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Chronic Pruritus in the Absence of Skin Disease: Pathophysiology, Diagnosis and Treatment

American Journal of Clinical Dermatology

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Am J Clin Dermatol. 2016;17(4):337-348.

Abstract and Introduction

Abstract

Chronic pruritus arises not only from dermatoses, but also, in up to half of cases, from extracutaneous origins. A multitude of systemic, neurological, psychiatric, and somatoform conditions are associated with pruritus in the absence of skin disease. Moreover, pruritus is a frequently observed side effect of many drugs. It is therefore difficult for physicians to make a correct diagnosis. Chronic pruritus patients frequently present to the dermatologist with skin lesions secondary to a long-lasting scratching behavior, such as lichenification and prurigo nodularis. A structured clinical history and physical examination are essential in order to evaluate the pruritus, along with systematic, medical history-adapted laboratory and radiological tests carried out according to the differential diagnosis. For therapeutic reasons, a symptomatic therapy should be promptly initiated parallel to the diagnostic procedures. Once the underlying factor(s) leading to the pruritus are identified, a targeted therapy should be implemented. Importantly, the treatment of accompanying disorders such as sleep disturbances or mental symptoms should be taken into consideration. Even after successful treatment of the underlying cause, pruritus may persist, likely due to chronicity processes including peripheral and central sensitization or impaired inhibition at spinal level. A vast arsenal of topical and systemic agents targeting these pathophysiological mechanisms has been used to deter further chronicity. The therapeutic options currently available are, however, still insufficient for many patients. Thus, future studies aiming to unveil the complex mechanisms underlying chronic pruritus and develop new therapeutic agents are urgently needed.

Introduction

Causing an intense need to scratch, pruritus (itch) is described as an unpleasant sensation that has a large impact on patients' quality of life. Pruritus is considered to be the most frequent symptom in dermatology. It is important to differentiate between the acute induction of pruritus, such as through histamine release following contact with certain plants or animals, or an allergic reaction after application of a drug or stimuli in an experimental model, and chronic forms of pruritus (CP; pruritus lasting for >6 weeks), which can be caused by many clinical conditions.[1,2] Peripheral and central sensitization processes are examples of complex mechanisms that take place in chronic pruritus.[2] Of note, up to half of patients with CP have presented lacking primary skin lesions but suffering mainly from pruritus of extracutaneous origins, such as that found in lymphoproliferative or neurological disorders.[3,4] Many of these patients presented to the dermatologist with secondary skin symptoms ranging from dry, irritated skin to severe scratch lesions. It is therefore essential for dermatologists to be familiar with the most important underlying diseases and drugs that can cause chronic pruritus.

Pathophysiology

Research has, in recent years, yielded fundamental new insights into various aspects of pruritus, including the causes, transmission, and involvement of mediators, receptors, and nerve fibers. We thus have an improved understanding of its pathogenesis, although certain aspects, such as the clinical assignment of an individual mechanism to various pruritic diseases, remain to be investigated in future research endeavors. The skin itself has an immense role in the induction and maintenance of pruritus even in the absence of a visible skin disease. An example of this can be seen in polycythemia vera, a disease characterized by elevated erythrocyte levels, for which pruritus is a classic symptom in 50 % of patients. A specific mutation (JAK2 V617F) of this disease affects cutaneous mast cells, causing increased degranulation following contact with water. Our current knowledge on the pathophysiology of itch is therefore important for better understanding its clinical presentation.

From the Periphery to the Central Nervous System

The skin is not primarily affected, but may instead be secondarily involved in the pathological processes behind CP when a visible skin disease is absent. In such instances, scratching, rubbing, and other mechanical responses are employed to counterbalance the itch. Scratching may not only result in excoriations and damage to the tissue, but also lead to inflammation, thus promoting nerve fiber activation and increasing itch intensity. This forms the basis of an enduring itch–scratch cycle. Keratinocytes,

fibroblasts, and certain immune system cells (mast cells, macrophages, eosinophils, neutrophils) release pruritogenic substances during inflammation.[5,6] A group of known pruritogens, consisting of histamine, tryptase, neurotrophins, leukotrienes, nerve growth factor, interleukins, and tumor necrosis factor, are known to stimulate a dense sensory network composed of peripheral cutaneous nerve fibers.[6] Epidermal and subepidermal, unmyelinated, mechano-insensitive C-fibers (CMi-fibers) and mechanoheat sensitive C-fibers (CMH-fibers) are both involved in the transmission of itch.[7,8] CMi-fibers express H1 receptors, which can be activated by histamine to signal itch, as well as heat TrpV1 receptors. CMH-fibers express TrpV1 and mucunain receptors (proteinase-activated receptor 2 [PAR2]). Cowhage, a substance present in the tropical legume *Mucuna pruriens*, is also known to activate them. CMH-fibers have an important role in the transmission of diverse nociceptive and non-nociceptive sensations (e.g., burning, stinging, and tingling).[7,9]

Pruritus can be signaled by certain central pathways at the spinal cord level.[6] Neurons that express gastricreleasing peptide receptors (GRPR) found in the lateral spinothalamic tract function in pruritus, but not in pain transmission.[5] Interestingly, neurokinin-1 receptors can transmit both pain and pruritus and are expressed by neurons found in the same tract.[5] A suppression of itch is, furthermore, thought to be caused by interneurons at the spinal level (e.g., the $Bhlbh5^+$ and $Prdm8^+$ interneurons found in mice). An impairment of these inhibitory neurons can lead to chronicity processes that perpetuate symptoms following an acute pruritic event.[5] Following the arrival of axons from the spinothalamic tract in the thalamus, neuronal signals are transmitted to cortical and subcortical brain regions.[5,6] Somatosensory centers and the regions of the brain responsible for processing emotions, attention, and motor activity (e.g., scratching behavior) have been activated during experimental pruritic stimulation. Interestingly, different brain activation patterns are produced by pruritus transmitted through different peripheral nerve fibers (i.e., CMi- and CMHfibers).[5]

