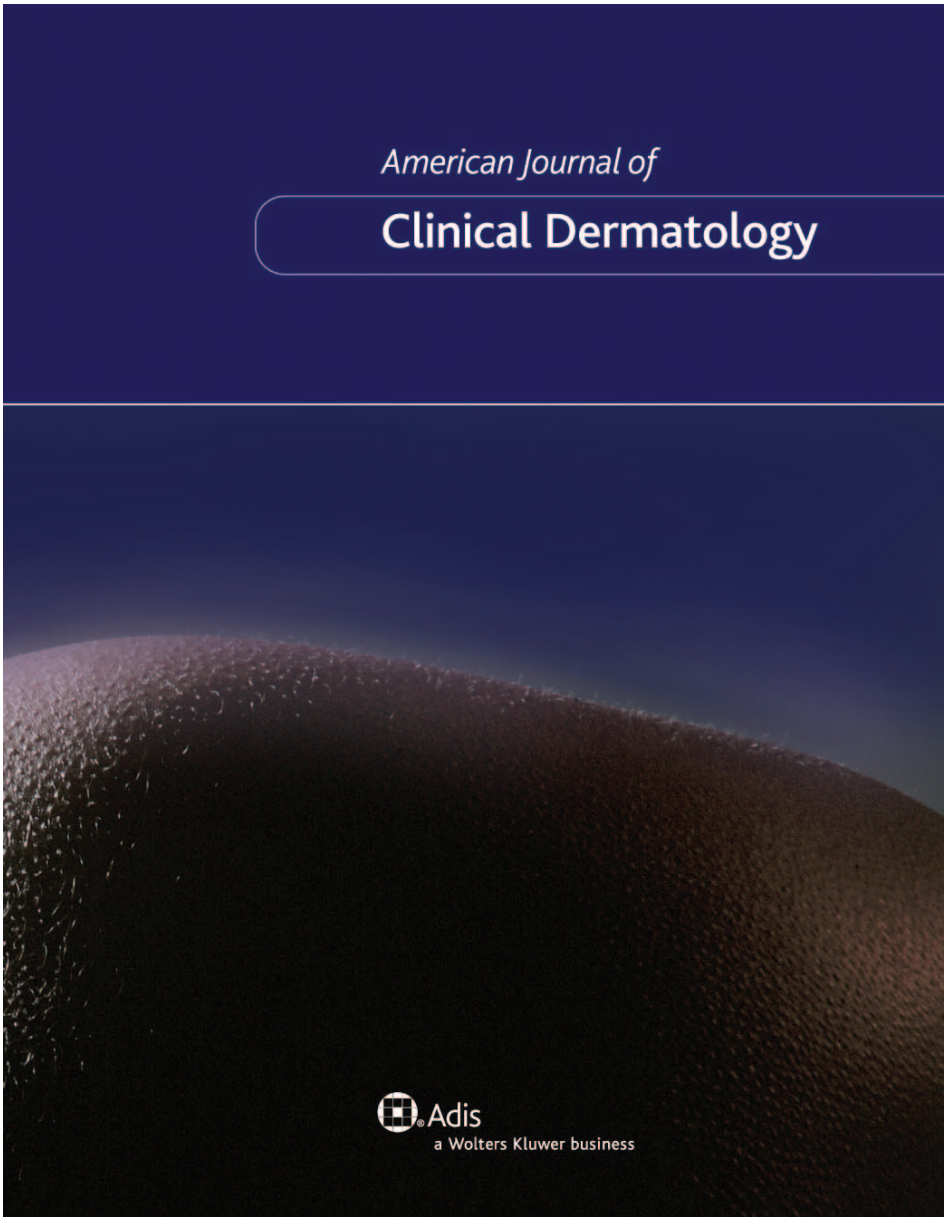

REVIEW ARTICLE

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Chronic Pruritus in the Absence of Specific Skin Disease

An Update on Pathophysiology, Diagnosis, and Therapy

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Abstract

Chronic pruritus is a major and distressing symptom of many cutaneous and systemic diseases and can significantly impair the patient's quality of life. Pruritus perception is the final result of a complex network involving dedicated nerve pathways and brain areas, and an increasing number of peripheral and central mediators are thought to be involved. Itch is associated with most cutaneous disorders and, in these circumstances, its management overlaps with that of the skin disease. Itch can also occur without associated skin diseases or primary skin lesions, but only with nonspecific lesions secondary to rubbing or scratching. Chronic itch with no or minimal skin changes can be secondary to important diseases, such as neurologic disorders, chronic renal failure, cholestasis, systemic infections, malignancies, and endocrine disorders, and may also result from exposure to some drugs. The search for the cause of pruritus usually requires a meticulous step-by-step assessment involving careful history taking as well as clinical examination and laboratory investigations.

Few evidence-based treatments for pruritus are available. Topical therapy, oral histamine H_1 receptor antagonists, and phototherapy with UV radiation can target pruritus elicitation in the skin, whereas antiepileptic drugs, opioid receptor antagonists, and antidepressants can block signal processing in the CNS.

Pruritus is defined as an unpleasant sensation inducing the desire to scratch.[1] It is a major and distressing symptom of numerous and diverse cutaneous and systemic diseases. In some instances, pruritus is not associated with skin diseases or specific skin changes, but only with lesions secondary to rubbing or scratching and even with no or minimal skin changes. Chronic itch, defined on the basis of a duration of 6 weeks or more, may be difficult to diagnose and manage, and may have a strong impact on the quality of life of patients.[1] This review focuses on recent advances in understanding the pathophysiology of itch, as well as on the diagnostic and therapeutic management of chronic itch not associated with skin diseases.

