presentations of 'itch' in Australian general practice. Aust Fam Physician. 2004;33:488.
19. McCormick A, Fleming D, Charlton J. Morbidity statistics from general practice. Fourth national study 1991–1992. London: Her Majestic's Stationery Office; 1995.
20. Szepietowski JC, Salomon J. Uremic pruritus: still an important clinical problem. J Am Acad Dermatol. 2004;51:842–3.
21. Yosipovitch G, Goon AT, Wee J, Chan YH, Zucker I, Goh CL. Itch characteristics in Chinese patients with atopic dermatitis using a new questionnaire for the assessment of pruritus. Int J Dermatol. 2002;41:212–6.
22. Song J, et al. Pruritus: progress toward pathogenesis and treatment, 9625936. BioMed Res Int. 2018;2018 https://doi.org/10.1155/2018/9625936.
23. Ikoma A, Steinhoff M, Ständer S, Yosipovitch G, Schmelz M. The neurobiology of itch. Nat Rev Neurosci. 2006;7:535–47.
24. LaMotte RH, Dong X, Ringkamp M. Sensory neurons and circuits mediating itch. Nat Neurosci. 2014;15:19–31.
25. Fowler E, Yosipovitch G. Chronic itch management: therapies beyond those targeting the immune system. Ann Allergy Asthma Immunol. 2019;123(2):158–65. https://doi.org/10.1016/j.anai.2019.01.016. Epub 2019 Jan 25

26. Davidson S, Giesler GJ. The multiple pathways for itch and their interactions with pain. Trends Neurosci. 2010;33:550–8.
27. Hyndman OR, Wolkin J. Anterior cordotomy: further observations on the physiologic results and optimum manner of performance. Arch Neuro Psychiatry. 1943;50:129–48.
28. Davidson S, et al. The itch-producing agents histamine and cowhage activate separate populations of primate spinothalamic tract neurons. J Neurosci. 2007;27:10007–14.
29. Davidson S, et al. Pruriceptive spinothalamic tract neurons: physiological properties and projection targets in the primate. J Neurophysiol. 2012;108:1711–23.
30. Han L, Ma C, Liu Q, Weng H-J, Cui Y, et al. A subpopulation of nociceptors specifically linked to itch. Nat Neurosci. 2013;16:174–82.
31. Shim WS, Oh U. Histamine-induced itch and its relationship with pain. Mol Pain. 2008;4:29. https://doi.org/10.1186/1744-8069-4-29. PMID: 18667087; PMCID: PMC2519061
32. Han SK, Mancino V, Simon MI. Phospholipase Cβ 3 mediates the scratching response activated by the histamine H1 receptor on C-fiber nociceptive neurons. Neuron. 2006;52:691–703.
33. Huang JF, Thurmond R. The new biology of histamine receptors. Curr Allergy AsthmaRep. 2008;8:21–7.
34. Greaves MW, Wall PD. Pathophysiology of itching. Lancet. 1996;348:938–40.
35. Snyder LM, et al. An unexpected role for TRPV4 in serotonin-mediated itch. J Investig Dermatol. 2016;136(1):7–9. https://doi.org/10.1016/j.jid.2015.11.010.
36. Ständer S, Yosipovitch G. Substance P and neurokinin 1 receptor are new targets for the treatment of chronic pruritus. Br J Dermatol. 2019;181(5):932–8. https://doi.org/10.1111/bjd.18025. Epub 2019 Jun 6
37. Cocchiara R, Lampiasi N, Albeggiani G, Bongiovanni A, Azzolina A, Geraci D. Mast cell production of TNF-alpha induced by substance P evidence for a modulatory role of substance P-antagonists. J Neuroimmunol. 1999;101:128–36.
38. Tarikci N, Kocatürk E, Güngör Ş, Topal IO, Can PÜ, Singer R. Pruritus in systemic diseases: a review of etiological factors and new treatment modalities. ScientificWorldJournal. 2015;2015:803752.
39. Toyoda M, Nakamura M, Makino T, Hino T, Kaqoura M, Morohashi M. Nerve growth factor and substance P are useful plasma markers of disease activity in atopic dermatitis. Br J Dermatol. 2002;147:71–9.
40. Costa SK, Starr A, Hyslop S, Gilmore D, Bran SD. How important are NK1 receptors for influencing microvascular inflammation and itch in the skin? Studies using Phoneutria nigriventer venom. Vasc Pharmacol. 2006;45:209–14.
41. Nolano M, Simone DA, Wendelschafer-Crabb G, Johnson T, Hazen E, Kennedy WR. Topical capsaicin in humans: parallel loss of epidermal nerve fibres and pain sensation. Pain. 1999;81:135–45.
42. Hagermark O, Strandberg K. Pruritogenic activity of prostaglandin E2. Acta Derm Venereol. 1977;57:37–43.
43. Greaves MW, McDonald-Gibson W. Itch: role of prostaglandins. Br Med J. 1973;3:608–9.
44. Gaspari AA, Lotze MT, Rosenberg SA, Stern JB, Katz SI. Dermatologic changes associated with interleukin 2 administration. JAMA. 1987;258:1624–9.
45. Ko MJ, Peng YS, Chen HY, Hsu SP, Pai MF, Yang JY, Wen SY, Jee SH, Wu HY, Chiu HC. Interleukin-31 is associated with uremic pruritus in patients receiving hemodialysis. J Am Acad Dermatol. 2014;71(6):1151–1159.e1.
46. Neis MM, Peters B, Dreuw A, Wenzel J, Bieber T, Mauch C, et al. Enhanced expression levels of IL-31 correlate with IL-4 and IL-13 in atopic and allergic contact dermatitis. J Allergy Clin Immunol. 2006;118:930–7.
47. Furue M, Yamamura K, Kido-Nakahara M, Nakahara T, Fukui Y. Emerging role of interleukin-31 and interleukin-31 receptor in pruritus in atopic dermatitis. Allergy. 2018;73(1):29–36.
48. Heyer G, Dotzer M, Diepgen TL, Handwerker HO. Opiate and H1 antagonist effects on histamine induced pruritus and allokinesis. Pain. 1997;73:239–43.
49. Saiah M, Borgeat A, Wilder-Smith OH, Rifat K, Suter PM. Epidural morphine induced pruritus: Propofol vs naloxone. Anesth Analg. 1994;78:1110–3.
50. Umeuchi H, Togashi Y, Honda T, Nakao K, Okano K, Tanaka T, et al. Involvement of central mu-opioid system in the scratching behavior in mice and the suppression of it by the activation of kappa-opioid system. Eur J Pharmacol. 2003;477:29–35.
51. Phan NQ, Lotts T, Antal A, Bernhard JD, Ständer S. Systemic kappa opioid receptor agonists in the treatment of chronic pruritus: a literature review. Acta Derm Venereol. 2012;92(5):555–60.