The multidimensional qualities of pruritus can be explained by the various pruritogens, peripheral and central receptors, nerve fibers, and central pathways that are involved in itch induction. Different therapeutic approaches are thus required due to the multitude of pathophysiological mechanisms associated with pruritus arising from different factors.[5,10] Complex chronic processes are believed to occur in the central nervous system, resulting in the perpetuation of pruritus following an acute pruritic event, for which an impaired inhibition at the spinal level[11] and central sensitization processes[5,12] are suspected to play an important role.

Chronic Pruritus in the Absence of Skin Diseases

See Fig. 1 for examples of pruritic conditions in the absence of skin disease.

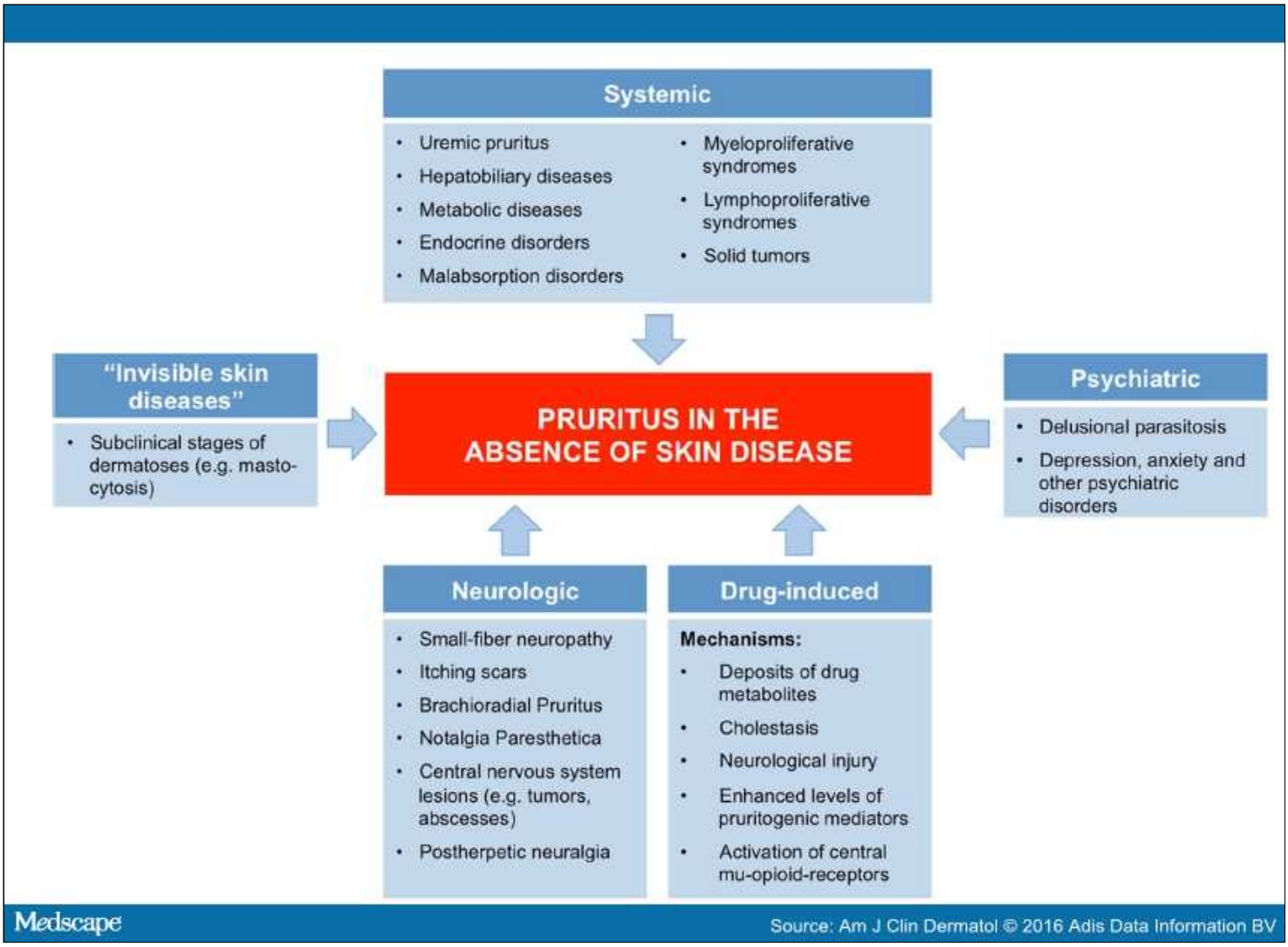

Figure 1.

Pruritic conditions in the absence of skin disease. Examples of relevant clinical entities leading to pruritus are shown organized by pruritus origin

Systemic Diseases. Various hematologic, metabolic, and endocrine diseases can cause generalized or localized pruritus without directly affecting the skin. The underlying pathological mechanisms vary depending on the disease.

