Pruritus

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"Itch is an unpleasant sensation which evokes the desire to scratch"
Samuel Hafenreffer, 1660

Key Points

- Pruritus is the most common dermatologic symptom and is the main symptom of several dermatoses; it also frequently occurs in systemic diseases
- It may manifest many years before systemic diseases, including malignant ones. In some cases, it is the first symptom of malignant systemic diseases
- Several etiopathologic mechanisms may cause pruritus with peripheral or central origin
- 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.

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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 of dermatologic diseases and also the one that better defines these diseases; additionally, it may be present in several systemic diseases. Pruritus may be disseminated or localized, affecting the skin surface; the squamous epithelium of the conjunctiva, mouth, nose, pharynx, and anogenital region; and the ciliated epithelium of the trachea [2, 3]. This symptom may be intense, even when patients have no visible skin changes. Pruritic areas around the primarily stimulated site that itch even after very weak stimuli are defined as areas of alloknesis [4].

Pruritus may be acute or chronic, the latter occurring, by definition, when the symptom lasts for 6 months or more [5]. Acute pruritus, because it occurs with pain, is a defense mechanism against external harmful agents. Chronic pruritus is difficult to ignore, leading to difficulties concentrating, sleep disorders, absence from school or work, and sometimes suicide attempts in patients with more severe symptoms [3, 6]. Additionally it is associated with a considerable reduction in quality of life and may be as debilitating as chronic pain [7].

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In addition to biological pruritus, triggered by several chemical mediators, itch may be also a psychosocial manifestation resulting from mechanisms of frustration, similar to what happens in nonhuman social animals (grooming) [8].

Epidemiology

Statistical data on the epidemiology of pruritus are scarce, possibly leading to an underestimation of its prevalence. This is because 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 is more frequently diagnosed in Asians than in Caucasians [9–11]. The prevalence of pruritus increases with age, because the elderly population not only usually presents with xeroderma but also has a higher prevalence of systemic problems that cause pruritus [12, 13]. Pruritus is more prevalent among individuals of low socioeconomic status and low income [9].

A cross-sectional study including almost 19,000 adults found a prevalence of 8–9% of acute pruritus in the study population [9] and an association between pruritus and chronic pain [14]. Recent research shows that the prevalence of chronic pruritus is around 13.5% in the general adult population [10] and around 16.8% in a sample of company employees attending a routine medical appointment [12]. In a study of 18,137 individuals with skin diseases, 42% reported having pruritus [15].

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 [16]. The Fourth National Study of Morbidity Statistics from General Practice [17], conducted in Great 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 8–15% of patients [13]. 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 [18]. This symptom may be present in up to 50% of patients with cholestasis, in 80–100% 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 [6]. In dermatologic diseases, the frequency of pruritus is relevant and depends on the underlying disease; it is present, for example, in all patients with urticaria and atopic dermatitis [19].

Classification

Pruritus may be of peripheral or central origin, and the perception of this symptom depends on the neurophysiologic and psychological changes it causes. Patients may report different sensations to define pruritus, such as itch, bite, tingle, perforation, pinch, and burn [6].

A neurophysiologic 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, for example, atopic individuals who present with neurogenic and pruritoceptive pruritus. In 2003 Twycros et al. [3] proposed a neurophysiologic classification:

(a) Pruritoceptive or dermal pruritus: induced by stimulation of C-nerve fibers by different pruritogens. It originates in the skin and may be caused by inflammatory mechanisms, xeroderma, or direct skin damage. It is present in scabies, urticaria, and insect bites
(b) Neuropathic pruritus: resulting from lesions at any point of the afferent nervous pathway,

such as occurs in postherpetic neuralgia, multiple sclerosis, and brain tumors

(c) Neurogenic pruritus: of central origin, but there are no lesions to nervous fibers. It results from an increase in the concentration of endogenous opioids, as in cholestasis and after the administration of exogenous opioids

(d) Psychogenic pruritus: triggered by psychiatric diseases such parasitophobia or by psychological factors such as anxiety disorders

