Pruritus is a common symptom reported in connective tissue and other common systemic disease states. Unfortunately, the unique pathophysiologic etiology of the often chronic and severe pruritus that is a debilitating component of many connective tissue disorders makes treatment with conventional anti-itch agents difficult. As the underlying mechanisms of pruritus have been identified, treatment strategies have evolved. Considering the diversity of available antipruritic therapies and the variability of underlying factors specific to disease states, individualized therapy recommendations are necessary.
Pruritus in Common Disease States

Important new areas of treatment target the central and peripheral mechanisms of pruritus and include anticonvulsants, antidepressants, opioid antagonists, and phototherapy. Further research is necessary to quantify the role of new and novel antipruritic therapies.


Pathophysiology and Classification of Pruritus

Pruritus (or itch), once considered to be low-intensity pain, is now known to be neurologically distinct from nociception. Once stimulated by a pruritogen, a specialized subset of C fibers within the skin sends signals to the dorsal horn of the spinal cord that are transmitted by the spinothalamic tract to the thalamus and on to the somatosensory cortex. These C fibers, also called pruriceptors, are distinguished from the most common type of C fibers by sensitivity to histamine and unresponsiveness to mechanical stimulation, whereas classical nociceptors are mechano-heat sensitive, have little response to histamine, and are responsible for transmitting pain. Pruriceptors also are known to have half the conduction velocities of nociceptors and receptor fields that are approximately 3 times larger.

Although pain and itch are now accepted as distinct entities, there are certainly interactions between the 2 systems. Scratching to the point of pain commonly relieves itch. It also has been shown that other painful stimuli, such as heat and electric stimulation, can reduce histamine-induced itch for several hours. On the contrary, administration of opioids, specifically μ-opioid receptor agonists, for analgesia causes a common side effect of pruritus. The administration of μ-opioid receptor antagonists such as naloxone and naltrexone has an antipruritic effect and can be a useful treatment in patients with uremic or cholestatic itch in whom an upregulation of endogenous opioids is the suspected mechanism.

Itch can be neurophysiologically classified based on mechanism into cutaneous or pruritoceptive, neuropathic, neurogenic, psychogenic, or mixed. Itch that originates in the skin is pruritoceptive neuropathic, neurogenic, psychogenic, or mixed. Itch that originates in the skin is pruritoceptive neuropathic, neurogenic, psychogenic, or mixed. Although pain and itch are now accepted as distinct entities, there are certainly interactions between the 2 systems. Scatching to the point of pain commonly relieves itch. It also has been shown that other painful stimuli, such as heat and electric stimulation, can reduce histamine-induced itch for several hours. On the contrary, administration of opioids, specifically μ-opioid receptor agonists, for analgesia causes a common side effect of pruritus. The administration of μ-opioid receptor antagonists such as naloxone and naltrexone has an antipruritic effect and can be a useful treatment in patients with uremic or cholestatic itch in whom an upregulation of endogenous opioids is the suspected mechanism.

Itch can be neurophysiologically classified based on mechanism into cutaneous or pruritoceptive, neuropathic, neurogenic, psychogenic, or mixed. Itch that originates in the skin is pruritoceptive neuropathic, neurogenic, psychogenic, or mixed. Although pain and itch are now accepted as distinct entities, there are certainly interactions between the 2 systems. Scatching to the point of pain commonly relieves itch. It also has been shown that other painful stimuli, such as heat and electric stimulation, can reduce histamine-induced itch for several hours. On the contrary, administration of opioids, specifically μ-opioid receptor agonists, for analgesia causes a common side effect of pruritus. The administration of μ-opioid receptor antagonists such as naloxone and naltrexone has an antipruritic effect and can be a useful treatment in patients with uremic or cholestatic itch in whom an upregulation of endogenous opioids is the suspected mechanism.

Psychogenic itch is associated with psychological abnormalities and primary skin lesions, which helps support the idea of a central origin of itch.

Alternately, itch can be classified based on the clinical presentation and symptom complex. While the clinical classification of pruritus may be diagnostically helpful, it generally does not aid in determining antipruritic therapy. Although cutaneous neurobiology appears to be similar for acute and chronic itch, chronic itch is thought to develop when central mechanisms undergo neuroplasticity and are sensitized toward itch; therefore, when treating chronic pruritus, it is important to target cutaneous, peripheral, and central mechanisms.

Pruritus as a Manifestation of the Disease

Dermatomyositis—Dermatomyositis is a chronic autoimmune inflammatory myopathy with characteristic skin involvement. Patients generally present with insidious onset of proximal muscle weakness and pain with pathognomonic skin changes of Gottron papules and Gottron sign. Frequently, the initial cutaneous manifestation is the heliotrope rash, which consists of highly pruritic, confluent, macular, violaceous erythema of the periorbital region. Other characteristic skin lesions associated with the disease include photodistributed violaceous erythema of the upper chest as well as the neck and upper back (shawl sign), poikiloderma, and calcinosis cutis.