Pruritus is a common symptom associated with lymphoproliferative diseases such as Hodgkin's lymphoma. Frequently more intense at nighttime, it can be generalized or localized in the affected lymph node stations.[13,14] Pruritus associated with Hodgkin's lymphoma tends to evolve on normal-looking skin. Scratching may cause excoriations, but these are not always attributed to the affected patients (Fig. 2a). Pruritus frequently occurs prior to the detection of Hodgkin's lymphoma (premonitory pruritus) and persists for several weeks to months before a diagnosis can be established. Although its pathogenesis remains unclear, the release of pruritogenic mediators such as interleukin-31, bradykinin, and histamine and increased amounts of IgE-mediated cutaneous deposition have been suggested as potential mechanisms.[15] Non-Hodgkin lymphoma and lymphocytic leukemia are among other lymphoproliferative diseases occasionally responsible for chronic pruritus.[13,14] In particular, severe pruritus is found in $CD4^+$ mycosis fungoides and its leukemic form, Sézary syndrome, which represent non-Hodgkin T-cell lymphoma with primary manifestation in the skin.

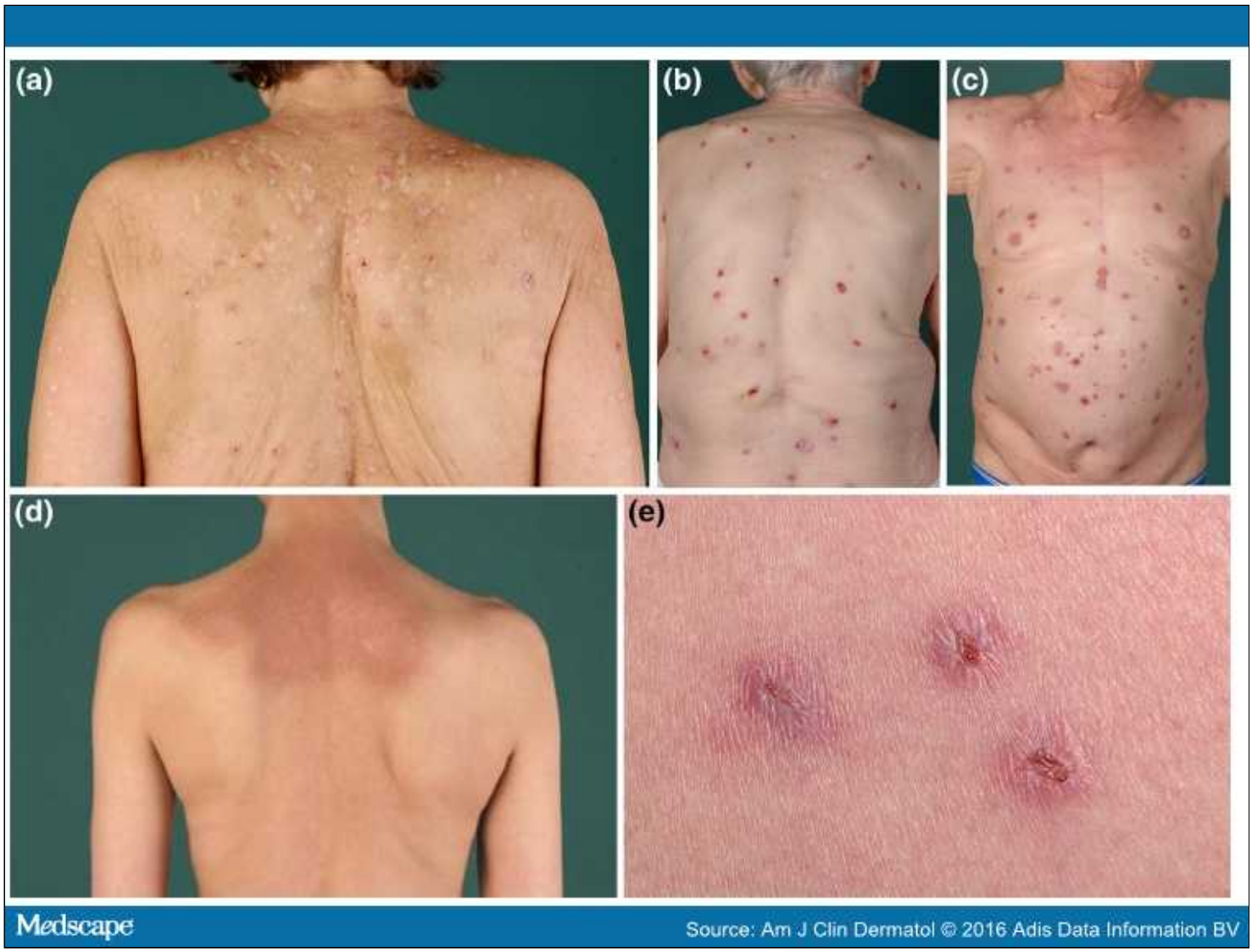

Figure 2.

Clinical examples of patients with chronic pruritus in the absence of skin disease. Examples of patients with Hodgkin lymphoma (**a**), uremic pruritus (**b**), diabetes mellitus (**c**), nostalgia paresthetica (**d**), and delusional parasitosis (**e**) are shown. Secondary lesions to chronic scratching behavior can be observed in all cases

Polycythemia vera and essential thrombocytosis[16] are characterized as myeloproliferative diseases. More than half of patients with polycythemia vera report having pruritus and many have been found to have the so-called 'aquagenic pruritus'. In aquagenic pruritus, contact with water can induce pruritus, in addition to a burning or stinging sensation ('aquadynia').[13] An increased degranulation of mast cells following contact with water is the main pruritic mechanism suspected to be involved.[17] Serotonins, prostaglandins, and iron deficiency (e.g., as a result of blood loss by therapeutic phlebotomies) also contribute to pruritus induction in polycythemia vera. Once induced, aquagenic pruritus typically persists for 30–60 min after contact with water and frequently does not result in scratch-induced excoriations. It can also occur in association with other factors (e.g., after intake of hydroxychloroquine) and must be distinguished from aquagenic urticaria and worsening xerosis following bathing.