Another classification of pruritus was defined by the International Forum for the Study of Itch (IFSI) in 2007 [5]. This classification is divided into two parts and gives priority to the clinical manifestations of pruritus, distinguishing between disorders with or without skin lesions and 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 lead 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, neurologic 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 the classification, patients were categorized according to their underlying disease, which was divided into several categories:

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

II. 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 such as metabolic or drug-induced

III. Neurologic disease: pruritus caused by "diseases of the central or peripheral nervous system" such as nerve compression, nerve damage, or nerve irritation

IV. Psychogenic or psychosomatic disease: pruritus caused by "psychiatric or psychosomatic disease"

V. Mixed: pruritus caused by the overlap and coexistence of several diseases

VI. 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 for further investigation.

Neurophysiology

The neuronal basis of the mechanisms underlying pruritus is complex and has been elucidated by new discoveries in the 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 [20]. Electrophysiology studies of peripheral nerves in humans and 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 [21].

Pruritoceptors carry impulses toward the dorsal horn of the spinal cord, where they make a synapse with the secondary neuron. 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 [22]. The transection of this ascending pathway impairs itch as well as pain and temperature sensations [23].

Electrophysiologic studies of the neurons of the STT in animal models show that nearly two-thirds of the nociceptive neurons of this tract are not pruritogenic and the other third is. Nonpruritogenic neurons of the STT are activated by mechanical stimuli, heat, or capsaicin, and pruritogenic 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 pruritogenic neurons, i.e., that transmit only the sensation of pruritus [24, 25]. 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 neurologic distinction between nerve cells that cause pain and cells that cause itching [26].

As a hypothesis, itch may result from activity in the pruriceptive neurons in the absence of sufficient activity in nonpruriceptive neurons. The neural circuitry hypothesized to evaluate the relative activity in pruriceptive and nonpruriceptive neuronal populations and to decode itch from pain is unknown, but is likely to reside in supra-segmental regions of the brain [21].

Mediators of Pruritus

Pruritus is triggered by pharmacologic mediators that act on nerve endings, the so-called pruritogenic agents. These pruritogens may be located both peripherally and centrally, and many of them act synergistically, by means of a myriad of mechanisms summarized in Table 61.1.

Table 61.1 Itch mediators and corresponding antipruritic agents

Mediators of pruritus	Antipruritic agent
Histamine	Antihistamines
Serotonin	Paroxetine, fluoxetine, mirtazapine, sertraline, citalopram, 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

Adapted from Hassan and Haji [118]

Histamine is the main peripheral mediator of pruritus, having been acknowledged for more than 60 years, and is secreted by degranulated mast cells and circulating basophils. This substance causes pruritus by directly stimulating nerve endings and also by interacting with H1 receptors present in C fibers [27], leading to vasodilation and edema [27]. There are other histamine receptors, such as H2 and H3, but these are not linked to the mediation of pruritus, although there has been an improvement of pruritus in patients with urticaria with the use of some H2 blockers. Histamine type 4 receptor (H4), present in dendritic cells, mast cells, and eosinophils, is involved in allergic inflammation [28] 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 [28]. The role of histamine in pruritic diseases such as urticaria, reactions to insect bites, skin mastocytosis, and some drug eruptions has already been established [2, 3]. However, this substance is not the main pruritogenic agent in systemic diseases, which is evidenced by the low response of patients with these diseases to antihistamine therapy [29].

Serotonin is a less potent pruritogenic agent than histamine. Its peripheral action is due to the release of histamine from mast cells [30], and 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 [3].

Substance P is synthesized in the body of C-type neurons and transported through peripheral nerve endings. Intradermal injection of substance P causes pruritus, edema, and erythema, resulting in the release of tumor necrosis factor α (TNF-α),

leukotriene B4, histamine, and prostaglandin D2 [31]. In atopic dermatitis, serum levels of substance P are elevated and correlated to disease severity [32]. This neuropeptide acts through the neurokinin 1 (NK1) receptor pathway. A study conducted by Costa et al. showed that aprepitant, the NK1 receptor antagonist, was tested as a potential antipruritic agent in Sézary syndrome [33]. Depletion of this substance by capsaicin is one of the mechanisms of controlling pruritus and pain [24].