52. Steinhoff M, Neisius U, Ikoma A, Fartasch M, Heyer G, Skov PS, et al. Proteinase- activated receptor-2 mediates itch: a novel pathway for pruritus in human skin. J Neurosci. 2003;23:6176–80.
53. Carstens E, Akyama T. Itch: mechanisms and treatment. 1st ed. Boca Raton, FL: CRC Press; 2014.
54. Xie Z, Hongzhen H. TRP channels as drug targets to relieve itch. Pharmaceuticals (Basel). 2018;11(4):100.
55. Peier AM, Reeve AJ, Andersson DA, Moqrich A, Earley TJ, Hergarden AC, et al. A heat-sensitive TRP channel expressed in keratinocytes. Science. 2002;296:2046–9.
56. Ständer S, Moormann C, Schumacher M, Buddenkotte J, Artuc M, Shpacovitch V, et al. Expression of vanilloid receptor subtype 1 in cutaneous sensory nerve fibers, mast cells, and epithelial cells of appendage structures. Exp Dermatol. 2004;13:129–39.

57. Stokes AJ, Shimoda LM, Koblan-Huberson M, Adra CN, Turner H. A TRPV2-PKAsignaling module for transduction of physical stimuli in mast cells. J Exp Med. 2004;200:137–47.
58. Peier AM, Moqrich A, Hergarden AC, Reeve AJ, Andersson DA, Story GM, et al. ATRP channel that senses cold stimuli and menthol. Cell. 2002;108:705–15.
59. Indo Y. Nerve growth factor, pain, itch and inflammation: lessons from congenital insensitivity to pain with anhidrosis. Expert Rev Neurother. 2010;10(11):1707–24.
60. Aloe L. Rita Levi-Montalcini: the discovery of nerve growth factor and modern neurobiology. Trends Cell Biol. 2004;14:395–9.
61. Groneberg DA, Serowka F, Peckenschneider N, Artuc M, Grutzkau A, Fischer A, et al. Gene expression and regulation of nerve growth factor in atopic dermatitis mast cells and the human mast cell line-1. J Neuroimmunol. 2005;161:87–92.
62. Dvorak M, Watkinson A, McGlone F, Rukwied R. Histamine induced responses are attenuated by cannabinoid receptor agonist in human skin. Inflamm Res. 2003;52:238–45.
63. Papadopoulou N, Kalogeromitros D, Staurianeas NG, Tiblalexi D, Theoharides TC. Corticotropin-releasing hormone receptor-1 and histidine decarboxylase expression in chronic urticaria. J Invest Dermatol. 2005;125(5):952–5.
64. Theoharides TC, Singh LK, Boucher W, Pang X, Letourneau R, Webster E, et al. Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects. Endocrinology. 1998;139:403–13.
65. Cowan A, Yosipovitch G, editors. Pharmacology of itch. Berlin: Springer-Verlag; 2015.
66. Weidner C, Klede M, Rukwied R, Lischetzki G, Neisius U, Skov PS, et al. Acute effects of substance P and calcitonin gene-related peptide in human skin - a microdialysis study. J Invest Dermatol. 2000;115:1015–20.
67. Rukwied R, Lischetzki G, McGlone F, Heyer G, Schmelz M. Mast cell mediators other than histamine induce pruritus in atopic dermatitis: a dermal microdialysis study. Br J Dermatol. 2000;142:1–8.
68. MiyamotoT NH, Kuraishi Y. Intradermal cholinergic agonists induce itch-associated response via M3 muscarinic acetylcholine receptors in mice. Jpn J Pharmacol. 2002;88:351–4.
69. Krajnik M, Zylicz Z. Understanding pruritus in systemic disease. J Pain Symptom Manag. 2001;21(2):151–68.
70. Zirvas MJ, Seraly MP. Pruritus of unknown origin: a retrospective study. J Am Acad Dermatol. 2001;45:892–6.
71. Urbonas A, Schwartz RA, Szepietowski JC. Uremic pruritus – an update. Am J Nephrol. 2001;21(5):343–50.
72. Mettang T, Pauli-Magnus C, Alscher DM. Uraemic pruritus new perspectives and insights from recent trials. Nephrol Dial Transplant. 2002;17:1558–63.
73. Szepitowski JC, Morita A, Tsuji T. Ultraviolet B induces mast cell apoptosis: a hypothetical mechanism of ultraviolet B treatment for uremic pruritus. Med Hypotheses. 2002;58(2):167–70.
74. Murphy M, Reaich D, Pai P, Finn P, Carmichael AJ. A randomized, placebo-controlled, double-blind trial of ondansetron in renal itch. Br J Dermatol. 2003;148:314–7.
75. Bergasa NV. The pruritus of cholestasis. J Hepatol. 2005;43:1078–88.
76. Cacoub P, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JC, et al. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC group. Multidepartment virus C. Arthritis Rheum. 1999;42:2204–12.
77. Bergasa NV, Mehlman JK, Jones EA. Pruritus and fatigue in primary biliary cirrhosis. Baillieres Best Pract Res Clin Gastroenterol. 2000;14:643–55.
78. Bolier R, Ronald PJ, Elferink O, Beuers U. Advances in pathogenesis and treatment of pruritus. Clin Liver Dis. 2013;17:319–29.
79. Kremer AE, Dijk RV, Leckie P, Schaap FG, Kuiper EM, Mettang T, et al. Serum autotaxin is increased in pruritus of cholestasis, but not of other origin and responds to therapeutic interventions. Hepatology. 2012;56(4):1391–400. (Epub ahead of print)
80. Zylicz Z, Twycross R, Jones EA. Pruritus in advanced disease. Oxford: Oxford University Press; 2004.
81. Krajnik M, Zylicz Z. Pruritus in advanced internal diseases. Pathogenesis and treatment. Neth J Med. 2001;58:27–40.
82. Weisshaar E, Kucenic MJ, Fleischer AB Jr, Bhard JD. Pruritus and dysesthesia. In: Bolognia JL, Jorizzo J, Rapini RP, editors. Dermatology. Mosby; 2015. p. 95–110.
83. Diehn F, Tefferi A. Pruritus in polycythaemia vera: prevalence, laboratory correlates and management. Br J Haematol. 2001;115:619–21.
84. Pieri L, Bogani C, Guglielmelli P, Zingariello M, Rana RA, Bartalucci N, et al. The JAK2V617 mutation induces constitutive activation and agonist hypersensitivity in basophils from patients with polycythemia vera. Haematologica. 2009;94:1537–45.
85. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105:3768–85.
86. Bowen GM, Stevens SR, Dubin HV, Siddiqui J, Cooper KD. Diagnosis of Sezary syndrome in a patient with generalized pruritus based on early molecular study and flow cytometry. J Am Acad Dermatol. 1995;33:678–80.