1. Neurophysiology of Itch

1.1 Skin-Nerve Interactions and Itch

The skin is highly innervated by primary sensory nerves, postganglionic cholinergic parasympathetic and postganglionic sympathetic nerves, resulting in a complex cutaneous afferent/efferent neuronal network. Itch-specific fibers are unmyelinated C fibers, mainly peptidergic, with slow conduction velocity and large innervation territories.[2] They account for about 5% of the afferent C fibers in human skin, respond to histamine and thermal stimuli but are insensitive to mechanical stimuli. Nerve fibers usually end at the dermal-epidermal junction, but some unmyelinated C fibers also project into the epidermis to the subcorneal layers.[3] Therefore, nerve fibers may reciprocally communicate with all skin cell types. The number of peripheral and central mediators thought to be involved in the generation of an itch sensation is rapidly increasing (table I). Opioid receptors, especially μ- and κ-receptors, modulate pruritus perception in the CNS and in the skin.[4] Activation of μ-opioid receptors stimulates itch perception, whereas activation of κ-opioid receptors suppresses itch perception. Keratinocytes can release mediators with both pruritic and antipruritic effects, including endovanilloids, endorphins, neuropeptides, proteases, and cytokines, and express on their cell surface the receptors for several itch mediators such as histamine, neuropeptides, neurotrophin, cannabinoids, nerve growth factor, proteinase-activated receptor-2, and the transient receptor potential vanilloid 1 ion channel (TRPV1). Physical (e.g. dry skin, skin barrier disruption) and chemical stimuli can induce keratinocytes to release pruritogenic or antipruritogenic substances.[3,5,6]

1.2 Spinal and Central Processing of Itch

Pruritoceptive primary afferent fibers activate spinal neurons in lamina I of the dorsal horn, which projects to the lateral part of the thalamus.[7] Substance P and calcitonin gene-related peptide are the most studied neurotransmitters, and present both peripheral and central activity.[8,9] In addition, a recent study in an animal model has proposed a relevant role for gastrin-releasing peptide in the spinal transmission of itch stimuli.[10] Direct excitatory connections from the thalamus project to the anterior cingulated cortex, insular cortex, and primary and secondary somatosensory cortices.[11] Histamine-induced itch produces the co-activation of some motor areas, suggesting the existence of an organic link between itch and scratching.[12] In contrast to pain sensation, which induces an 'avoiding' motor response, pruritus evokes an 'active' scratching motor activity. The inhibition of itch by painful stimuli can occur at both the central and peripheral levels. It is commonly observed in patients with severe pruritus who stop scratching when skin lesions start bleeding and become painful. Conversely, spinal administration of opioids suppresses pain and induces segmental severe itch. Some mediators of itch (e.g. substance P, neuropeptides) can also induce pain.[13] Itch and pain share the same cortical brain areas, but a different pattern of activation exists. Itch processing is characterized by a weaker activation of somatosensory cortices with a stronger activation of ipsilateral motor areas as compared with pain processing.[14,15]

2. Classification of Itch

Two recently proposed classifications of pruritus are based on the neurophysiologic origin of pruritus or the clinical picture and symptoms of the patient. Twycross et al.[16] classified itch into four categories: (i) pruritoceptive (originating in the skin); (ii) neuropathic (lesioned neurons themselves generate itch); (iii) neurogenic (central mediators generate itch without neuronal damage); and (iv) psychogenic (somatoform). Psychogenic pruritus should be suspected only after cautious exclusion of other causes. It is advisable that an expert in psychosomatics or

Table I. Principal peripheral and central mediators involved in the generation or modulation of itch (modified from Paus et al.,[3] with permission)

Mediators	Sources	Function
Acetylcholine	Autonomic cholinergic nerves, keratinocytes, lymphocytes, melanocytes, dermal fibroblasts, endothelial cells	Peripheral induction of itch, especially in atopic dermatitis
Calcitonin gene-related peptide	Sensory nerve fibers	Central modulation of itch and sensitization of nerve endings
Neurokinins, substance P	Sensory nerve fibers	Regulation of nerve growth factor expression and substance release from mast cells
Pituitary adenylate cyclase-activating polypeptide, vasoactive intestinal polypeptide	Nerve fibers, lymphocytes, endothelial cells, Merkel cells	Induces release of histamine
Gastrin-releasing peptide	Small and medium-size dorsal root ganglion	Itch sensation in the dorsal spinal cord
Corticotrophin-releasing hormone, pro-opiomelanocortin	Keratinocytes, mast cells	Release of histamine and of many cytokines
Nerve growth factor, brain-derived neurotrophic factor, neurotrophin-4	Keratinocytes, mast cells, fibroblasts, eosinophils	Induction of chemotaxis of eosinophils and inhibition of apoptosis in atopic dermatitis
TNFα, IL-1, IL-6, IL-31	Leukocytes, keratinocytes, endothelial cells, nerves	Upregulated in atopic dermatitis and prurigo nodularis
Endocannabinoids	Nerves, immune cells, keratinocytes, hair follicles	Peripheral antipruritic activity
Endovanilloids	Sensory neurons, mast cells, epidermal and hair follicle keratinocytes, Langerhans cells, smooth muscle cells, sebocytes	Induction and modulation of itch and pain
Opioids	Nerves, keratinocytes	Central induction of pruritus. Increased μ-receptor expression in atopic dermatitis
Kallikreins, proteases	Keratinocytes, endothelial cells, mast cells, platelets	Kallikreins may induce itch, while chymases degrade itch mediators
Histamine	Mast cells, keratinocytes, leukocytes	Stimulates specific itch fibers
Prostaglandins	Sensory nerve fibers, keratinocytes	Itch induction
Leukotriene B4	Sensory nerve fibers, keratinocytes	Itch induction

IL = interleukin; **TNF** = tumor necrosis factor.

psychiatry should confirm the diagnosis of somatoform pruritus independent of any other organic origin.[17] Psychological factors may influence itch perception or can complicate chronic itch even in the absence of a true psychiatric morbidity.