Prostaglandins, considered in isolation, are not pruritogenic agents, but may potentiate the effect of histamine and of other mediators of pruritus [35]. The use of cyclooxygenase inhibitors does not improve pruritus in the general patient population, but appears to be useful in patients with human immunodeficiency virus (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 [36].

Cytokines: The involvement of *interleukin 2* (IL-2) 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 [37]. 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. High levels of *interleukin-31* (IL-31) are present in the skin of patients with atopic dermatitis and prurigo nodularis, indicating that this substance may be a possible cause of pruritus in patients with these conditions [38, 39].

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 antihistamine agent) [40] 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 [41], but is not affected by antihistamines [41]. Additionally it has been demonstrated that the stimulation of κ-opioid receptors blocks the effect of μ-receptor agonists [42], showing that opioid-induced pruritus may be the balance of the interaction between the system of receptors μ and κ. 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 [43]. When activated, these fibers secrete substance P, which activates mast cells, thus closing the cycle that stimulates pruritus [4]. Upregulation of PAR-2 receptors has been observed in patients with atopic dermatitis [43].

Transient receptor potential channels (*TRP*): These molecules are calcium-permeable channels that 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 [44]. Evidence suggests that TRPV1 is a fundamental integrating element in pruritic and pain pathways. It has been discovered that sensory neuronal activation by histamine and PAR2 receptor also involves the activation/sensitization of TRPV1, that TRPV1 expression is amplified in keratinocytes of prurigo nodularis, and that stimulation of TRPV1 channels releases multiple pruritoceptive mediators such as interleukins and neuropeptides [45]. It has been postulated that TRPV3 might be a regulator and/or cotransducer of TRPV1-mediated pruritus and pain. A study by Stokes et al. [46] 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 icilin stimulate TRPM8 [47];

Neurotrophin and nerve growth factor (*NGF*) is overexpressed in prurigo nodularis and its therapeutic administration is pruritogenic [48]. In atopic dermatitis, NGF is released by keratinocytes, mast cells, and fibroblasts, and plasma levels of NGF are also elevated and correlate with disease activity [49]. In addition, expression of neurotrophin-4 is elevated in the cutaneous lesions of patients with atopic dermatitis and prurigo nodularis [48, 49].

Endocannabinoids and cannabinoid receptors: 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. [50] This suggests that CB1 signaling may be involved in initiation of itch.

Corticotropin-releasing hormone (*CRH*) and its analog, urocortin, lead to histamine release upon intradermal injection [51]. CRH is also involved in mast cell degranulation occurring during periods of acute stress. The exact function played by leukotrienes in itch is unclear. Studies have reported the use of leukotriene receptor antagonists zileuton and zafirlukast for antipruritic action in atopic dermatitis [52]

Calcitonin gene-related peptide: Many neurons of the dorsal root ganglion coexpress substance P, calcitonin gene-related peptide (CGRP), and PAR2. CGRP plays a modulatory role in inflammation and pruritus. It would seem that CGRP has an inhibitory effect on substance P-induced itching as it prolongs itch latency following injection [53], but increased levels of CGRP are seen in atopic dermatitis, nummular eczema. and prurigo nodularis [53]. Like substance P, CGRP-mediated itch may result from mast cell activation.

Acetylcholine (*ACh*) is a neurotransmitter which binds to both muscarinic and nicotinic receptors. In mice, activation of the muscarinic M3 receptors causes pruritus [54]. Intracutaneously injected ACh caused itch in atopic eczema [55]. Histamine-sensitive as well as histamine-insensitive C-nerve fibers are stimulated by ACh. Atopic dermatitis patients are more sensitive to ACh and less sensitive to histamine than normal subjects [54].