87. Pujol RM, Gallardo F, Llistosella E, et al. Invisible mycosis fungoides: a diagnostic challenge. J Am Acad Dermatol. 2002;47:S168–71.

88. Misery L, Ständer S. Chapter 18. Cutaneous T-cell lymphoma. In: Görge T, Schiller M, editors. Pruritus. London: Springer-Verlag Limited; 2010. p. 121–4.
89. Jabbour SA. Cutaneous manifestations of endocrine disorders: a guide for dermatologists. Am J Clin Dermatol. 2003;4:315–31.
90. Caravati CM Jr, Richardson DR, Wood BT, Cawley EP. Cutaneous manifestations of hyperthyroidism. South Med J. 1969;62:1127–30.
91. Neilly JB, Martin A, Simpson N, MacCuish AC. Pruritus in diabetes mellitus: investigation of prevalence and correlation with diabetes control. Diabetes Care. 1986;9:273–5.
92. Goodkin R, Wingard E, Bernhard JD. Brachioradial pruritus: cervical spine disease and neurogenic/neurogenic pruritus. J Am Acad Dermatol. 2003;48(4):521–4.
93. Gelfand JM, Rudikoff D. Evaluation and treatment of itching in HIV-infected patients. Mt Sinai J Med. 2001;68:298–308.
94. Eisman S. Pruritic papular eruption in HIV. Dermatol Clin. 2006;24:449–57.
95. Daniel GL, Longo WE, Vernava AM III. Pruritus ani. Causes and concerns. Dis Colon Rectum. 1994;37:670–4.
96. Reich A, Ständer S. Drug-induced pruritus: a review. Acta Derm Venereol. 2009;89:236–44.
97. Kaplan AP. Drug-induced skin disease. J Allergy Clin Immunol. 1984;74:573–9.
98. Nowak DA, Yeung J. Diagnosis and treatment of pruritus. Can Fam Physician. 2017;63(12):918–24.
99. Weisshaar E, Szepietowski JC, Darsow U, et al. European guideline on chronic pruritus. Acta Derm Venereol. 2012;92:563–81.
100. Yosipovitch G, Bernhard JD. Clinical practice. Chronic pruritus N Engl J Med. 2013;368(17):1625–34.
101. Yosipovitch G, David M. The diagnosis and therapeutic approach to idiopathic generalized pruritus. Int J Dermatol. 1999;38:881–7.
102. Weisshaar E, Kucenic MJ, Fleischer AB. Pruritus: a review. Acta Derm Venereol. 2003;213(Suppl):5–32.
103. Ständer S, Streit M, Darsow U, et al. Diagnostic and therapeutic measures in chronic pruritus. J Dtsch Dermatol Ges. 2006;4:350–70.
104. Sommer F, Hensen P, Böckenholt B, et al. Underlying diseases and co-factors in patients with severe chronic pruritus: a 3-year retrospective study. Acta Derm Venereol. 2007;87:510–6.
105. Bingham LG, Noble JW, Davis MD. Wet dressings used with topical corticosteroids for pruritic dermatoses: a retrospective study. J Am Acad Dermatol. 2009;60:792–800.
106. Ali SM, Yosipovitch G. Skin pH: from basic science to basic skin care. Acta Derm Venereol. 2013;93(3):261–7. (Epub ahead of print)
107. Papoiu AD, Yosipovitch G. Topical capsaicin: the fire of a "hot" medicine is reignited. Expert Opin Pharmacother. 2010;11:1359–71.
108. Patel T, Ishiuji Y, Yosipovitch G. Menthol: a refreshing look at this ancient compound. J Am Acad Dermatol. 2007;57:873–8.
109. Young TA, Patel TS, Camacho F, et al. A pramoxine-based anti-itch lotion is more effective than a control lotion for the treatment of uremic pruritus in adult hemodialysis patients. J Dermatolog Treat. 2009;20:76–81.
110. Suys E. Randomized study of topical tacrolimus ointment as possible treatment for resistant idiopathic pruritus ani. J Am Acad Dermatol. 2012;66:327–8.
111. Drake LA, Fallon JD, Sober A. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. J Am Acad Dermatol. 1994;31:613–6.
112. Harrison IP, Spada F. Breaking the Itch-scratch cycle: topical options for the management of chronic cutaneous itch in atopic dermatitis. Medicines (Basel). 2019;6(3):76.
113. Guttman-Yassky E, Hanifn JM, Boguniewicz M, et al. The role of phosphodiesterase 4 in the pathophysiology of atopic dermatitis and the perspective for its inhibition. Exp Dermatol. 2019;28:3–10. https://doi.org/10.1111/exd.13808.
114. Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. J Am Acad Dermatol. 2016;75(494–503):e6. https://doi.org/10.1016/j.jaad.2016.05.046.
115. Yosipovitch G, Gold LF, Lebwohl MG, et al. Early relief of pruritus in atopic dermatitis with crisaborole ointment, a nonsteroidal, phosphodiesterase 4 inhibitor. Acta Derm Venereol. 2018;98:484–9.
116. Avila C, Massick S, Kaffenberger BH, Kwatra SG, Bechtel M. Cannabinoids for the treatment of chronic pruritus: a review. J Am Acad Dermatol. 2020;82(5):1205–12.
117. Honda T, Kabashima K. Prostanoids and leukotrienes in the pathophysiology of atopic dermatitis and psoriasis. Int Immunol. 2019;31(9):589–95.
118. O'Shea JJ, Schwartz DM, Villarino AV, et al. The JAK-STAT pathway: impact on human disease and therapeutic intervention. Annu Rev Med. 2015;66:311–28.
119. Kim BS, Sun K, Papp K, Venturanza M, Nasir A, Kuligowski ME. Effects of ruxolitinib cream on pruritus and quality of life in atopic dermatitis: Results from a phase 2 randomized dose-ranging vehicle- and activecontrolled study. J Am Acad Dermatol. 2020;82(6):1305–13. S0190962220302139. https://doi.org/10.1016/j.jaad.2020.02.009.
120. Vaa BE, Tefferi A, Gangat N, Pardanani A, Lasho TL, Finke CM, Wolanskyj AP. Pruritus in primary myelofibrosis: management options in the era of JAK inhibitors. Ann Hematol. 2016;95(7):1185–9. https://doi.org/10.1007/s00277-016-2674-2.
121. Verstovsek S, Passamonti F, Rambaldi A, Barosi G, Rumi E, Gattoni E, Pieri L, Zhen H, Granier M, Assad

A, Cazzola M, Kantarjian HM, Barbui T, Vannucchi AM. Ruxolitinib for essential thrombocythemia refractory to or intolerant of hydroxyurea: long-term phase 2 study results. Blood. 2017;130(15):1768–71. https://doi.org/10.1182/blood-2017-02-765032.