The International Forum for the Study of Itch (IFSI) distinguished three clinical groups of patients: (i) pruritus on primarily inflamed skin; (ii) pruritus on normal skin; and (iii) pruritus with chronic nonspecific secondary scratch lesions.[1] These three groups can be further classified into six subtypes after clinical and laboratory assessment (table II). Pruritus without skin changes has been previously named 'essential pruritus' or 'pruritus sine materia.' It has been recommended that these two definitions should no longer be used because they may generate confusion.[1] Indeed, most patients with chronic pruritus unrelated to skin diseases have skin lesions secondary to scratching or simply skin dryness. Therefore, it is very important to distinguish a definite skin disease from nonspecific (scratch- or rubbing-induced) skin changes. Pruritus is the most common symptom of most inflammatory skin disorders (e.g. atopic dermatitis, psoriasis, contact dermatitis, urticaria, drug reactions, pemphigoid, dermatitis herpetiformis), parasitic or infectious diseases (e.g. scabies, mycoses, chickenpox), as well as cutaneous T-cell lymphoma.

Nonspecific skin lesions associated with chronic itch include linear excoriations and crusts, skin marking (i.e. lichenification), and excoriated papules and nodules up to the picture of prurigo nodularis.[18] Prurigo nodularis is dominated by the presence of numerous excoriated papules and nodules, leaving hyperpigmented macules on the extensor surface of the limbs and the back.[18] In many cases it is an idiopathic disorder, but in some cases, prurigo nodularis may be the expression of atopic dermatitis or persistent insect bite reactions, and can also be

Table II. Etiologic classification of itch according to the International Forum for the Study of Itch (data from Ständer et al.[1])

Subtype	Relevant examples
Dermatologic: arising from skin; dry skin and any specific skin disease	**Inflammatory:** contact dermatitis, atopic dermatitis, asteatotic eczema, nummular eczema, stasis dermatitis, seborrheic dermatitis, urticaria, psoriasis, lichen planus, drug reactions, polymorphous light eruption, mastocytosis, pemphigoid, dermatitis herpetiformis, dermatomyositis **Infections:** pediculosis, scabies, parasitic disease, tinea corporis, impetigo, smallpox **Neoplastic:** cutaneous T-cell lymphomas **Dermatoses of pregnancy:** pruritic urticarial papules and plaques of pregnancy, prurigo of pregnancy, pemphigoid gestationis
Systemic: arising from diseases of organs other than the skin, metabolic or other multifactorial disturbances or from drugs	**Endocrine and metabolic disorders:** chronic renal failure (dialysis), liver diseases with or without cholestasis, thyroid diseases **Infections:** HIV, parasites, hepatitis C virus **Hematologic diseases:** polycythemia vera, lymphomas **Tumors:** solid organ tumors, carcinoid **Drug-induced pruritus** (with or without cholestasis)
Neurologic (neurogenic/neuropathic): arising from disorders of the central or peripheral nervous system and possibly also from liver disease	Multiple sclerosis; spinal or cerebral neoplasms, abscesses, or infarcts; phantom itch; postherpetic neuralgia; transverse myelitis; notalgia paresthetica; brachioradial pruritus; meralgia paresthetica; other conditions associated with nerve damage, compression or irritation, such as entrapment neuropathy, radiculopathy, or polyneuropathy (including diabetes mellitus, vitamin B_{12} deficiency, etc.)
Psychogenic/psychosomatic	Delusion of parasitosis, psychogenic excoriations, somatoform pruritus, associated with psychiatric disorders
Mixed	Coexistence of dermatologic and neurologic itch in HIV-infected patients or in patients with atopic dermatitis, association of uremic itch with skin xerosis, association of Hodgkin disease with potentially misleading paraneoplastic cutaneous manifestations, such as unexplained adult-onset eczema
Other (of unknown origin)	Senile 'idiopathic' pruritus, aquagenic 'idiopathic' pruritus, pruritus in anorexia nervosa

diagnosed in patients with systemic infections such as hepatitis C virus (HCV), HIV, atypical mycobacteria infections, lymphoproliferative diseases (lymphoma), solid tumors (bladder and gastric cancer), and other diseases.[18] Patients with prurigo nodularis have a high frequency of psychiatric morbidity.[19]

3. Diagnostic Work-Up for Chronic Pruritus with Nonspecific Skin Signs

The management of pruritus with nonspecific skin signs may be difficult, time consuming, and frustrating for both the patient and the physician. Patients must be informed about the complexity of this symptom and about the likelihood of step-by-step assessments as needed. At first, the characteristics of pruritus (timing, location, severity, relieving and exacerbating factors) should be recorded and a complete physical examination aimed at excluding a dermatologic condition and detecting signs suggestive of a systemic cause should be performed. The dermatologic examination should carefully evaluate the presence of any cutaneous changes, including minimal lesions, dermographism, complications of scratching, and skin xerosis, the latter being a relevant cause or co-factor of chronic itch. A thorough medical history should be collected with emphasis on drug exposure, travel history (to exclude endemic infections), contact with environmental irritating and sensitizing substances, lifestyle (diet, substance abuse, working activity, hobbies, etc.), concomitant extracutaneous symptoms, prior hospitalizations, or recent use of volume expanders (such as hydroxyethyl starch)[20] [table III]. Mental state and personality characteristics should also be investigated.