Skin manifestations of dermatomyositis often are symptomatic and cause the patients much discomfort with pruritus and skin burning. A survey of patients with controlled muscle disease but unknown control of skin manifestations showed that the majority continue to experience moderate pruritus despite inactive muscle disease. In fact, of 26 respondents, 18 reported that they continued to experience pruritus. The authors suggest 2 etiologies for their itching: the inflammatory component of the disease and the side effect of disease treatment. For example, one study found that hydroxychloroquine was linked to a highly pruritic eruption in nearly one-third of patients with dermatomyositis (12/39), a much higher prevalence than in patients with lupus. The pruritus associated with dermatomyositis can be severe. Another study evaluating the effect of pruritus on quality of life found that compared to
Pruritus in Common Disease States

psoriasis and atopic dermatitis, pruritus in dermatomyositis caused a greater impairment.\textsuperscript{15} Furthermore, treatment response of cutaneous and muscular disease can be discordant.\textsuperscript{16} Treatment of cutaneous manifestations includes aggressive sun protection and topical corticosteroids, methotrexate sodium,\textsuperscript{17} antimalarial agents,\textsuperscript{18,19} topical tacrolimus,\textsuperscript{20,21} tamoxifen and anastrozole,\textsuperscript{22} dapsone,\textsuperscript{23} and intravenous immunoglobulin.\textsuperscript{24} Pruritus is often improved by treating cutaneous dermatomyositis but may be seen as a side effect of treatment, as nonallergic pruritic eruptions have been reported in patients on methotrexate, antimalarial agents, and tamoxifen. While systemic therapies that treat the underlying disease generally are beneficial, specific antipruritic treatments used in dermatomyositis include antihistamines (hydroxyzine hydrochloride, doxepin hydrochloride) and class 1 (superpotent) or class 2 (potent) topical corticosteroids.\textsuperscript{25,26} Tacrolimus ointment 0.1% has been reported to be effective in resistant cutaneous dermatomyositis and associated pruritus.\textsuperscript{27,28}

Scleroderma—Scleroderma is a spectrum of related disorders; the majority share the feature of skin thickening secondary to excess collagen fibers. The exact etiology and pathogenesis are unknown, but the activation of the immune system, particularly fibroblasts, T and B lymphocytes, and endothelial cells, are indicated as key factors of excess collagen production.\textsuperscript{29} Scleroderma is first classified into localized or systemic disease. Systemic scleroderma (SSc) is further broken down on the basis of internal organ involvement and extent of skin involvement.

Certain proteins currently are being researched to discover their involvement in the excess collagen production associated with scleroderma. Transforming growth factor \( \beta \) (TGF-\( \beta \)) also is thought to be involved because most patients with SSc show elevated levels of the receptor for TGF-\( \beta \). Pannu et al\textsuperscript{30} demonstrated that aberrantly expressed TGF-\( \beta \) receptor type 1 may instigate an autocrine loop that upregulates collagen-producing fibroblasts. Eight of 9 SSc strains exhibited increased levels of this protein, which was associated with increased collagen synthesis.\textsuperscript{30} Fibrillin as well as human \( \beta \)-defensins are being investigated for potential involvement.\textsuperscript{31,32} Skin thickening, Raynaud phenomenon, calcinosis, and telangiectasia are common skin manifestations of both localized scleroderma and SSc.

Pruritus is associated with the inflammatory state of the skin in the earliest stages of diffuse cutaneous SSc.\textsuperscript{33,34} It typically is associated with nonpitting edema of the extremities that takes place prior to collagen deposition.\textsuperscript{35} There have been few treatment modalities that immediately alleviate pruritus besides antihistamines and adequate lubrication. Treatment of the underlying disease with nonsteroidal anti-inflammatory and immunosuppressive drugs typically does not alleviate pruritus, though it may lessen the disease course and aid in softening of the skin. While low-dose systemic glucocorticoids have been effective for severe cases of pruritus, topical steroids rarely have been of benefit.\textsuperscript{33} Tacrolimus ointment 0.1% applied twice daily under occlusion appears to allow faster resolution of the inflammatory phase and aids in skin softening in preliminary reports, though antipruritic effects were not mentioned.\textsuperscript{36} Another relatively new treatment is UVA1 therapy. The antipruritic action of UVA1 is thought to be due to inhibitory effects on histamine release from basophils and mast cells.\textsuperscript{37,38} Studies have shown that UVA1 therapy can improve pruritus and reduce skin stiffness and thickness; furthermore, it is generally well tolerated.\textsuperscript{39,40} UVA1 therapy along with antihistamines and lubricants appear to be the most effective and safest antipruritic agents in the treatment of scleroderma.