122. Vannucchi AM, Kiladjian JJ, Griesshammer M, Masszi T, Durrant S, Passamonti F, Harrison CN, Pane F, Zachee P, Mesa R, He S, Jones MM, Garrett W, Li J, Pirron U, Habr D, Verstovsek S. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med. 2015;372(5):426–35. https://doi.org/10.1056/NEJMoa1409002.
123. Brumfiel CM, Patel MH, Severson KJ, Zhang N, Li X, Quillen JK, Zunich SM, Branch EL, Nelson SA, Pittelkow MR, Mangold AR. Ruxolitinib cream in the treatment of cutaneous lichen planus: a prospective open-label study. J Invest Dermatol. 2022;142(8):2109–2116.e4. S0022202X22000835. https://doi.org/10.1016/j.jid.2022.01.015.
124. Spoerl S, Mathew NR, Bscheider M, Schmitt-Graeff A, Chen S, Mueller T, Verbeek M, Fischer J, Otten V, Schmickl M, Maas-Bauer K, Finke J, Peschel C, Duyster J, Poeck H, Zeiser R, von Bubnoff N. Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease. Blood. 2014;123(24):3832–42. https://doi.org/10.1182/blood-2013-12-543736.
125. Gilchrest BA, Rowe JW, Brown RS, Steinman TI, Arndt KA. Ultraviolet phototherapy of uremic pruritus: long-term results and possible mechanism of action. Ann Intern Med. 1979;91:17–21.
126. Ko MJ, Yang JY, Wu HY, et al. Narrowband ultraviolet B phototherapy for patients with refractory uraemic pruritus: a randomized controlled trial. Br J Dermatol. 2011;165:633–9.
127. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, King BA, Thyssen JP, Silverberg JI, Bieber T, Kabashima K, Tsunemi Y, Costanzo A, Guttman-Yassky E, Beck LA, Janes JM, AM DL, Gamalo M, Brinker DR, Cardillo T, Nunes FP, Paller AS, Wollenberg A, Reich K. Br J Dermatology. 2020;183(2):242–55. https://doi.org/10.1111/bjd.18898.
128. Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R, de la Peña A, Nunes FP, Janes J, Gamalo M, Donley D, Paik J, AM DL, Nickoloff BJ, Simpson EL. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel double-blinded randomized placebo-controlled multiple-dose study. J Am Acad Dermatol. 2019;80(4):913–921.e9. S0190962218301294. https://doi.org/10.1016/j.jaad.2018.01.018.
129. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, King BA, Thyssen JP, Silverberg JI, Bieber T, Kabashima K, Tsunemi Y, Costanzo A, Guttman-Yassky E, Beck LA, Janes JM, AM DL, Gamalo M, Brinker DR, Cardillo T, Nunes FP, Paller AS, Wollenberg A, Reich K. Br J Dermatol. 2020;183(2):242–55. https://doi.org/10.1111/bjd.18898.
130. Bushmakin AG, Mamolo C, Cappelleri JC, Stewart M. The relationship between pruritus and the clinical signs of psoriasis in patients receiving tofacitinib. J Dermatol Treat. 2015;26(1):19–22. https://doi.org/10.3109/09546634.2013.861891.
131. Feldman SR, Thaçi D, Gooderham M, Augustin M, de la Cruz C, Mallbris L, Buonanno M, Tatulych S, Kaur M, Lan S, Valdez H, Mamolo C. Tofacitinib improves pruritus and health-related quality of life up to 52 weeks: results from 2 randomized phase III trials in patients with moderate to severe plaque psoriasis. J Am Acad Dermatol. 2016;75(6):1162–1170.e3. S0190962216305916. https://doi.org/10.1016/j.jaad.2016.07.040.
132. Papp KA, Krueger JG, Feldman SR, Langley RG, Thaci D, Torii H, Tyring S, Wolk R, Gardner A, Mebus C, Tan H, Luo Y, Gupta P, Mallbris L, Tatulych S. (2016) Tofacitinib an oral Janus kinase inhibitor for the treatment of chronic plaque psoriasis: Long-term efficacy and safety results from 2 randomized phase-III studies and 1 open-label long-term extension study. J Am Acad Dermatol 74(5) 841-850. S0190962216000268 https://doi.org/10.1016/j.jaad.2016.01.013
133. Valenzuela F, Paul C, Mallbris L, Tan H, Papacharalambous J, Valdez H, Mamolo C. Tofacitinib versus etanercept or placebo in patients with moderate to severe chronic plaque psoriasis: patient-reported outcomes from a Phase 3 study. J Eur Acad Dermatol Venereol. 2016;30(10):1753–9. https://doi.org/10.1111/jdv.13702.
134. Griffiths CE, Vender R, Sofen H, Kircik L, Tan H, Rottinghaus ST, Bachinsky M, Mallbris L, Mamolo C. Effect of tofacitinib withdrawal and re-treatment on patient-reported outcomes: results from a Phase 3 study in patients with moderate to severe chronic plaque psoriasis. J Eur Acad Dermatol Venereol. 2017;31(2):323–32. https://doi.org/10.1111/jdv.13808.
135. Ständer S, Luger T, Cappelleri JC, Bushmakin AG, Mamolo C, Zielinski MA, Tallman AM, Yosipovitch G. Validation of the itch severity item as a measurement tool for pruritus in patients with psoriasis: results from a Phase 3 tofacitinib program. Acta Derm Venereol. 2018;98(3):340–5. 5129. https://doi.org/10.2340/00015555-2856.
136. Wang F, Morris C, Bodet ND, Kim BS. Treatment of refractory chronic pruritus of unknown origin with tofacitinib in patients with rheumatoid arthritis. JAMA Dermatol. 2019;155(12):1426. https://doi.org/10.1001/jamadermatol.2019.2804.
137. Bissonnette R, Papp KA, Poulin Y, Gooderham M, Raman M, Mallbris L, Wang C, Purohit V, Mamolo C, Papacharalambous J, Ports WC. Br J Dermatol. 2016;175(5):902–11. https://doi.org/10.1111/bjd.14871.

138. Papp KA, Bissonnette R, Gooderham M, Feldman SR, Iversen L, Soung J, Draelos Z, Mamolo C, Purohit V, Wang C, Ports WC. Treatment of plaque psoriasis with an ointment formulation of the Janus kinase inhibitor tofacitinib: a Phase 2b randomized clinical trial. BMC Dermatol. 2016;16(1):15. https://doi.org/10.1186/s12895-016-0051-4.
139. Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C, Zhu L, Papacharalambous J, Vincent MS, Peeva E. Efficacy and safety of oral janus kinase 1 inhibitor abrocitinib for patients with atopic dermatitis. JAMA Dermatol. 2019;155(12):1371. https://doi.org/10.1001/jamadermatol.2019.2855.