Clinical Presentation

Pruritus in Systemic Diseases

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 50% of patients complaining of pruritus and without apparent dermatologic lesions at the time of the medical visit have its etiology identified [56], showing that pruritus may precede the diagnosis of the underlying disease by years.

There are many etiologic hypotheses for the several manifestations of pruritus in systemic diseases, some of which have not yet been confirmed. This is one of the main reasons why the treatment of this symptom is still difficult and often does not give a definitive solution for the patient. Patient follow-up and a good doctor–patient relationship are essential to manage this symptom, which in most cases is extremely debilitating and has no curative treatment. Symptoms are summarized in Table 61.2.

Table 61.2 Systemic diseases that can induce pruritus (examples)

Metabolic and endocrine diseases	Chronic renal disease
	Liver diseases with or without cholestasis
	Hyperparathyroidism
	Hyper- and hypothyroidism
	Carcinoid syndrome
	Iron deficiency
Infective diseases	HIV and AIDS
	Parasitoses
Hematologic disorders	Polycythemia vera
	Leukemia
	Lymphoma (Hodgkin's lymphoma, cutaneous lymphoma)
Neurologic diseases	Multiple sclerosis
	Brain tumors
	Notalgia paresthetica
	Brachioradial pruritus
	Postzosteric neuralgia
Psychiatric or psychosomatic diseases	Depression
	Affective disorders
	Hallucinosis
	Obsessive and compulsory disorders
	Schizophrenia
	Eating disorders

Adapted from Weisshaar et al. [85]

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 [57, 58]. 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 [59], 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 [57]. Although plasma concentrations of histamine are higher in uremic patients than in nonuremic 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 $5HT_3$ receptors [60]. Studies obtained controversial results on the improvement of chronic kidney disease-associated pruritus with the use of opioid antagonists. Ultraviolet B (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 22–90% of patients with severe renal failure complains 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 [62], 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 20–50% 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 [63]. In addition to pruritus, these patients show postinflammatory hyperpigmentation on 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 it leads the patient to think about suicide and becomes one of the indications for liver transplantation [62].

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 [64]. 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 phenothiazine, estrogens, and tolbutamide. Extrahepatic bile duct obstruction may also cause pruritus [2, 62].

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 [65]. 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, is a specific finding for cholestatic pruritus but not for other types of systemic pruritus [66]. 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 the binding of this drug to the pregnane X receptor, which inhibits ATX expression [66].

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 [65].

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 pruritus 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 [67, 68].

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 [69].

Polycythemia vera: Approximately 50% of patients with polycythemia vera complain of pruritus [70] characterized by the sensation of "biting" and usually triggered by contact with water (aquagenic pruritus). Pruritus may precede the 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 [70]. Other studies show that the release of high levels of histamine resulting from the increased number of basophil granulocytes may trigger pruritus [68]. Pruritus appears to be more pronounced in patients with the JAK2V617 mutation [71].

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 [68, 69]. 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. Dermatologic 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 [69]. Several factors, such as the secretion of leukopeptidases and bradykinin, histamine, and high immunoglobulin E levels deposited in the skin, may contribute to pruritus in lymphomas [68, 69].

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 [69].

Systemic mastocytosis: Causative agents of degranulation of mast cells cause generalized pruritus in these patients [68].

Cutaneous T-cell lymphoma (*CTCL*) encompasses a diverse group of diseases characterized by malignant T lymphocytes that initially home to the skin. Mycosis fungoides is the most common variant and Sézary syndrome the rarest [72]. A characteristic hallmark of CTCL, especially Sézary syndrome, is pruritus, the sensation of itch which is repeatedly observed in various CTCL types [73, 74]. 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 [73, 74]. Pruritus as a symptom is almost invariably present in CTCL progressing into generalized erythrodermic mycosis fungoides 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 unknown. 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 who are resistant to therapy. Further research is mandatory to unravel the molecular mechanisms and provide more specific treatment of pruritus in CTCL [75].

Pruritus in Endocrinologic Diseases

Pruritus is present in several endocrinologic diseases such as hyperthyroidism, hypothyroidism, diabetes mellitus, multiple endocrine neoplasia, carcinoid syndrome, and hyperparathyroidism [69].