Uremic pruritus, or chronic kidney disease-associated pruritus (CKD-aP), affects patients with advanced stages of CKD, mostly those receiving dialysis. According to recent reports, 25–45 % of patients receiving hemodialysis suffer from CKD-aP.[18,19] The underlying pathological mechanisms remain unclear. Increased levels of uremic toxin and parathormone, as well as xerosis and subclinical skin inflammation, are suspected to play a role in its pathophysiology. Additionally, the endogenous opioid systemis possibly implicated due to an overexpression of μ-opioid and downregulation of κ-opioid activity,[20] which explains the efficacy, at least partially, of μ-opioid antagonists and κ-opioid agonists in the treatment of uremic pruritus. Furthermore, recent experimental

data suggests central neuropathic and neuroplastic changes in patients with CKD-aP, explaining the positive response to GABAergic drugs in these patients.[21]

Uremic pruritus usually begins within 3 months in dialysis patients, greatly impacting their quality of life. Researchers have discovered certain risk factors for uremic pruritus in dialysis patients. The male sex and those with certain comorbidities (e.g., congestive heart failure, hepatitis C infection, neurological diseases, depression, and higher serum calcium/phosphorus levels) were found to be more frequently affected.[18] CKD-aP may occur even before pre-dialysis.[22] The skin appearance is normal in most patients with uremic itch, although changes in skin color and xerosis are common. Scratch lesions and excoriations with or without impetigo ensue, and in some cases, prurigo nodularis is observed (Fig. 2b).

Chronic cholestatic and non-cholestatic hepatobiliary diseases are accompanied by CP.[23] Up to 80 % of patients with genetic and non-genetic hepatobiliary diseases, mainly those with cholestatic features, suffer from pruritus.[24] Cholestatic pruritus attributed to primary biliary cholangitis (PBC) typically begins localized at the palmar and plantar surfaces and then generalizes to other areas of the body. Pruritus can also occur in the absence of cholestasis, such as in patients with cirrhosis of various origins, alcohol-induced liver damage, or a chronic hepatitis C virus infection.[24] Cholestatic pruritus has been found to be more intense at nighttime, for which scratching does not provide relief. Patients with prurigo nodularis present infrequently, but have localized lichenifications, single excoriations, or visibly normal skin. Past research has shown that levels of autotaxin and lysophosphatidic acid are enhanced in CP patients with hepatobiliary diseases. Levels of these substances decrease under a successful anti-pruritic therapy. Other pruritogenic agents such as bile acids, endogenous opioids, serotonin, and progesterone metabolites have been suspected to be implicated in the pathogenesis of cholestatic pruritus.[23]

Other metabolic and endocrine diseases are also associated with CP. A small fiber neuropathy caused by diabetes mellitus can also induce itch[25] (see subsection neuropathic pruritus and Fig. 2c). Pruritus may develop in patients with hyperthyroidism, for which pruritus is suggested to be mediated by excessive amounts of thyroid hormones that may activate kinins. Hyperparathyroidism has also been linked to chronic pruritus. Celiac disease, chronic inflammatory bowel disease, and concomitant ferropenic anemia are examples of malabsorption syndromes that are associated with CP.[24]

Drug-induced Pruritus. Pruritus is a frequent adverse effect of drug-related exanthemas, although CP due to drug intake can also arise despite the absence of a rash. Drug-induced CP with no visible symptoms is an issue of great concern due to an increasing multi-morbidity and the resulting polypharmacy in elderly patients.[26] The mechanisms underlying druginduced pruritus are dependent on the specific drug causing the symptom to develop ( ). Pruritus can develop from certain drugs and cease rapidly with discontinued use (e.g., in morphine-based analgesics), although pruritus has the potential to become chronic despite discontinued use of the causal agent. In this case, it can have a delayed onset or occur directly through intake of the causal agent.[27,28] Drug metabolites in the skin, cholestatic liver damage, peripheral or central nervous system injury, central μ-opioid receptor activation, and enhanced levels of pruritogenic mediators (e.g., bradykinin, leukotrienes) form a group of presumed mechanisms for drug-induced pruritus.[27] It is necessary to determine the underlying mechanisms in order to establish a targeted therapy, although these are often unable to be identified.[27,28] provides a summary of important itch-causing drugs in non-damaged skin and potential underlying mechanisms.

Table 1. Presumed mechanisms underlying drug-induced pruritus in undamaged skin (examples) Modified from Reich et al. [27]

Mechanism	Drug class
Cholestatic pruritus	Antihypertensives
	Antiarrythmics
	Anticoagulants
	Antidiabetics
	Antithyroid agents
	Antibiotics (carbapenems, trimethoprim/sulfamethoxazole)
	Corticosteroids
	Psychotropic drugs

Increased bradykinin levels	Agiotensin-converting enzyme inhibitors
Activation of peripheral serotonin receptors	Selective serotonin re-uptake inhibitors
Sebostasis	Tamoxifen
Pruritogenic effect of IL-2	IL-2
Deposition of HES in peripheral nerves	HES
Increased synthesis of leukotrienes	Nonsteroidal anti-inflammatory drugs
Mast cell degranulation	Antibody against *CTLA4* (e.g., ipilimumab)
	Opioids
Impact on skin differentiation (can evolve with xerosis, acneiform rash)	EGFR inhibitors (e.g., erlotinib)
Central modulation of μ-opioid-receptors	Opioids