140. Ahn J, Choi Y, Simpson EL. Therapeutic new era for atopic dermatitis: part 2. Small molecules. Ann Dermatol. 2021;33(2):101. https://doi.org/10.5021/ad.2021.33.2.101.
141. Guttman-Yassky E, Thaçi D, Pangan AL, Hong HC, Papp KA, Reich K, Beck LA, Mohamed MF, Othman AA, Anderson JK, Gu Y, Teixeira HD, Silverberg JI. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized placebo-controlled trial. J Allergy Clin Immunol. 2020;145(3):877–84. S0091674919316082. https://doi.org/10.1016/j.jaci.2019.11.025.
142. Worm M, Bauer A, Elsner P, Mahler V, Molin S, TSS N. Br J Dermatol. 2020;182(5):1103–10. https://doi.org/10.1111/bjd.18469.
143. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kaino H, Nagata T. Delgocitinib ointment a topical Janus kinase inhibitor in adult patients with moderate to severe atopic dermatitis: a phase 3 randomized double-blind vehicle-controlled study and an open-label long-term extension study. J Am Acad Dermatol. 2020;82(4):823–31. S019096221933289X. https://doi.org/10.1016/j.jaad.2019.12.015.
144. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Oda M, Kabashima K, Nagata T. Phase 2 clinical study of delgocitinib ointment in pediatric patients with atopic dermatitis. J Allergy Clin Immunol. 2019;144(6):1575–83. S0091674919310450. https://doi.org/10.1016/j.jaci.2019.08.004.
145. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Murata R, Kaino H, Nagata T. Long-term safety and efficacy of delgocitinib ointment a topical Janus kinase inhibitor in adult patients with atopic dermatitis. J Dermatol. 2020;47(2):114–20. https://doi.org/10.1111/1346-8138.15173.
146. Bissonnette R, Papp KA, Poulin Y, et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. Br J Dermatol. 2016;175:902–11.
147. Papp KA, Bissonnette R, Gooderham M, et al. Treatment of plaque psoriasis with an ointment formulation of the Janus kinase inhibitor, tofacitinib: a phase 2b randomized clinical trial. BMC Dermatol. 2016;16:15. https://doi.org/10.1186/s12895-016-0051-4.
148. Fukuyama T, Ehling S, Cook E, Bäumer W. Topically administered janus-kinase inhibitors tofacitinib and oclacitinib display impressive antipruritic and anti-inflammatory responses in a model of allergic dermatitis. J Pharmacol Exp Ther. 2015;354(3):394–405.
149. Zhong Y, Xu H, Zhong Y, et al. Identification and characterization of the Cucurbitacins, a novel class of small-molecule inhibitors of tropomyosin receptor kinase A. BMC Complement Altern Med. 2019;19:295.
150. Roblin D, Yosipovitch G, Boyce B, et al. Topical TrkA kinase inhibitor CT327 is an effective, novel therapy for the treatment of pruritus due to psoriasis: results from experimental studies, and efficacy and safety of CT327 in a phase 2b clinical trial in patients with psoriasis. Acta Derm Venereol. 2015;95:542–8.
151. Haas K, Weighardt H, Deenen R, et al. Aryl hydrocarbon receptor in keratinocytes is essential for murine skin barrier integrity. J Investig Dermatol. 2016;136:2260–9.
152. Smith SH, Jayawickreme C, Rickard DJ, et al. Tapinarof is a natural AhR agonist that resolves skin inflammation in mice and humans. J Investig Dermatol. 2017;137:2110–9.
153. Napolitano M, Patruno C. Aryl hydrocarbon receptor (AhR) a possible target for the treatment of skin disease. Med Hypotheses. 2018;116:96–100.
154. O'Donoghue M, Tharp MD. Antihistamines and their role as antipruritics. Dermatol Ther. 2005;18:333–40.
155. Patel T, Yosipovitch G. Therapy of pruritus. Expert Opin Pharmacother. 2010;11(10):1673–82.
156. Gunal AI, Ozalp G, Yoldas TK, Gunal SY, Kirciman E, Celiker H. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. Nephrol Dial Transplant. 2004;19:3137–9.
157. Stander S, Backenholt B, Schürmeyer- Horst F, et al. Treatment of chronic prurituswith the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof of-concept study. Acta Derm Venereol. 2009;89:45–51.
158. Mayo MJ, Handem I, Saldana S, Jacobe H, Getachew Y, Rush AJ. Sertraline as a first-line treatment for cholestatic pruritus. Hepatology. 2007;45:666–74.
159. Hundley JL, Yosipovitch G. Mirtazapine for reducing nocturnal itch in patients with chronic pruritus: a pilot study. J Am Acad Dermatol. 2004;50:889–91.
160. Demierre MF, Taverna J. Mirtazapine and gabapentin for reducing pruritus in cutaneous T-cell lymphoma. J Am Acad Dermatol. 2006;55:543–4.
161. Steinhoff M, et al. Pruritus: management algorithms and experimental therapies. Semin Cutan Med Surg. 2011;30(2):127–37. https://doi.org/10.1016/j.sder.2011.05.001.
162. Edwards AM, Stevens MT, Church MK. The effects of topical sodium cromoglicate on itch and flare in human skin induced by intradermal histamine: a randomised double-blind vehicle controlled intra-subject design trial. BMC Res Notes. 2011;4:47. https://doi.org/10.1186/1756-0500-4-47.

163. Suchin KR. Pruritus of unknown etiology including senile pruritus. In: Lebwohl M, Heymann WR, Berth-Jones J, Coulson I, editors. Treatment of skin disease – comprehensive therapeutic strategies. Mosby; 2002. p. 519–22.
164. Prince MI, Burt AD, Jones DEJ. Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. Gut. 2002;50:436–9.
165. Suchin KR, Suchin EJ. Pruritus of renal and liver disease. In: Lebwohl M, Heymann WR, Berth-Jones J, Coulson I, editors. Treatment of skin disease – comprehensive therapeutic strategies. Mosby; 2002. p. 515–8.
166. Daly BM, Shuster S. Antipruritic action of thalidomide. Acta Derm Venereol. 2000;80:24–5.
167. Moraes M, Russo G. Thalidomide and its dermatologic uses. Am J Med Sci. 2001;321(5):321–6.
168. Phan NQ, Bernhard JD, Luger TA, St.nder S. Antipruritic treatment withs systemic μ-opioid receptor antagonists: a review. J Am Acad Dermatol. 2010;63:142–8.
169. Kumagai H, Ebata T, Takamori K, Muramatsu T, Nakamoto H, Suzuki H. Effect of a novel kappa-receptor agonist, nalfurafine hydrochloride, on severe itch in 337 haemodialysis patients: a phase III, randomized, double-blind, placebo-controlled study. Nephrol Dial Transplant. 2010;25:1251–7.