Initial laboratory investigations may include total and differential blood count, liver and renal function tests, lactate dehydrogenase, serum glucose, iron, ferritin, thyroid function tests, erythrocyte sedimentation rate, protein electrophoresis, and urinalysis. Chest x-ray, ultrasound examination of abdomen, and stool examinations for occult blood, ova, and parasites can also be considered.[21,22] Serum tumor markers are not adequate to detect an occult cancer, with the exception of prostate-specific antigens.[23] If a food additive intolerance is

suspected, an elimination diet and placebo-controlled oral challenges with the food additive may be tried, but they are difficult to complete.[24]

4. Neuropathic Itch: Brachioradial Pruritus and Notalgia Paresthetica

Localized recalcitrant pruritus without skin changes can be secondary to neurologic causes. In particular, peripheral nerve damage is implicated in anogenital pruritus secondary to lumbosacral radiculopathy,[25] and may be involved in brachioradial pruritus,[26] and notalgia paresthetica.[27]

Brachioradial pruritus is usually localized on the dorsolateral aspect of the upper arm and/or forearm, often occurring in fair-skinned people living in the tropics or subtropics. The ice-pack sign (relief with the application of ice packs) is nearly pathognomonic for this condition.[28] The causative pathophysiologic basis may be neurologic damage from either the peripheral nerves (e.g. solar radiation, local injury) or from the central sensory pathways (e.g. cervical spine disease with spinal root or cord compression). The role of sunlight as a trigger in some patients, along with the involvement of photo-exposed areas of the forearm, especially in the summer, and the association with signs of actinic damage, have contributed to the concept of brachioradial pruritus as a possible photo-induced condition.[29]

Notalgia paresthetica is a sensory neuropathy involving the dorsal spinal nerves. Several factors responsible for notalgia paresthetica have been hypothesized: increased dermal innervation, viscerocutaneous reflex mechanism, chemical neurotoxicity, and spinal nerve injury caused by trauma or entrapment. Patients with notalgia paresthetica have a characteristic hyperpigmented patch on their back, usually in the interscapular region.[27,29,30] Meralgia paresthetica, an entrapment neuropathy of the lateral femoral cutaneous nerve, may present with prominent numbness, paresthesia, and pain, and more rarely with true itch, in the anterolateral thigh.[31]

5. Relevant Clinical Examples of Pruritus Associated with Systemic Diseases

5.1 Uremic Pruritus

Pruritus is present in 15–49% of patients with chronic renal failure and in up to 90% of patients receiving dialysis.[32] The pathogenesis is still obscure but present data point

Table III. Relevant information to be collected from a patient's history

Item	Examples and/or comments
Personal and family history of cutaneous and extracutaneous disorders	Atopy, hypersensitivity reactions, and systemic diseases
Previous and concomitant drugs	
Surgical procedures or recent hospitalizations	Use of volume expanders (hydroxyethyl starch)
Travel history	Infections or infestations that are endemic in particular geographic areas
Work and leisure activities	Exposure to irritating or sensitizing substances, fiberglass, mineral wool, biotic agents, etc.
Lifestyle and personal habits	Eating, smoking, alcohol consumption, drug abuse and addiction, sexual history, indoor environment, etc.
History of spinal injury	Arthritis, trauma, or chronic repetitive microtrauma (in presence of a suspected 'neuropathic' itch)
Mental state and personality characteristics	
Recent development of other symptoms and/or signs, including but not limited to:	The following conditions should be suspected:
burning, pain, stinging, tingling, paresthesia, hypoesthesia or hyperesthesia, numbness, muscle weakness, cramps	sensory or sensorimotor neuropathy (neuroanatomic damage)
motor deficits	brain lesions
nocturnal sweating, fever, unexplained weight loss	Hodgkin lymphoma
weight loss	malignancies of various origin, HIV infection, malabsorption, hyperthyroidism
fatigue	malignancies, HIV infection, anemia
nausea, anorexia, malaise, fatigue	cholestasis
flushing and diarrhea	carcinoid syndrome

toward a central role of the immune and opioidergic systems. Hemodialysis-related pruritus seems to be induced by an immune system derangement, resulting in a proinflammatory state.[33] An imbalance in the opioidergic system, with hyperactivity of μ-opioid receptors, has also been observed.[1,2,33] Other factors may include calcium-phosphate imbalance, hyperparathyroidism, anemia, higher serum levels of histamine, and peripheral neuropathy.[32,33] In two-thirds of patients, pruritus is generalized, while in the others it is localized, particularly on the back. In nearly half of patients it appears on a daily basis, whereas in the other half it occurs more rarely. Some patients report pruritus during or soon after dialysis.[33] Pruritus and its severity seem to correlate with duration of dialysis and skin dryness, but without general agreement.[32,33] Chronic pruritus is a strong independent predictor of poor quality of life and of severe sleep disturbances in dialysis patients.[34,35]

Many attempts have been made to relieve this bothersome symptom; however, with generally limited success.[36] Patients may benefit from the regular use of emollients to control skin xerosis.[33] Sedating antihistamines may be helpful, but no randomized controlled trials (RCTs) support their use.[33] Thalidomide, gabapentin, and nalfurafine, a κ-opioid receptor agonist, have proven to be effective in RCTs, but the potential toxicity associated with these drugs limits their use.[37-39] Some studies demonstrated that UVB is still the treatment of choice in moderate to severe pruritus, but the need for regular sessions of therapy over the dialysis treatment may be impractical for many patients.[40,41] General considerations regarding treatment of uremic pruritus are reported in table IV.