EGFR epidermal growth factor receptor, *HES* hydroxyethyl starch, *IL-2* interleukin 2

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Neurologic Pruritus. A malfunction (neuropathic pruritus) or hyperstimulation via pruritogens (neurogenic pruritus) in the somatosensory system can also induce pruritus.[28] The clinical presentation of neuropathic pruritus, such as its distribution (e.g., localization or generalization), qualities (e.g., burning or stinging sensations), and concurrent symptoms (e.g., pain), is altered according to the malfunction's origin in the somatosensory system, ranging from the periphery to the central nervous system.[29,30]

Damage to epidermal C-fibers may cause itch that can often be accompanied by other sensory positive (e.g., pain, stinging, burning) or negative (e.g., numbness) symptoms.[12] Various diseases, including diabetes mellitus (Fig. 2c), HIV, shingles, lupus, cutaneous sarcoidosis, Fabry disease, and rheumatoid arthritis are known to induce a small-fiber neuropathy (neuropathy of cutaneous C-fibers).[31] Localized impairment of cutaneous C-fibers and pruritus can also develop due to other diseases such as burning mouth syndrome and vulvodynia.[32] Further peripheral mechanisms consist of cutaneous nerve growth, as seen in abnormal wound healing, and localized peripheral nerve damage, as observed in post-herpetic neuralgia, in which pain and pruritus also occur simultaneously in the affected dermatome.[12]

Spinal nerve compressions can cause itch along the affected dermatome, such as in brachioradial pruritus. In such cases, other sensory symptoms (e.g., paresthesias) are usually also present. Compression of the cervical spinal cord or spinal ganglia attributed to anatomical changes at C5/6 can cause pruritus in the forearms (C5/6 dermatome).[12,33] Secondary lichenification, xerosis, and prurigo nodularis caused by scratching can be found in the affected areas. Notalgia paresthetica is another example of a compression syndrome in which pruritus at the scapulae begins due to compression of the dorsal branches of the spinal nerves at T2–T6. Mechanical responses to the itching often lead to hyperpigmentation of the affected areas (Fig. 2d).[33,34] Tumors, surgical procedures at the affected region, anatomical variations, and orthopedic changes also lead to compression syndromes. Tumor abscesses and aneurysms, as well as spinal cord and cerebral lesions, may also produce itch.

It has been speculated that, in neurogenic pruritus, itching results from a neurotransmitter imbalance, an increased binding of pruritogens directly at the nerve fiber, or as a result of changes in the regulation of certain receptors located in the central nervous system. In contrast to neuropathic pruritus, the nerve fibers themselves are not impaired in neurogenic pruritus. In cholestatic pruritus, for example, researchers have hypothesized that pruritogenic mediators bind to neurons in the central nervous system, thus causing itch. Increased levels of endogenous opioids are assumed to have an important role in various conditions. For this reason, opioid antagonists (e.g., naloxone) are considered to be therapeutic.[10]

Somatoform and Psychiatric Pruritus. In somatoform pruritus, also known as 'functional itch disorder', chronic pruritus can occur as the main symptom in the absence of a skin disease. Psychiatric factors and diseases (e.g., depression) play a central role in the development of the symptomatology.[31] Typical symptoms include initiation of itch during a stressful or traumatizing life event and nocturnal variations of the symptom with predominance during inaction.[31]

Pruritus has been found to be a frequent symptom in psychiatric patients.[35,36] A classic example is delusional parasitosis, in which patients falsely believe that their skin is infested with parasites and report sensory symptoms such as itching, biting, or crawling under the skin. In an effort to remove the pathogens, patients often damage their own skin, leading to excoriations and ulcerations (Fig. 2e).[37]

Although its underlying mechanisms are uncertain, a link between pruritus and mental health has been established. It is speculated that psychiatric conditions may lead to an increased response of the peripheral and central nervous system to puritogenic stimuli.[38] It is therefore crucial to evaluate the psychosomatic state when assessing a patient with chronic pruritus.[36] Improvements attributed to psychotherapy or psychotropic drugs and an exacerbation of itch due to stress do not demonstrate that pruritus arises from mental health conditions. As reported by many CP patients, symptoms are aggravated in stressful situations, for which increased mast cell degranulation induced by stress hormones provides a possible explanation. Patients with chronic pruritus frequently develop psychiatric comorbidities (e.g., generalized anxiety, reactive depression) due to their impaired quality of life,[39] thus providing clinicians with the challenge of differentiating between comorbidities as a cause of pruritus or a consequence thereof. Nevertheless, itch is exacerbated and perpetuated by depression, anxiety, and other various psychiatric conditions in patients with chronic pruritus. Educational and cognitive behavioral approaches may thus benefit such patients.[40] For this purpose, determining the underlying mechanisms of psychogenic pruritus is of high priority for researchers aiming to develop a targeted therapy.[36]

Diagnostics

In order to diagnose the underlying disease leading to chronic pruritus within a reasonable timeframe, it is necessary to perform a structured and systematic approach using a detailed patient history, clinical examinations, laboratory tests, and collaboration with other disciplines. In accordance with the classification system established by the International Forum for the Study of Itch (IFSI; www.itchforum.net), patients can be divided into three clinical groups[1] following the initial clinical examination. If a dermatosis is present (IFSI classification group I: chronic pruritus on inflamed skin; formerly 'pruritus cum materia'), diagnostics and therapy take place in compliance with dermatological guidelines and standards. Systemic, neurological, and psychiatric diseases, as well as invisible dermatoses (e.g., mastocytosis), should be taken into consideration for pruritus on seemingly normal skin (IFSI II: chronic pruritus on normal skin; formerly 'pruritus sine materia'). The third clinical group (IFSI III: chronic pruritus with scratch lesions) consists of patients with lesions due to chronic scratching that superimpose the initial groups I and II. This group, composed of entities such as prurigo nodularis and lichen simplex, represents the greatest diagnostic effort as a result of underlying systemic, neurological, and psychiatric diseases.