170. Wikstrm B, Gellert R, Ladefoged SD, et al. Kappa-opioid system in uremic pruritus: multicenter, randomized, doubleblind, placebo-controlled clinical studies. J Am Soc Nephrol. 2005;16:3742–7.
171. Peer G, Kivity S, Agami O, et al. Randomised crossover trial of naltrexone in uraemic pruritus. Lancet. 1996;348:1552–4.
172. Pauli-Magnus C, Mikus G, Alscher DM, et al. Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. J Am Soc Nephrol. 2000;11:514–9.
173. Dawn AG, Yosipovitch G. Butorphanol for treatment of intractable pruritus. J Am Acad Dermatol. 2006;54:527–31.
174. Mathur VS, Kumar J, Crawford PW, et al. A multicenter, randomized, double-blind, placebo-controlled trial of nalbuphine ER tablets for uremic pruritus. Am J Nephrol. 2017;46:450–8.
175. Albert-Vartanian A, Boyd MR, Hall AL, et al. Will peripherally restricted kappa-opioid receptor agonists (pKORAs) relieve pain with less opioid adverse effects and abuse potential? J Clin Pharm Ther. 2016;41:371–82.
176. Heitman A, Xiao C, Cho Y, et al. Tradipitant improves worst itch and disease severity in patients with chronic pruritus related to atopic dermatitis. J Am Acad Dermatol. 2018;79:AB300.
177. Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, Ming JE, Ren H, Kao R, Simpson E, Ardeleanu M, Weinstein SP, Pirozzi G, Guttman-Yassky E, Suárez-Fariñas M, Hager MD, Stahl N, Yancopoulos GD, Radin AR. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371(2):130–9. https://doi.org/10.1056/NEJMoa1314768.
178. Simpson EL, Gadkari A, Worm M, Soong W, Blauvelt A, Eckert L, Wu R, Ardeleanu M, Graham NMH, Pirozzi G, Sutherland ER, Mastey V. Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): a phase IIb randomized placebo-controlled clinical trial in adult patients with moderate to severe atopic dermatitis (AD). J Am Acad Dermatol. 2016;75(3):506–15. S0190962216301931. https://doi.org/10.1016/j.jaad.2016.04.054.
179. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, Silverberg JI, Deleuran M, Kataoka Y, Lacour J-P, Kingo K, Worm M, Poulin Y, Wollenberg A, Soo Y, Graham NMH, Pirozzi G, Akinlade B, Staudinger H, Mastey V, Eckert L, Gadkari A, Stahl N, Yancopoulos GD, Ardeleanu M. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N Engl J Med. 2016;375(24):2335–48. https://doi.org/10.1056/NEJMoa1610020.
180. Thaçi D, Simpson EL, Deleuran M, Kataoka Y, Chen Z, Gadkari A, Eckert L, Akinlade B, Graham NMH, Pirozzi G, Ardeleanu M. Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2). J Dermatol Sci. 2019;94(2):266–75. S0923181119300283. https://doi.org/10.1016/j.jdermsci.2019.02.002.
181. Andrew Blauvelt, Marjolein de Bruin-Weller, Melinda Gooderham, Jennifer C. Cather, Jamie Weisman, David Pariser, Eric L. Simpson, Kim A. Papp, H Chih-Ho Hong, Diana Rubel, Peter Foley, Errol Prens, Christopher E.M. Griffiths, Takafumi Etoh, Pedro Herranz Pinto, Ramon M. Pujol, Jacek C. Szepietowski, Karel Ettler, Lajos Kemény, Xiaoping Zhu, Bolanle Akinlade, Thomas Hultsch, Vera Mastey, Abhijit Gadkari, Laurent Eckert, Nikhil Amin, Neil M.H. Graham, Gianluca Pirozzi, Neil Stahl, George D. Yancopoulos, Brad Shumel (2017) Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year randomised double-blinded placebo-controlled phase 3 trial. Lancet 389(10086) 2287-2303. S0140673617311911 https://doi.org/10.1016/S0140-6736(17)31191-1
182. de Bruin-Weller M, Thaçi D, Smith CH, Reich K, Cork MJ, Radin A, Zhang Q, Akinlade B, Gadkari A, Eckert L, Hultsch T, Chen Z, Pirozzi G, Graham NMH, Shumel B. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled randomized phase III clinical trial (LIBERTY AD CAFÉ). Br J Dermatol. 2018;178(5):1083–101. https://doi.org/10.1111/bjd.16156.

183. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, Beck LA, Guttman-Yassky E, Pariser D, Blauvelt A, Weisman J, Lockshin B, Hultsch T, Zhang Q, Kamal MA, Davis JD, Akinlade B, Staudinger H, Hamilton JD, Graham NMH, Pirozzi G, Gadkari A, Eckert L, Stahl N, Yancopoulos GD, Ruddy M, Bansal A. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis. JAMA Dermatol. 2020;156(1):44. https://doi.org/10.1001/jamadermatol.2019.3336.
184. Mette Deleuran, Diamant Thaçi, Lisa A. Beck, Marjolein de Bruin-Weller, Andrew Blauvelt, Seth Forman, Robert Bissonnette, Kristian Reich, Weily Soong, Iftikhar Hussain, Peter Foley, Michihiro Hide, Jean-David Bouaziz, Joel M. Gelfand, Lawrence Sher, Marie L.A. Schuttelaar, Chen Wang, Zhen Chen, Bolanle Akinlade, Abhijit Gadkari, Laurent Eckert, John D. Davis, Manoj Rajadhyaksha, Heribert Staudinger, Neil M.H. Graham, Gianluca Pirozzi, Marius Ardeleanu (2020) Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. J Am Acad Dermatol 82(2) 377-388. S019096221932465X https://doi.org/10.1016/j.jaad.2019.07.074
185. Silverberg JI, Yosipovitch G, Simpson EL, Kim BS, Wu JJ, Eckert L, Guillemin I, Chen Z, Ardeleanu M, Bansal A, Kaur M, Rossi AB, Graham NMH, Patel N, Gadkari A. Dupilumab treatment results in early and sustained improvements in itch in adolescents and adults with moderate to severe atopic dermatitis: analysis of the randomized phase 3 studies SOLO 1 and SOLO 2 AD ADOL and CHRONOS. J Am Acad Dermatol. 2020;82(6):1328–36. S0190962220303054. https://doi.org/10.1016/j.jaad.2020.02.060.
186. Beck KM, Yang EJ, Sekhon S, Bhutani T, Liao W. Dupilumab treatment for generalized prurigo nodularis. JAMA Dermatol. 2019;155(1):118. https://doi.org/10.1001/jamadermatol.2018.3912.