Table IV. Treatments for uremic pruritus

General measures[32,33]
Regular use of emollients (even in patients who do not have pruritus)
Cool environment, loose clothes, avoid wool and artificial fibers
Improvement in the efficiency of the dialysis technique
Correction of the alterations of calcium-phosphorus metabolism
Parathyroidectomy can be considered in the case of secondary hyperparathyroidism
Topical treatments in localized mild pruritus[32,33]
Emollients
Capsaicin[a]
Phototherapy with UVB[32,33,40,41]
Treatment of choice in moderate to severe uremic pruritus
Broad-band UVB more effective than narrow-band UVB
Systemic approaches in generalized pruritus[36-39]
Thalidomide[a]
Gabapentin[a]
Nalfurafine[a]

a Efficacy proven in randomized placebo-controlled trials.

5.2 Cholestatic Pruritus

Cholestasis refers to a reduction in bile flow, which may be due to extra-hepatic (usually obstructive) or intra-hepatic causes (e.g. primary sclerosing cholangitis, primary biliary cirrhosis, chronic hepatitis, malignant tumors, pregnancy).[42] A large number of drugs may induce cholestasis, with or without liver injury, after weeks to months from the start of treatment.[43] Pruritus can occur in up to 80% of patients with primary biliary cirrhosis.[44] The pathogenesis of cholestasis-associated pruritus remains poorly understood, and may be multifactorial. Peripherally acting pruritogens (bile acids) and altered central neurotransmission have been implicated.[43,44]

The management of cholestatic pruritus has been extensively reviewed, and current recommendations are summarized in table V.[44,47] Naloxone, naltrexone, rifampin (rifampicin), colestyramine (cholestyramine), and phenobarbital (phenobarbitone) are recommended as agents of choice by the American guidelines for the treatment of pruritus in primary biliary cirrhosis.[44] However, the available RCTs have been conducted in small numbers of patients, are few in number, and have used heterogeneous methods. Cumulative evidence from pooled RCTs suggests that rifampin and opioid antagonists demonstrate a reduction in pruritus, whereas there are insufficient data to judge the efficacy of colestyramine.[45] Some evidence also supports the use of the serotonin reuptake inhibitor sertaline[46] and ursodeoxycholic acid,[47] with the latter drug being the mainstay of therapy in primary biliary cirrhosis.

5.3 Pruritus Accompanying Systemic Infections Including HIV Infection

Pruritus may be a symptom of cutaneous and extracutaneous infection, as well as of intestinal parasitic infestation. In particular, certain viral infections may have a prominent role in chronic pruritus.

Pruritus is one of the most frequent symptoms encountered in HIV infection and can even be the first clinical symptom. It can be isolated or associated with different skin diseases (such as seborrheic dermatitis, atopic dermatitis, psoriasis, eosinophilic folliculitis) or may result from the release of pruritogenic mediators, neurologic disturbances, drug intake, or systemic disorders (lymphoma, infections, infestations).[48] The immune dysregulation can cause the perturbation of cytokine milieu, with a trend towards a predominant T helper-2 response. For

this reason, eosinophilia is not an uncommon finding. An important skin rash is the pruritic papular eruption, which is correlated with the magnitude of immunodeficiency.[49] Some case series showed that the prevalence of prurigo nodularis was higher in patients with CD4-positive cell counts of <200 cells/mm^3 and among patients not receiving highly active antiretroviral therapy (HAART), whereas patients with HIV viral loads >55 000 copies/mL had a higher prevalence of 'idiopathic' pruritus.[50] Some HIV-associated pruritic skin diseases may be ameliorated by HAART. Both psoralen plus UVA (PUVA) and UVB have proven to be successful in HIV-associated pruritus, with UVB preferred over PUVA due to safety reasons.[40,48,49] Other symptomatic treatments have mostly been used in small case series or uncontrolled studies.[48] Some reports support the efficacy of thalidomide for the treatment of prurigo nodularis in HIV-infected patients, who appear, however, particularly prone to developing peripheral neuropathy.[51]

Pruritus has been reported in up to 15% of patients with chronic HCV infection, and may be a presenting symptom. The pathogenesis of HCV-related itch is still obscure. Chronic hepatitis with moderate to severe fibrosis has been suggested to result in low-grade cholestasis, with pruritus resulting from the disappearance of the bile duct. In the absence of cholestasis, itch may be an adverse effect of antiviral therapy, as it happens in up to 29% of patients treated with interferon-α plus ribavirin.[52] Both HIV and HCV infection are associated with prurigo nodularis.[18]

5.4 Malignancy-Related Pruritus

Pruritus can be present as a paraneoplastic syndrome in association with some solid tumors including lung, colon, breast, stomach, and prostate. In the palliative care setting, pruritus has been estimated to affect 5–27% of patients.[53]

Table V. Treatments for pruritus associated with cholestasis[44-47]