Hyperthyroidism: Four percent to 11% of patients with thyrotoxicosis present with pruritus [76, 77]. Triggering mechanisms may include: (1) activation of kinins in the skin; (2) decrease of itch threshold due to vasodilation; and (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 symptoms [76].

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 [78].

Carcinoid syndrome: Patients with carcinoid syndrome may present with pruritus combined with flushing, diarrhea, and cardiac symptoms [76].

Primary hyperparathyroidism: A substantial number of patients with primary hyperparathyroidism complain of pruritus [77]. The pathophysiology of pruritus in this disease is not well known, although these patients usually present with deficiency of vitamin D and minerals such as 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 [6]. 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 one-third of patients seeing a dermatologist have emotional and psychosocial factors involved in their disease; however, there is still great reluctance to include psychiatric treatment as part of the management of dermatoses [3, 7]. It is extremely important to raise awareness of these diseases and to provide appropriate guidance to patients, despite their reluctance.

Pruritus in Neurologic Diseases

Neurologic diseases such as multiple sclerosis, focal lesions, tumors, abscesses, and stroke may include pruritus as part of their clinical picture. Localized neurologic 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 [79].

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 dermatologic 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 [80, 81].

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. In addition, 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 [80].

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 Dermatologic Diseases

Dermatologic 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, prurigus, and lichen planus, but analyzing the specific approaches for these diseases beyond the remit of this chapter.

Pruritus Ani

Anal and perianal pruritus affects 1–5% of the general population in the proportion of four males to one female [82]. 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 dermatologic lesion, or secondary to hemorrhoids, anal fistulas and fissures, psoriasis, contact eczema, lichen sclerosus, sexually transmitted diseases, parasitosis, and neoplasms. Primary causes include dietary factors such as 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 [82]. Patients with severe pruritus require high-potency corticosteroids and sometimes topical immunomodulators such as tacrolimus [69].

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 symptoms 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 [69].

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 [69].

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 [83]. 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 [84]. Drugs that may induce or maintain chronic pruritus are listed in Table 61.3.

Table 61.3 Drugs that may induce or maintain chronic pruritus (without a rash)

Class of drug	Substance (examples)
ACE inhibitors	Captopril, enalapril
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, doxepin, fluoxetine, fluvoxamine, imipramine, lithium, mirtazapine, nortriptyline, paroxetine, sertraline
Antidiabetic drugs	Glimepiride, metformin
Antihypertensive drugs	Clonidine, doxazosin, hydralazine, methyldopa, prazosin, reserpine
Anticonvulsants	Carbamazepine, clonazepam, gabapentin, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid
Anti-inflammatory drugs	Acetylsalicylic acid, celecoxib, diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam
AT II antagonists	Irbesartan, telmisartan, valsartan
β-Blockers	atenolol, bisoprolol, metoprolol, nadolol, pindolol, propranolol
Bronchodilators, mucolytic agents, respiratory stimulants	Aminophylline, doxapram, ipratropium bromide, salmeterol, terbutaline
Calcium antagonists	Amlodipine, diltiazem, felodipine, nifedipine, nimodipine, verapamil
Diuretics	Amiloride, furosemide, hydrochlorothiazide, spironolactone, triamterene
Hormones	Clomifene, danazol, oral contraceptives, estrogens, progesterone, steroids, testosterone and derivatives, tamoxifen
Immunosuppressive drugs	Cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus, thalidomide
Antilipids	Clofibrate, fenofibrate, fluvastatin, lovastatin, pravastatin, simvastatin
Neuroleptics	Chlorpromazine, haloperidol, risperidone
Tranquilizers	Alprazolam, chlordiazepoxide, lorazepam, oxazepam, prazepam
Uricostatics	Allopurinol, colchicine, probenecid

Adapted from Weisshaar et al. [85]

Diagnosis

The first step in the therapeutic approach of pruritus is attempting to evaluate whether itch is attributed to a dermatologic cause or to an underlying disease. In a practical approach, patients with pruritus may be divided into the following groups: (1) patients with primary pruritic dermatologic disease; (2) patients with dermatologic lesions secondary to pruritus; (3) patients with pruritus and without dermatologic lesions [85]. In most cases, no systemic diseases are found in patients with generalized pruritus, who are classified as patients with pruritus sine materia [85, 86] (Tables 61.4 and 61.5).