187. Rambhia PH, Levitt JO. Recalcitrant prurigo nodularis treated successfully with dupilumab. JAAD Case Rep. 2019;5(5):471–3. S2352512619301195. https://doi.org/10.1016/j.jdcr.2019.03.016.
188. Mollanazar NK, Elgash M, Weaver L, Valdes-Rodriguez R, Hsu S. Reduced itch associated with dupilumab treatment in 4 patients with prurigo nodularis. JAMA Dermatol. 2019;155(1):121. https://doi.org/10.1001/jamadermatol.2018.3906.
189. Almustafa Z, Weller K, Autenrieth J, Maurer M, Metz M. Dupilumab in treatment of chronic prurigo: a case series and literature review. Acta Derm Venereol. 2019;99(10):905–6. 5509. https://doi.org/10.2340/00015555-3243.
190. Holm JG, Agner T, Sand C, Thomsen SF. Dupilumab for prurigo nodularis: case series and review of the literature. Dermatol Ther. 2020;33(2) https://doi.org/10.1111/dth.13222.
191. Calugareanu A, Jachiet M, Tauber M, Nosbaum A, Aubin F, Misery L, Droitcourt C, Barbarot S, Debarbieux S, Saussine A, Bagot M, de Masson A, Sénéschal J, Staumont-Sallé D, Bouaziz J-D. Effectiveness and safety of dupilumab for the treatment of prurigo nodularis in a French multicenter adult cohort of 16 patients. J Eur Acad Dermatol Venereol. 2020;34(2) https://doi.org/10.1111/jdv.15957.
192. Kaye A, Gordon SC, Deverapalli SC, Her MJ, Rosmarin D. Dupilumab for the Treatment of Recalcitrant Bullous Pemphigoid. JAMA Dermatol. 2018;154(10):1225. https://doi.org/10.1001/jamadermatol.2018.2526.
193. Seidman JS, Eichenfeld DZ, Orme CM. Dupilumab for bullous pemphigoid with intractable pruritus. Dermatol Online J. 2019;25:13030/qt25q9w6r9.
194. Zhai LL, Savage KT, Qiu CC, Jin A, Valdes-Rodriguez R, Mollanazar NK. Chronic pruritus responding to dupilumab—a case series. Medicines. 2019;6(3):72. https://doi.org/10.3390/medicines6030072.
195. Silverberg JI, Brieva J. A successful case of dupilumab treatment for severe uremic pruritus. JAAD Case Rep. 2019;5(4):339–41. S2352512619300402. https://doi.org/10.1016/j.jdcr.2019.01.024.
196. Simpson EL, Flohr C, Eichenfield LF, Bieber T, Sofen H, Taïeb A, Owen R, Putnam W, Castro M, DeBusk K, Lin C-Y, Voulgari A, Yen K, Omachi TA. Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: A randomized placebo-controlled phase II trial (TREBLE). J Am Acad Dermatol. 2018;78(5):863–871.e11. S0190962218301026. https://doi.org/10.1016/j.jaad.2018.01.017.
197. Guttman-Yassky E, Blauvelt A, Eichenfield LF, Paller AS, Armstrong AW, Drew J, Gopalan R, Simpson EL. Efficacy and Safety of Lebrikizumab a High-Affinity Interleukin 13 Inhibitor in Adults With Moderate to Severe Atopic Dermatitis. JAMA Dermatol. 2020;156(4):411. https://doi.org/10.1001/jamadermatol.2020.0079.
198. Wollenberg A, Howell MD, Guttman-Yassky E, Silverberg JI, Kell C, Ranade K, Moate R, van der Merwe R. Treatment of atopic dermatitis with tralokinumab an anti–IL-13 mAb. J Allergy Clin Immunol. 2019;143(1):135–41. S0091674918308509. https://doi.org/10.1016/j.jaci.2018.05.029.
199. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CEM, Papp K, Puig L, Nakagawa H, Spelman L, Sigurgeirsson B, Rivas E, Tsai T-F, Wasel N, Tyring S, Salko T, Hampele I, Notter M, Karpov A, Helou S, Papavassilis C. Secukinumab in plaque psoriasis—results of two phase 3 trials. N Engl J Med. 2014;371(4):326–38. https://doi.org/10.1056/NEJMoa1314258.
200. Thaçi D, Blauvelt A, Reich K, Tsai T-F, Vanaclocha F, Kingo K, Ziv M, Pinter A, Hugot S, You R,

Milutinovic M. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR a randomized controlled trial. J Am Acad Dermatol. 2015;73(3):400–9. S0190962215016837. https://doi.org/10.1016/j.jaad.2015.05.013.

201. Feldman SR, Green L, Kimball AB, Siu K, Zhao Y, Herrera V, Nyirady J, Alexis AF. Secukinumab improves scalp pain itching scaling and quality of life in patients with moderate-to-severe scalp psoriasis. J Dermatol Treat. 2017;28(8):716–21. https://doi.org/10.1080/09546634.2017.1329502.
202. Yosipovitch G, Soung J, Weiss J, Muscianisi E, Meng X, Gilloteau I, Elewski B. Secukinumab provides rapid relief from itching and pain in patients with moderate-to-severe psoriasis: patient symptom diary data from two phase 3 randomized placebo-controlled clinical trials. Acta Derm Venereol. 2019;99(9):820–1. 5462. https://doi.org/10.2340/00015555-3195.
203. Ahn J, Choi Y, Simpson EL. Therapeutic new era for atopic dermatitis: part 1. Biologics. Ann Dermatol. 2021;33(1):1. https://doi.org/10.5021/ad.2021.33.1.1.
204. Yosipovitch G, Reich A, Steinhoff M, Beselin A, Kent T, Dossenbach M, Berggren L, Henneges C, Luger T. Impact of ixekizumab treatment on itch and psoriasis area and severity index in patients with moderate-to-severe plaque psoriasis: an integrated analysis of two phase III randomized studies. Dermatol Ther. 2018;8(4):621–37. https://doi.org/10.1007/s13555-018-0267-9.
205. Ryan C, Menter A, Guenther L, Blauvelt A, Bissonnette R, Meeuwis K, Sullivan J, Cather JC, Yosipovitch G, Gottlieb AB, Merola JF, Duffin KC, Fretzin S, Osuntokun OO, Burge R, Naegeli AN, Yang FE, Lin C-Y, Todd K, Bleakman AP. Efficacy and safety of ixekizumab in a randomized double-blinded placebo-controlled phase IIIb study of patients with moderate-to-severe genital psoriasis. Br J Dermatol. 2018;179(4):844–52. https://doi.org/10.1111/bjd.16736.