Drug	Dosage	Possible adverse effects	Notes
First-line medical approach[a]			
Naloxone	0.2 μg/kg/min IV infusion preceded by 0.4 mg IV bolus	Opioid withdrawal-like syndrome	Transient adverse effects in a significant proportion of patients in RCTs
Naltrexone	Day 1, 25 mg PO bid, then 50 mg/day PO	Opioid withdrawal-like syndrome, potential hepatotoxicity	Transient adverse effects in a significant proportion of patients in RCTs
Rifampin (rifampicin)	300–600 mg/day PO	Hepatotoxicity (controversial data about real risk)	Adverse effects similar to placebo in RCTs
Colestyramine (cholestyramine)	4–16 g/day PO	Constipation, bloating, malabsorption, interaction with many drugs	Adverse effects similar to placebo in RCTs
Phenobarbital (phenobarbitone)	2–5 mg/kg/day PO	Sedation	
Surgical management of biliary obstruction when indicated			
Stenting or removal of gallstones			
Other approaches[b]			
Medical treatments			
Anticholestatic agents: ademetionine (S-adenosylmethionine); ursodeoxycholic acid (not effective in primary biliary cirrhosis-associated pruritus; apparently effective and safe in cholestasis of pregnancy)			
Cannabinoids (dronabinol)			
Antidepressants: sertraline			
UVB phototherapy			
Others: anesthetics: propofol, lidocaine (lignocaine); bright-light therapy towards the eyes; antioxidants; androgens (danazol)			
Invasive procedure in patients resistant to medical therapies (tried in a small number of cases)			
Nasobiliary drainage or partial external diversion of bile; ileal diversion; hemodialysis; charcoal hemoperfusion; plasmapheresis and plasma perfusion; extracorporeal albumin dialysis, with molecular adsorbent recirculating system; plasma separation and anion adsorption			

a Shown to be effective in RCTs.

b Only open-label trials or RCTs in small series of patients.

bid = twice a day; **IV** = intravenous; **PO** = orally; **RCTs** = randomized controlled trials.

The pathogenesis is complex and may involve central and peripheral mechanisms, including the production of pruritogenic substances by the tumor or itch induced by drugs used in palliative care (opioids).[54] Malignancy-related pruritus is usually generalized. In some patients, localization of pruritus correlates with the site of the tumor: carcinomas of the cervix, rectum/sigmoid colon, and prostate may present with pruritus of the vulva, anus, and scrotum, respectively.[55] In these cases, pruritus may derive from direct activation of peripheral nerve fibers at tumor sites.[56] Brain or spinal tumors may manifest with facial or nasal itch, and dermatomal itch, respectively.[57,58]

Pruritus is common in patients with hematologic malignancies. Itch is reported by about 30% of patients with Hodgkin disease, especially those with the nodular sclerosing subtype. It is considered a B symptom, and can precede any identifiable sign of the tumor by up to 5 years.[55] Nearly half of patients with polycythemia vera have pruritus, either spontaneous or soon after contact with water (aquagenic pruritus), especially at high temperature; and in more than 20% of patients it can persist despite adequate disease control. Other than true itch sensation, aquagenic pruritus is accompanied by stinging or pin-point sensations lasting 10–30 minutes after contact with water, and in most cases is a transient benign disorder. Aquagenic pruritus, which seems to be more common among polycythemia vera JAK2 617V>F homozygous patients, may be the sole marker of the disease and can appear as many as 3–5 years before the true onset of the disease.[59,60] Aquagenic pruritus has also been described in patients with acute lymphoblastic leukemia, and myelodysplastic syndrome alone or in association with T-cell non-Hodgkin lymphoma.[60] Generalized pruritus has also been reported in patients with other hematologic malignancies, such as chronic lymphocytic leukemia, non-Hodgkin lymphoma, and multiple myeloma.[61,62]

5.5 Endocrine Disorders and Iron Deficiency

Pruritus can be associated with thyroid abnormalities (hyperthyroidism more frequently) and with diabetes mellitus. Hypothyroidism, hypoparathyroidism, and pseudohypoparathyroidism can cause pruritus secondary to severe skin dryness.[63] Although the relationship between diabetes and pruritus is still controversial, some reports suggest an increased frequency of vulvar pruritus only in women with poorly controlled diabetes.[63] However, diabetes may cause neuropathy, and consequently can be implicated in neuropathic itch.

Iron deficiency is another well known cause of chronic pruritus. High rates of this association have been recently reported, suggesting the opportunity to include ferritin and iron studies among the routine examinations of patients with chronic pruritus of apparently unknown origin.[64] Pathogenic mechanisms remain unknown. Restoring the serum ferritin within the normal range through iron supplementation has been reported to be helpful. In any case, the presence of iron deficiency should lead to the exclusion of any condition responsible for such a deficiency, including malignancies.[64]

5.6 Drug-Induced Pruritus

Pruritus occurs in 10–50% of patients receiving intravenous administration of opioids, and in 20–100% of patients when opioids are given by epidural or intraspinal injections. Postulated mechanisms include a direct central effect, as well as histamine and serotonin release.[65] An extensive review of numerous RCTs investigating the therapeutic approach to opioid-induced itch has been recently published.[65] Few drugs can be used to treat established opioid-induced pruritus. Histamine H_1 receptor antagonists have little effect.[65] Intravenous nalbuphine and propofol significantly reduced opioid-induced itch in adults undergoing surgery (RCTs).[66] Nalbuphine seems to be more effective than propofol (RCT).[67] Ondansetron diminished postoperative itch and vomiting after opioid administration[68] and was also found to attenuate intrathecal fentanyl-induced pruritus.[65] Prevention of opioid-induced itch can also be obtained with low doses of opioid antagonists (naloxone, naltrexone, and nalmefene), but they may reverse the analgesic effects.[66,69,70] An agonist/antagonist drug such as nalbuphine can reduce pruritus without compromising analgesia.[71] Of note, recent RCTs have shown that premedication with either mirtazapine or gabapentin is capable of preventing pruritus caused by intrathecal morphine.[72,73]

Essentially any other drug may cause an adverse reaction in the skin, which can be associated with pruritus. Pruritic reactions are usually morbilliform or urticarial; however, a growing number of drugs can induce pruritus without any skin rash.[74,75] No universally accepted method for assessing the causality of an adverse drug reaction has been approved.[76] A congruous temporal sequence between the beginning of drug therapy and onset of itch, improvement after drug withdrawal, and recurrence after drug rechallenge are useful elements.[74,76] Drug-induced pruritus is likely to be underestimated in the general population, and especially in elderly patients, and it can be misdiagnosed as senile 'idiopathic' pruritus.[75,76] Antihypertensive drugs, especially angiotensin converting enzyme inhibitors, can induce pruritus alone, or pruritus associated with angioedema and other pruritic cutaneous disorders (i.e. urticaria, maculopapular and lichenoid eruptions).[77] In the elderly,

drug-induced pruritus is frequently observed in patients taking multiple medications, which may more easily induce adverse effects because of impaired metabolism and/or pharmacologic interactions. A list of the principal drugs able to induce pruritus without skin changes is given in table VI.