A continuing history is beneficial for the differential diagnostic classification in group II and III.[1] The localization should initially be described. It should be noted that pruritus often begins localized, but may generalize during the course of the disease. This is typical for dermatological, systemic, and psychiatric diseases.[1] Neuropathic diseases (e.g., brachioradial pruritus, notalgia paresthetica, and small fiber neuropathy) should be taken into consideration for persistently affected, circumscribed areas. Further questions ( ) serve to characterize the symptom. It is important to determine the symptom duration as it has an especially important diagnostic role. The detection rate of carcinomas (e.g., hepatocellular carcinoma) and hematologic diseases is highest within the first 12 months after the onset of pruritus. In a national cohort study in Denmark, paraneoplastic pruritus was recently carefully studied based on available medical data registers provided by health insurance companies.[41] Patients coded with an ICD diagnosis of pruritus between 1978 and 2011 (*n* = 12,813) were tracked until their first tumor diagnosis or death. The population's expected national tumor incidence rates were standardized with the collected tumor incidence rate, and a so-called standardized incidence ratio (SIR) was calculated. With 1.13, the SIR for all tumor diagnoses was slightly increased (95 % confidence interval [CI] 1.07–1.20; observed tumors 1173, expected tumors 1039); in men (1.22 [95 % CI 1.12–1.33]) it was slightly higher than in women (1.05 [95 % CI 0.97–1.14]). Sub-analyses revealed a relevant correlation between pruritus and liver carcinoma (SIR 3.61 [95 % CI 2.53–4.99]), lymphoma (SIR 1.68 [95 % CI 1.40–1.99) and Hodgkin's lymphoma (SIR 6.96 [95 % CI 4.05–11.15]). In women, a link to an increased risk of carcinomas (not caused by HIV) on the external genitalia (SIR 6.12 [95 % CI 3.57–9.81]) and anus (SIR 3.13 [95 % CI 1.15–6.819]) was found. Furthermore, an increased incidence for Kaposi sarcoma (SIR 35.85 [95 % CI 13.16–78.169]) and other skin carcinomas (non-melanoma skin cancer, basal cell carcinoma; SIR 1.43 [95 % CI 1.08–1.869]) was established. The latency between the documentation of pruritus and neoplasms was particularly remarkable in the analysis. Tumor rates were highest in the first 3 months (SIR 2.14 [95 % CI 1.67–2.70]) following coding, continuing for approximately 12 months before normalizing.

Table 2. Medical history: key questions in chronic pruritus[a]

Question	Interpretation
1) How long has the itch been present?	Question regarding duration (≤12 months: lymphoma or liver tumor possible. If so, please consider also Q.11)
2) Did it develop shortly after or together with a new illness identified/surgery performed/new medication?	Question regarding an easily recognizable connection. Women: please consider also pregnancy. Medications can also cause pruritus months after its initiation
3) Did the itch appear together with any skin changes?	Yes: Dermatoses or scratch lesions No: Pruritus in systemic, neurological, psychiatric diseases
4) Where is the itch located?	Localized (e.g., neuropathic causes such as notalgia paresthetica)
	Generalized
	Daily varying localizations (e.g., as described in prostate cancer)
5) Are family members also affected?	Consider infestations such as scabies
6) Does contact with water cause the itch?	Aquagenic pruritus, can also occur in connection with polycythemia vera
7) Does scratching, rubbing or pressure cause the itch?	Mechanically induced pruritus occurs in atopic dermatitis (so-called alloknesis), urticaria facticia, mastocytosis, hydroxyethyl starch-induced pruritus, cholestatic pruritus

8) Previous therapies?	Important for planning future therapies
9) Do you experience a reduced quality of life?	Simple question for assessing the burden induced by pruritus. Alternatively, patients can receive the questionnaire 'ItchyQol'
10) What is the current intensity on a numerical rating scale (NRS) from 0 (no pruritus) to 10 (severe pruritus)?	Important for documenting progress. Always ask Q.9 and Q.10 during follow-up visits
11) Do you have night sweats, lymph node swelling, or unwanted weight loss?	Symptoms associated with malignant underlying diseases

[a]In addition to general medical history questions regarding underlying diseases, allergies, atopic disposition, current medications, etc

Moreover, the duration of the pruritus indicates possible therapy resistance. Pruritus persisting for <6 weeks (acute pruritus) is relatively simple to treat as the chronic manifestation of the symptom generally develops only after several months, depending on the severity, scratching behavior, and cause, requiring a different therapy than the simple symptomatic therapy of the early symptom.

Before assigning patients to the group 'chronic pruritus on normal skin or with chronic scratch lesions', laboratory and radiological diagnostic procedures ( ) should be conducted in accordance with recommendations from the current guidelines and in conjunction with a general practitioner or specialist for internal medicine. Interdisciplinary specialist groups agree that initial diagnostics should be minimal in order to remove common and malignant underlying diseases from consideration ( ). In ruling out malignant underlying diseases, a rate of one tumor for every 155 examined patients with pruritus was calculated.[41] Some of the more common diagnoses attributed to patients with chronic pruritus include chronic renal insufficiency (often requiring dialysis), hepatobiliary disorders (e.g., PBC, primary sclerosing cholangitis, drug-induced cholestasis, chronic hepatitis C virus infection), diabetes mellitus, iron deficiency anemia, polycythemia vera, and Hodgkin's lymphoma. Solid neoplasms are among the more uncommon diagnoses; however, these should be taken into consideration after ruling out common diagnoses.[42] Chronic pruritus associated with the administration of modern antineoplastic substances is also increasingly observed, representing a new diagnostic and therapeutic challenge for dermatologists.