206. Yosipovitch G, Foley P, Ryan C, Cather JC, Meeuwis KA, Burge R, Bleakman AP, Lin C-Y, Malatestinic W, Gottlieb A. Ixekizumab improved patient-reported genital psoriasis symptoms and impact of symptoms on sexual activity vs placebo in a randomized double-blind study. J Sex Med. 2018;15(11):1645–52. S1743609518311664. https://doi.org/10.1016/j.jsxm.2018.09.004.
207. Reich K, Pinter A, Lacour JP, Ferrandiz C, Micali G, French LE, Lomaga M, Dutronc Y, Henneges C, Wilhelm S, Hartz S, Paul C. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S a phase III study. Br J Dermatol. 2017;177(4):1014–23. https://doi.org/10.1111/bjd.15666.
208. Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, Braun D, Banerjee S. Anti–interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med. 2012;366(13):1190–9. https://doi.org/10.1056/NEJMoa1109997.
209. Griffiths CEM, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, Cameron GS, Erickson J, Zhang L, Secrest RJ, Ball S, Braun DK, Osuntokun OO, Heffernan MP, Nickoloff BJ, Papp K. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet. 2015;386(9993):541–51. S0140673615601258. https://doi.org/10.1016/S0140-6736(15)60125-8.
210. Blauvelt A, Papp K, Gottlieb A, Jarell A, Reich K, Maari C, Gordon KB, Ferris LK, Langley RG, Tada Y, Lima RG, Elmaraghy H, Gallo G, Renda L, Park SY, Burge R, Bagel J, IXORA-R Study Group. A head-to-head comparison of ixekizumab vs. guselkumab in patients with moderate-to-severe plaque psoriasis: 12-week efficacy safety and speed of response from a randomized double-blinded trial. Br J Dermatol. 2020;182(6):1348–58. https://doi.org/10.1111/bjd.18851.
211. Gottlieb AB, Gordon K, Hsu S, Elewski B, Eichenfield LF, Kircik L, Rastogi S, Pillai R, Israel R. Improvement in itch and other psoriasis symptoms with brodalumab in phase 3 randomized controlled trials. J Eur Acad Dermatol Venereol. 2018;32(8):1305–13. https://doi.org/10.1111/jdv.14913.
212. Papp KA, Blauvelt A, Bukhalo M, Gooderham M, Krueger JG, Lacour J-P, Menter A, Philipp S, Sofen H, Tyring S, Berner BR, Visvanathan S, Pamulapati C, Bennett N, Flack M, Scholl P, Padula SJ. Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis. N Engl J Med. 2017;376(16):1551–60. https://doi.org/10.1056/NEJMoa1607017.
213. Papp KA, Blauvelt A, Kimball AB, Han C, Randazzo B, Wasfi Y, Shen Y-K, Li S, Griffiths CEM. Patientreported symptoms and signs of moderate-to-severe psoriasis treated with guselkumab or adalimumab: results from the randomized VOYAGE 1 trial. J Eur Acad Dermatol Venereol. 2018;32(9):1515–22. https://doi.org/10.1111/jdv.14910.
214. Thaçi D, Pinter A, Sebastian M, Termeer C, Sticherling M, Gerdes S, Wegner S, Krampe S, Bartz H, Rausch C, Mensch A, Eyerich K. Guselkumab is superior to fumaric acid esters in patients with moderate-to-severe plaque psoriasis who are naive to systemic treatment: results from a randomized active-comparator-controlled phase IIIb trial (POLARIS). Br J Dermatol. 2020;183(2):265–75. https://doi.org/10.1111/bjd.18696.
215. Ruzicka T, Hanifin JM, Furue M, Pulka G, Mlynarczyk I, Wollenberg A, Galus R, Etoh T, Mihara R, Yoshida H, Stewart J, Kabashima K. Anti–interleukin-31 receptor a antibody for atopic derma-

titis. N Engl J Med. 2017;376(9):826–35. https://doi.org/10.1056/NEJMoa1606490.
216. Ständer S, Yosipovitch G, Legat FJ, Lacour J-P, Paul C, Narbutt J, Bieber T, Misery L, Wollenberg A, Reich A, Ahmad F, Piketty C. Trial of nemolizumab in moderate-to-severe prurigo nodularis. N Engl J Med. 2020;382(8):706–16. https://doi.org/10.1056/NEJMoa1908316.
217. Mikhak Z, Bissonnette R, Siri D, Tyring SK, Tessari E, Gandhi R, Fang F, Paolini JF. 560 KPL-716 anti-oncostatin M receptor beta antibody reduced pruritus in atopic dermatitis. J Invest Dermatol. 2019;139(5):S96. S0022202X19308279. https://doi.org/10.1016/j.jid.2019.03.636.
218. Maurer M, Giménez-Arnau AM, Sussman G, Metz M, Baker DR, Bauer A, Bernstein JA, Brehler R, Chu CY, Chung WH, Danilycheva I, Grattan C, Hébert J, Katelaris C, Makris M, Meshkova R, Savic S, Sinclair R, Sitz K, Staubach P, Wedi B, Löffler J, Barve A, Kobayashi K, Hua E, Severin T, Janocha R. Ligelizumab for chronic spontaneous urticaria. N Engl J Med. 2019;381(14):1321–32. https://doi.org/10.1056/NEJMoa1900408.
219. Reszke R, Krajewski P, Szepietowski JC. Emerging therapeutic options for chronic pruritus. Am J Clin Dermatol. 2020;21(5):601–18. https://doi.org/10.1007/s40257-020-00534-y. PMID: 32607945; PMCID: PMC7473844
220. Damsky W, King BA. JAK inhibitors in dermatology: the promise of a new drug class. J Am Acad Dermatol. 2017;76:736–44.
221. Shneider BL, Spino C, Kamath BM, et al. Placebo-controlled randomized trial of an intestinal bile salt transport inhibitor for pruritus in Alagille syndrome. Hepatol Commun. 2018;2:1184–98.
222. Mayo MJ, Pockros PJ, Jones D, et al. A randomized, controlled, phase 2 study of maralixibat in the treatment of itching associated with primary biliary cholangitis. Hepatol Commun. 2019;3:365–81.
223. Hegade VS, Kendrick SF, Dobbins RL, et al. Effect of ileal bile acid transporter inhibitor GSK2330672 on pruritus in primary biliary cholangitis: a double-blind, randomised, placebo-controlled, crossover, phase 2a study. Lancet. 2017;389:1114–23.
224. Al-Dury S, Wahlström A, Wahlin S, et al. Pilot study with IBAT inhibitor A4250 for the treatment of cholestatic pruritus in primary biliary cholangitis. Sci Rep. 2018;8:6658. https://doi.org/10.1038/s41598-018-25214-0.
225. Legat FJ. The antipruritic effect of phototherapy. Front Med. 2018;5:333.
226. Rivard J, Lim HW. Ultraviolet phototherapy for pruritus. Dermatol Ther. 2005;18:344–54.