Table VI. Principal drugs able to induce pruritus without skin changes[43,74,75,77]

Drug group	Examples
Antihypertensive drugs	ACE inhibitors[a]
	Angiotensin II antagonists (sartans)[a]
	β-Adrenoceptor antagonists (β-blockers)[a]
	Calcium channel blockers[a]
	Methyldopa
	Sildenafil[a]
Antiarrhythmic drugs	Amiodarone[a]
Anticoagulants	Ticlopidine[a]
	Fractionated heparins
Antidiabetic drugs	Biguanides[a]
	Sulfonylurea derivates
Hypolipemic drugs	HMG-CoA reductase inhibitors (statins)
Antibacterials and chemotherapeutics	Penicillins[a]
	Cephalosporins
	Macrolides[a]
	Carbapenems[a]
	Monobactams
	Quinolones
	Tetracyclines[a]
	Lincosamides[a]
	Streptogramins
	Metronidazole
	Rifampin (rifampicin)
	Thiamphenicol
	Trimethoprim/sulfamethoxazole (cotrimoxazole)[a]
	Antimalarials
Psychotropic drugs	Tricyclic antidepressants[a]
	Selective serotonin reuptake inhibitors
	Antipsychotics[a]
Antiepileptic drugs	Carbamazepine
	Fosphenytoin
	Oxcarbazepine
	Phenytoin
	Topiramate
Cytostatics	Chlorambucil
	Paclitaxel
	Tamoxifen
Cytokines, growth factors, and monoclonal antibodies	Granulocyte-macrophage colony-stimulating factor
	Interleukin-2
	Matuzumab
	Lapatinib
	Epidermal growth factor receptor inhibitors
Plasma volume expanders	Hydroxyethyl starch
Others	Antithyroid agents[a]
	NSAIDs[a]
	Corticosteroids[a]
	Sex hormones[a]
	Opioids
	Inhibitors of xanthine oxidase

a Can induce cholestatic liver injury.

6. General Considerations in the Treatment of Pruritus

Removal of the causative agent, whenever possible, and appropriate treatment of the underlying disease is essential. Skin care measures to alleviate skin dryness such as use of moisturizers, reduction in frequency of bathing, humidification of dry indoor environments, prevention of excessive sweating, and avoidance of hot baths, soap, and irritant fabrics are generally recommended.[21] In particular, the skin of elderly people benefits from regular use of emollients.[21,22] Improper use of topical medications (e.g. corticosteroids for prolonged periods, possible sensitizing agents such as topical antihistamines and anesthetics) must be avoided.

6.1 Targeting Pruritus Elicitation in the Skin

Dermatologic itch must be managed through treatment of the specific skin disorder or skin changes. Irresistible episodes of pruritus can be controlled by application of cold compresses and wet dressings with topical corticosteroids.[78] Topical antipruritics such as camphor, menthol, oatmeal baths, and polidocanol are commonly used, but evidence from RCTs is lacking.

Oral antihistamines are frequently prescribed in the case of any pruritic condition, sometimes as an *ex juvantibus* criterion. Sedative and/or anti-inflammatory qualities of certain H_1 receptor antagonists are thought to be useful to control itch. However, with the exception of urticaria and mastocytosis, the role of antihistamines for the management of other pruritic disorders is still controversial.[79,80] Nevertheless, a recent retrospective analysis of 67 patients with chronic pruritic dermatoses or chronic pruritus of unknown origin has shown good antipruritic effects with high-dosage nonsedating H_1 receptor antagonists, used as monotherapy or in combination.[81]

Phototherapy with various UV sources, especially UVB, is widely used in patients with chronic pruritus. It has a wide anti-inflammatory cutaneous activity, and can offer relief without many of the adverse effects and risks of systemic medications. Its efficacy has been demonstrated in some RCTs.[40,41,82,83]

Some itchy conditions (e.g. notalgia paresthetica, prurigo nodularis, aquagenic pruritus, and also uremic pruritus) may respond to topical capsaicin, a substance binding to the TRPV1