Table 3. Basic examinations for generalized chronic pruritus on ordinary skin (follow-up laboratory test: 1x/year). Modified from the European Guideline [42]

Basic examinations	
Initial laboratory tests	Blood count with differential, ferritin
	Erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP)
	Creatinine, urea, calculated glomerular filtration rate (GFR), K+, urine (stick test)
	Bilirubin, transaminases (GPT/ALAT and GOT/ASAT), gammaglutamyl transferase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH)
	Thyroid-stimulating hormone (TSH)
	Fasting blood glucose
Supplementary examinations	
For pathological values in the initial examination	Further laboratory and radiological diagnostics of the disease
Localization and clinical history adapted diagnostics (examples)	For anal pruritus: parasites, worm eggs, digital examination of the rectum, prostate-specific antigen (PSA)
	For aquagenic and genital pruritus, pruritus of unknown origin: lactose and sorbitol intolerance test
	Pruritus during pregnancy:

	For ordinary skin findings: dermatological examination to exclude polymorphic eruption of pregnancy (PEP), gestational pemphigoid
	For abnormal skin findings: ALAT, bile acid (fasting)

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In particular, elderly patients frequently represent a challenge for medical history, differential diagnosis, and therapy. Multiple potentially pruritogenic diseases exist simultaneously without a clear link to the beginning of pruritus. It is thus difficult to discern the factors that contribute to the symptom from these many variables (medications, diabetes, renal insufficiency, xerosis, etc.). Therefore, gradual clinical diagnostics, as well as an elimination of potential pruritogenic factors, are highly recommended. In recent years, this approach has been adopted around the globe, thus simplifying the process and improving patient care.[3]

Treatment

General Considerations

Treatment of chronic pruritus is divided into different groups according to the various aspects of the symptom, its causes, and induced disorders such as sleep disturbances or depressive disorders.[3] This applies to all forms of chronic pruritus. Regardless of the underlying disease, symptom relief is most important to patients. A symptomatic therapy that is initially relatively nonspecific and independent from the underlying mechanisms should be introduced parallel to investigating the cause. A general behavior pattern (to avoid factors that promote xerosis and skin damage) and replenishing, hydrating emollients may also be recommended.[28] In addition, extemporaneous or standardized antipruritic substances containing urea, polidocanol, and menthol, among others, are recommended. Taking these measures can greatly improve pruritus without existing dermatoses. The attending dermatologist should also simultaneously introduce a therapy for present skin alterations such as xerosis, lichenification, or scratch lesions.

Although it is known that histamine-dependent mechanisms are the sole cause of pruritus in urticaria, antihistamines contribute to the symptom relief of many other diseases for which an increase in mast cells (e.g., prurigo nodularis) or mast cell degranulation (e.g., aquagenic pruritus) is described. Experts also suggest early consideration of and therapy for accompanying disorders (e.g.,

hypnotic drugs, sedating antidepressants, and low potential neuroleptics for sleep disturbances; consultation with a psychosomatic specialist for mental symptoms).

After determining the cause, a corresponding therapy is then implemented. If the symptom persists despite these measures, it is assumed that it has become chronic, which requires a specific topical and systemic therapy. In this case, the fastest approach to treatment should be aimed for in order to discourage further chronicity of the symptom. The current guideline advocates topical substances such as capsaicin and calcineurin inhibitors for such patients.[42] Both substances have an effect on cutaneous neurons, among other substances, and serve to suppress chronic pruritus. Prior to introducing a systemic therapy, ultraviolet light therapy (PUVA, UVB311, UVB wideband) can be conducted. This therapy option is not only effective for prurigo nodularis and pruritus associated with dermatoses, but also for pruritus on normal skin (e.g., uremic pruritus). However, it should be kept in mind that UV light therapy can increase the risk for skin cancer. This regimen should thus not be recommended to patients who may undergo transplantation due to chronic renal failure or chronic hepatobiliary disorders at a later stage.

Substances such as opioid receptor antagonists (e.g., oral naltrexone, intravenous naloxone), anticonvulsants (e.g., gabapentin, pregabalin), selective serotonin re-uptake inhibitors (SSRIs; e.g., paroxetine), and tricyclic (e.g., doxepin) and tetracyclic (e.g., mirtazapine) antidepressants are recommended. Data from clinical studies, case series, and case reports on the various underlying diseases is available and summarized in the guideline.[42] It should be noted that the substances used for treating chronic pruritus are frequently used off-label, with few exceptions (e.g., antidepressants for coexisting psychiatric symptoms, anticonvulsants for simultaneous paresthesias or neuropathy); however, a sufficiently high dosage and long therapy duration are of high importance. The symptomatic therapy should not be discontinued or altered too early, as its effectiveness may otherwise be misjudged. For example, it is generally accepted that anticonvulsants and antidepressants show an onset of action after a maximum of 8 and 12 weeks, respectively. Approximately 65 % of patients with chronic pruritus are thus currently treatable with this treatment method.[43] However, for the remaining 35 %, therapy remains unsatisfactory and the development of new specific substances is urgently needed. Some therapies that have proven their efficacy in practice are presented here.