In patients with pruritic dermatologic disease, the diagnosis and management of pruritus aims to treat the dermatosis [85–90]. However, in individuals who have no dermatologic 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 [85–90].

Table 61.4 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 topical and systemic drugs

Table 61.5 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)

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 [85–90]. 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, and 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 [85]. When several family members are affected, scabies or other parasites should be considered. The relationship between pruritus and special physical activities are suggestive 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 cutis and asteatotic eczema (Table 61.4).

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 occurred, the period of the day when the disease worsens, whether pruritus is intermittent or continuous, and 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 symptoms [85, 86] (Table 61.5).

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 of both 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. [19] 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 involves the search for dermatologic lesions that characterize pruritic dermatosis, xeroderma, jaundice, weight loss, hematomas, and excoriations caused by scratching [85–87]. General physical examination also should include palpation of the liver, kidneys, spleen, and lymph nodes.

Laboratory tests: 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, and qualitative urine test. Other tests, such as immunoelectrophoresis, may also be performed in cases of clinical suspicion of the disease [85, 86].

Imaging tests: Chest X-ray and full abdominal ultrasound. Other tests may be requested according to clinical suspicion or medical judgment [85].

Histopathologic tests may sometimes elucidate the diagnosis, but are not routinely performed [85].

Patients with generalized pruritus and normal test results should be periodically monitored because they may present with malignant disease or other systemic diseases later in life, with pruritus as 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.

Therapeutic Approach

Considering that pruritus has various causes, there is no standardized recommendation for treatment. Topical and systemic therapies should be individualized, taking into account age, previous diseases, current medications, allergies, pruritus severity, and impact on quality of life [88, 89]. According to recent studies, the therapy should also address both cutaneous and central mechanisms of pruritus (Fig. 61.1).

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, nonexposure to contact allergens, discontinuation of a medication, treatment of systemic, neurologic, or psychiatric diseases, and even surgical treatments for removal of an underlying tumor [88, 89]. 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 [88]. We should keep in mind that, in some cases, there is no totally effective therapy for itch relief. Therefore, patient counseling on measures for relieving pruritus is essential. Xeroderma occurs in a great number of these patients and should