Table VII. Principal systemic therapies for pruritus other than antihistamines

Medication	Dosage	Indication	Adverse effects
Fluvoxamine	25 mg/day PO for 3 days then 50–100 mg/day PO as needed	Various pruritic diseases[95]	Drowsiness, vertigo, fatigue, headache, sexual dysfunction, nausea, vomiting
Gabapentin	300–1800 mg/day PO; in dialysis patients, 100–300 mg PO after every dialysis session may be sufficient	Neuropathic,[25] uremic itch[a][36,37,87]	Drowsiness, constipation
Mirtazapine	15–45 mg/day PO	Generalized pruritus[93]	Drowsiness, increased weight and appetite, dry mouth
Naloxone	0.2 μg/kg/min IV infusion daily preceded by 0.4 mg IV bolus over 24 hours	Cholestatic itch[a][44,45]	Hepatotoxicity, nausea and vomiting, difficulty sleeping, reversal of analgesia
Naltrexone	Day 1, 25 mg bid, then 50 mg/day PO	Cholestatic itch[a][44,45]	Hepatotoxicity, nausea and vomiting, difficulty sleeping, reversal of analgesia
Paroxetine	20 mg/day PO	Malignancy-related pruritus[a],[94] other pruritic diseases[95]	Insomnia, sexual dysfunction
Phototherapy: UVA plus psoralen, UVB	Must be individually determined	Prurigo nodularis[a],[82,83] uremic pruritus[a][40,41]	Burns, photodamage, skin cancer
Thalidomide	100–200 mg/day PO	Prurigo nodularis, uremic pruritus[a][39]	Teratogenic, peripheral neuropathy, drowsiness, constipation

a Randomized controlled trials available.

bid = twice a day; **IV** = intravenous; **PO** = orally.

receptor. TRPV1 receptors are nonselective heat-activated cation channels, located in the CNS and in cutaneous nerve fibers. They are involved in the transmission and modulation of itch. Capsaicin induces desensitization of nerve fibers, inhibition of neuropeptide accumulation, and suppression of painful and pruritic sensations.[84] Topical calcineurin inhibitors (tacrolimus and pimecrolimus), which are approved for treatment of atopic dermatitis, have been found to bind to TRPVl on cutaneous nerve fibers, and to cause an initial release of substance P and calcitonin gene-related peptide from primary afferent nerve fibers.[84] This effect explains the transient burning occurring during the first days of treatment. Topical calcineurin inhibitors are useful for treating the pruritus associated with some dermatoses, such as atopic dermatitis.

Thalidomide, which can be useful in the treatment of prurigo nodularis, actinic prurigo, as well as uremic pruritus, acts as an immunomodulatory drug, a tumor necrosis factor-α inhibitor, and also a peripheral and central nerve depressant, but has an unfavorable safety profile.[39]

Novel approaches to dermatologic itch, which deserve further evaluation, are H_4 receptor antagonists,[80] topically applied opioid receptor antagonists,[85] and cannabinoid receptor agonists such as palmitoylethanolamide, stearoylethanolamide, and stearoylisopropylamide.[86]

The treatment of prurigo nodularis is particularly challenging. Phototherapy (UVB, oral PUVA) has been proven to be effective and safe in a RCT, but the need for regular sessions of therapy is impractical for many patients.[83] No RCTs are available with any other drug, including emollients, corticosteroids, topical capsaicin, topical tacrolimus, cyclosporine (ciclosporin), thalidomide, naltrexone, antidepressants, and oral retinoids.[18] Results are variable, but long-term combinations and rotational treatments can be effective.

6.2 Targeting Pruritus Elicitation in the CNS

Gabapentin, carbamazepine, and derivatives, commonly used as antiepileptic drugs, are capable of blocking the neuropathic afferent pathway and therefore may be helpful in neuropathic itch. Gabapentin was also recently proven to be well tolerated and effective in the treatment of uremic pruritus and various pruritic disorders.[37,87] Its mechanism of action is unclear and has been hypothesized to be both central and peripheral. Gabapentin and pregabalin inhibit release of calcitonin gene-related peptide from primary afferent neurons through an increase of GABA in the spinal cord.[87] Compared with gabapentin, pregabalin is characterized by a more rapid response, but evidence from RCTs in the treatment of pruritus is lacking.[88]

Opioid receptor antagonists, such as naloxone and naltrexone, have an important influence on the neurogenic component of itch by inhibiting itch transmission. Systemically administered opioid receptor antagonists showed antipruritic effects not only in hepatogenic pruritus, but also in hydroxyethyl starch-induced pruritus and various pruritic skin diseases, such as atopic dermatitis, cutaneous lymphoma, and prurigo nodularis.[89,90] However, adverse effects and costs lead to considering these drugs as a second-line approach to chronic pruritus. Butorphanol possesses both κ-agonist activity and μ-antagonist activity, and has been successfully used in small case series of patients with intractable pruritus.[91]

Antidepressants directly influence central pruritus perception by as-yet unknown mechanisms. It is speculated that they interfere in the neuronal reuptake of neurotransmitters, such as serotonin and norepinephrine, and thereby reduce pruritus perception. Accordingly, tricyclic (e.g. amitriptyline, clomipramine, doxepin) and tetracyclic (e.g. mirtazapine) antidepressants have been employed with some success in chronic pruritus and prurigo nodularis.[18,92,93] Doxepin and mirtazapine have additional antihistaminic effects. The selective serotonin reuptake inhibitor paroxetine was reported to have antipruritic effects in polycythaemia vera, psychogenic pruritus, paraneoplastic pruritus, and idiopathic pruritus in a small RCT.[94] A recent open-label study supports the usefulness and good tolerability of paroxetine and fluvoxamine in patients with chronic pruritus.[95] Paroxetine may produce a variety of cutaneous and noncutaneous adverse effects requiring adequate monitoring of the patient.[96]

A list of the most frequently used systemic therapies for pruritus, other than antihistamines, is given in table VII.

7. Conclusions

Pruritus is a very common and sometimes disabling symptom. Pruritus not associated with skin disorders or specific skin changes may be a symptom indicating the presence of an important disease. The diagnostic approach to patients with chronic itch may be complex and require multi-disciplinary interactions. New studies are shedding light on the complex mechanisms that induce chronic itch, and are revealing that multiple mediators may be involved in complex interactive pathways. The management of chronic severe itch is difficult and to be successful may require combination therapy for prolonged time periods.

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