Gabapentin and Pregabalin

Gabapentin is an anticonvulsant and pain modulator utilized in treating neuropathies. Binding to the a2-d-subunit of calcium channels of peripheral and central nociceptive neurons, this substance impedes calcium influx into neurons, thus inhibiting nerve depolarization. It is commonly used in treating postherpetic neuralgia,[44] neuropathic disorders associated with pain and pruritus,[45] brachioradial pruritus,[46] and pruritus of unknown origin,[47] also proving to be a safe and effective drug for pruritus associated with CKD.[48] Pregabalin is another substance sharing many similarities with gabapentin. Case reports have published results proving its efficacy in treating aquagenic pruritus,[49] CKD-aP, and certain types of drug-induced pruritus, including cetuximab-induced pruritus.[50] In conclusion, gabapentin and pregabalin are beneficial in treating neuropathic pruritus and pruritus associated with CKD. They may also prove to be therapeutic options for chronic pruritus of unknown origin, although confirmatory studies with large patient cohorts are currently pending. In case of an insufficient therapeutic effect, anticonvulsants can be administered in combination with antidepressants, such as tricyclic antidepressants or serotonin reuptake inhibitors.[42]

Naltrexone

Endogenous opioids located in the central nervous system are suspected to have a role in inducing pruritic sensations in patients with systemic diseases. μ-Opioid receptor antagonists have, in double-blind, controlled studies, demonstrated mild antipruritic effects on cholestatic pruritus.[51] Alternative treatment options for cholestatic pruritus include cholestyramine, rifampicin (up to 600 mg/day) and sertraline.

The effectiveness of naltrexone on CKD-aP is controversial.[52,53] According to anecdotal case reports and case series, the opioid antagonists naltrexone and naloxone have provided relief for patients affected by prurigo nodularis, post-burn pruritus, aquagenic pruritus, hydroxyethyl starch-induced pruritus and pruritus of unknown origin.[54] Due to the variable, non-controlled study designs used in these case series, the beneficial effects should be interpreted with caution.[54]

Antidepressants

Researchers have established that mirtazapine, a tetracyclic antidepressant with additional antihistaminic and serotonergic effects, provides relief for those with urticaria and pruritus of unknown origin.[55] Amitriptyline, among other tricyclic antidepressants, is often used for treating chronic pain and pruritus, but has a high rate of secondary effects. Twenty milligrams of paroxetine, an SSRI, exhibited positive antipruritic effects when taken daily as treatment method for polycythemia vera,[56] paraneoplastic pruritus,[57] and somatoform pruritus.[58] Its antipruritic effects have also been demonstrated for pruritus of non-

dermatological origin in a randomized controlled trial.[59] A two-armed proof-of-concept study investigating the effects of paroxetine and fluvoxamine on patients with pruritus of various origins, including extracutaneous origins, yielded positive results, for which patients reported significant antipruritic effects.[60]

Emerging Drugs

Several clinical trials testing new compounds are currently ongoing.[61] Neurokinin-1 receptor inhibitors, such as aprepitant, have shown promising results in the treatment of pruritus arising from atopic dermatitis, prurigo nodularis, and cutaneous T-cell lymphoma.[61–63] Interleukin-31 antagonists and anti-nerve growth factor antibodies have gained interest in recent years in the management of inflammatory dermatoses causing itch.[64–66] Other compounds of interest include κ-opioid receptor agonists (e.g., nalfurafine and butorphanol) for the treatment of uremic pruritus[66–68] and bile acid transporter inhibitors for cholestatic pruritus.

Adjuvant Therapy: Interrupting the Itch–Scratch Cycle

Pruritus therapy also consists of combating the vicious itch–scratch cycle, for which behavioral therapy should be taken into consideration to discourage scratching. This cycle dominates certain diseases such as prurigo nodularis. Affected patients are in danger of developing an unconscious, automatic scratching behavior. The management of atopic dermatitis has been simplified for many patients as a result of systematic educational programs that have been successfully implemented as an important component of treatment.[69,70] Said programs comprise strategies for breaking the cycle of pruritus and scratching and provide advice for relaxation and stress management, as well as methods and techniques for handling relapses. 'Coping with Itch', a nursing program for patients with pruritic skin diseases, has proven its efficacy in a randomized controlled study.[40] Another educational program developed specifically for patients with chronic pruritus of all origins was, in recent years, developed in order to teach relaxation techniques and serve as a complementary treatment for managing chronic pruritus.[71]

Conclusion

A multitude of systemic, neurological, psychiatric, and somatoform conditions may cause pruritus in the absence of skin disease. To unveil the underlying causes, it is recommended to take a systematic diagnostic approach, including a structured clinical history and physical examination, as well as laboratory and eventual radiological procedures. Chronic pruritus remains a therapeutic challenge for clinicians, especially due to its associated persistent mechanisms such as impaired inhibition at spinal level or sensitization processes involving the peripheral and central nervous system. Future studies are needed to better understand its underlying mechanisms and to develop new therapeutic agents.

Sidebar

Key Points

- Chronic pruritus in the absence of skin disease may arise from a multitude of systemic, neurologic, psychiatric, and somatoform conditions or be induced by prescription or over-the-counter medication.
- In order to diagnose the underlying disease leading to the chronic pruritus, a structured and systematic approach using a detailed patient history, clinical examination, laboratory tests, and collaboration with other disciplines is necessary.
- Although many treatment options are currently available, chronic pruritus remains a therapeutic challenge for the clinician, especially due to chronicity processes that occur in long-lasting disease.

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Acknowledgments
We thank E.R. Burnett for proofreading and editing this manuscript.

Compliance with Ethical Standards

Funding
No funding was received for the preparation of this review.

Am J Clin Dermatol. 2016;17(4):337-348.