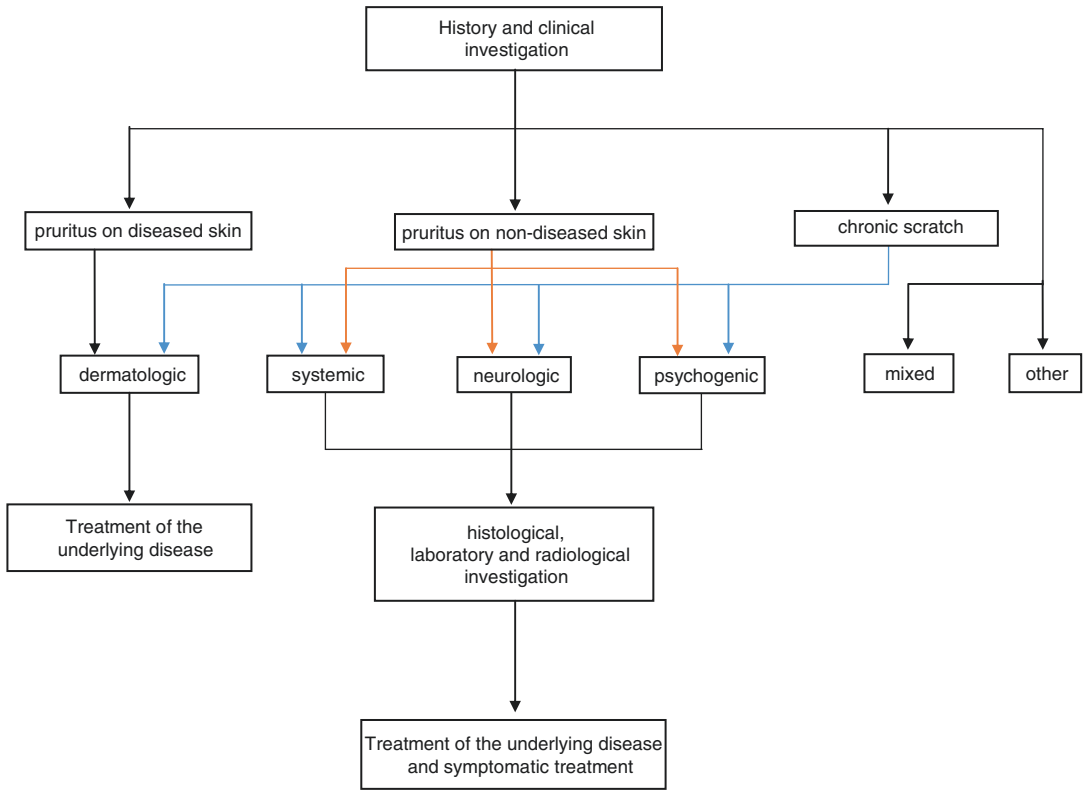

Fig. 61.1 Algorithm for the assessment of pruritus (Adapted from Weisshaar et al. [88])

always be addressed with the use of emollients. Being careful with active substances that may cause skin irritation and increase pruritus is also important. 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 intake of alcohol and spicy foods help alleviate the symptom [88, 89]. It should be considered that chronic pruritus is often caused by several factors and may be intensified by many cofactors, suggesting a multifactorial origin [90].

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 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

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 [85]. 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 the 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, such as in severe atopic dermatitis [91]. In this 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 [92].

Corticosteroids are not antipruritic agents, acting only in situations where the pruritus is caused by inflammatory skin reaction. In randomized clinical trials, moderate- to high-potency glucocorticoids have been proved to be an effective treatment for inflammatory skin diseases, such as atopic eczema, psoriasis, lichen planus, and genital lichen sclerosus et atrophicus [85]. 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 [93]. Usually its concentration varies from 0.025% to 0.075%. However, irritation on the injection site is a side effect, greatly limiting its utilization. Topical capsaicin is proven as an effective treatment for notalgia paresthetica and for hemodialysis patients with localized pruritus, as well as for patients with brachioradial pruritus [34, 79].

Menthol: Topical menthol relieves itching by activating cold-sensitive Aδ fibers, which are responsible for transmitting a cool sensation through the activation of a transient receptor potential cation channel subfamily M member 8 (TRPM8) [47]. 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 [94].

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 [3].

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 a number of cases. In a randomized clinical trial with chronic kidney disease-associated pruritus,

pramoxine 1% cream significantly reduced pruritus when compared with the isolated vehicle [95]. The 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 [96]. However, a common adverse effect of these agents is a burning sensation that begins a few days after repeated application of the product.

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 [97]. Potential adverse events include sleepiness and allergic contact dermatitis.

Systemic Treatment

Antihistamines: Sedating antihistamines, which are H1-receptor antagonists, are the most often used drugs in medical practice as a first-line therapy for pruritus, despite the shortage of clinical trials proving their efficacy for pruritic diseases, with the exception of urticaria. The benefit observed in medical practice may result from the sedative action of these medications, which can help patients with sleeping problems and relieve the symptoms. Nonsedating histamine H1- and H2-receptor antagonists have limited efficacy in the treatment of chronic pruritus [85, 98]. Antihistamines have little effect on hemodialysis patients and patients with cholestatic disease [57, 61].

Neuroactive drugs: Structural analogs to the neurotransmitter γ-aminobutyric acid, such as gabapentin and pregabalin, 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 with placebo [99]. Case reports show that these drugs may also be used in the treatment of postherpetic neuralgia, brachioradial pruritus, and prurigo nodularis [86]. The most common adverse events are constipation, weight gain, sleepiness, ataxia, and blurred vision.

Opioid agonist-antagonists: In patients with chronic urticaria, atopic eczema, and cholestasis, μ-opioid antagonists (naltrexone, nalmefene, and naloxone) have shown antipruritic effects [100]. Naltrexone and naloxone were effective for resistant itching associated with uremia and cholestasis. In randomized controlled trials conducted in Japan, nalfurafine hydrochloride (a κ-opioid agonist) significantly reduced itching in hemodialysis patients with chronic kidney disease [101, 102]. However, some studies involving patients with chronic kidney disease have shown inconsistent results [103, 104]. According to reports, butorphanol, a μ-opioid antagonist and κ-opioid agonist administered via intravenous route and approved by Food and Drug Administration for migraine treatment, reduced intractable pruritus associated with non-Hodgkin lymphoma, cholestasis, and the use of opioids [105]. Initial adverse effects of these agents, such as nausea, loss of appetite, abdominal colic, diarrhea, and insomnia, limit their utilization.

Tricyclic antidepressants: Serotonin reuptake inhibitors (paroxetine, sertraline, fluvoxamine, and fluoxetine) have been used to reduce psychogenic pruritus and various types of generalized pruritus [106]. A double-blind study demonstrated the efficacy of sertraline (daily dose of 100 mg) for the treatment of cholestatic pruritus [107]. Studies have suggested that the antidepressant mirtazapine (daily dose of 15 mg) may relieve nocturnal itching related to some types of cancer [108]. 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 symptoms [109]. Tricyclic antidepressants, such as amitriptyline, have also been used in the treatment of chronic pruritus (neuropathic and psychogenic forms, for example) [85]. 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 [3]. Ondansetron, a serotonin receptor antagonist, has been used for controlling pruritus in patients with cholestasis and hemodialysis patients. Case reports have shown important benefits, while randomized controlled trials have not demonstrated the same relevance.

Sodium cromoglycate: A mast cell stabilizer that has effects on the improvement of pruritus in patients with Hodgkin's lymphoma [110].

Rifampicin is 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 [111].

Cholestyramine reduces the levels of bile salts through chelation in the intestinal lumen. It is indicated in the treatment of cholestatic pruritus, but does not work when there is bile duct obstruction. It may also be used in hemodialysis patients [112].

Activated charcoal has shown positive results in relieving pruritus in hemodialysis patients with pruritus, at a daily dose of 6 g [112].

Thalidomide it 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% [113, 114].

Phototherapy: Observational studies have suggested that narrow-band UVB (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 [115, 116]. In a randomized clinical trial involving patients with refractory itch secondary to chronic kidney disease [117], 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 [112].

Psychotherapeutic treatments may be used in cases of psychogenic pruritus. Some patients with pruritus that is difficult to control have depressive symptoms and may also benefit from psychotherapeutic treatment.

Glossary

Amyelinic C fibers One of three classes of nerve fiber in the central nervous system and peripheral nervous system. There are a myriad of mediators capable of stimulating these afferent nerves leading to itch, including biogenic amines, proteases, cytokines, and peptides. Some of these mediators can also evoke sensations of pain, and the sensory processing underlying both sensations overlaps in complex ways.

Capsaicin An active component of chili peppers, which are plants belonging to the genus *Capsicum*. Capsaicin is used to help relieve a certain type of pain known as neuralgia.

JAK2V617 mutation The *JAK2*V617 mutated allele is present in virtually all patients with polycythemia vera (PV) and in about 60% of those with essential thrombocythemia (ET) and primary myelofibrosis (PMF), which are the other two main clinical entities included within the group of myeloproliferative neoplasms. The presence of the mutation, and/or the burden of *JAK2*V617 allele, has been found to correlate with defined laboratory abnormalities and clinical features in the different myeloproliferative neoplasms.

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