Lupus Erythematosus—Lupus erythematosus is a disease that can have a wide range of systemic and cutaneous manifestations. Pruritus in systemic lupus erythematosus (SLE) occurs in roughly 2.8% to 45% of patients, according to various reports.\textsuperscript{41,42} It is unclear if the itching is due to the disease process or if it is an adverse drug reaction seen especially with antimalarial drugs such as chloroquine phosphate. Hoffman and Gray\textsuperscript{43} reported a case of aseptic meningitis upon administration of ibuprofen to a patient with SLE and suggested that the pruritus experienced by the patient may have been secondary to a hypersensitivity reaction. In a study on pimecrolimus, pruritus was observed in 40% (4/10) of patients after initiation of therapy and was considered to be an adverse drug reaction.\textsuperscript{44}

Therapy must be adjusted to the subtype of cutaneous involvement as well as signs of systemic disease. In the absence of systemic disease, focus can be placed on cutaneous manifestations. Mainstays of therapy for cutaneous disease include topical or intralesional corticosteroids.\textsuperscript{45} Severe widespread or unresponsive lesions may require more aggressive therapy with oral corticosteroids, antimalarial agents, or azathioprine.\textsuperscript{45,46} Unfortunately, the response of cutaneous disease to the immunosuppressive drugs used to treat SLE to control organ involvement often is disappointing.\textsuperscript{42} Etanercept was reported to be successful for intractable pruritus in one patient with subacute cutaneous lupus erythematosus\textsuperscript{47}; otherwise, specific therapy for pruritus in the context of lupus has not been described.

Sjögren Syndrome—Sjögren syndrome is an autoimmune disease characterized by glandular
dysfunction that leads to desiccation of the skin and mucous membranes.\(^{48}\) It has a primary and secondary form that often occurs in conjunction with other collagen vascular diseases such as lupus. The etiology and pathogenesis of \(\text{Sjögren syndrome}\) are unclear but could be due to immunoregulatory properties of sex hormones because most patients with \(\text{Sjögren syndrome}\) are female. Glandular destruction appears to be mediated by \(\text{CD4}^+\) lymphocytes.\(^{48}\) Xerosis in primary \(\text{Sjögren syndrome}\) also has been found to be highly associated with anti–SS-A (\(\text{Sjögren syndrome antigen A}\)) and anti–SS-B (\(\text{Sjögren syndrome antigen B}\)) antibodies.\(^{49}\)

The primary cutaneous lesions involved in \(\text{Sjögren syndrome}\) are xerosis and angular cheilitis, which affect roughly 50\% of individuals, followed by eyelid dermatitis, cutaneous vasculitis, and erythema annulare.\(^{48}\) Xerosis and erythema annulare are found more frequently in patients with primary versus secondary \(\text{Sjögren syndrome}.\)\(^{49}\)

Skin and vaginal involvement are secondary to xerosis. If the pruritus is intense, dermatitis herpetiformis should be considered in the differential diagnosis. The 2 diseases share a common genetic link of HLA-DR3.\(^{11,50}\) Xerosis and pruritus associated with \(\text{Sjögren syndrome}\) can be managed with use of humidifiers and moisturizers. Treatment of \(\text{Sjögren syndrome}\) typically revolves around managing the ocular and oral manifestations, with systemic therapy reserved for refractory or severe cases.\(^{51}\) It is not described in the literature if patients treated with systemic immunosuppressive therapy experience relief of xerosis.

**Primary Biliary Cirrhosis**—Primary biliary cirrhosis (PBC) is a progressive chronic disease leading to cholestasis and is typically described in middle-aged women. It is categorized as an autoimmune condition, though some lines of study on the etiology have shown both the environment and autoantibodies as probable factors.\(^{52}\) Dermatologic manifestations include dermographism, melanosis, xerosis, and xanthomatous lesions. Dermatologic manifestations were the presenting symptom of PBC in more than one-third (19/49) of participants in a study by Koulentaki et al.\(^{53}\) Some patients have been reported to present with symptoms that indicated connective tissue disease, such as arthralgia, fatigue, and morbillous or urticarial skin lesions.\(^{54}\)

Pruritus is a common side effect of PBC that occurred in 70\% (34/49) of participants in one study and had a substantial impact on quality of life.\(^{53}\) It is hypothesized that patients with cholestasis might undergo central sensitization for itch to the point that noxious stimuli are perceived as pruritus by the patient, which results in continuous activation of the C fibers, perhaps by pruritogens retained because of cholestasis.\(^{56}\) Some studies have associated pruritus with a single nucleotide alteration, which leads to a substitution of valine for glutamate in the multidrug resistance protein 2 gene, \(\text{MRP2}.\) This gene makes the multidrug resistance–associated protein 2 (\(\text{mrp2}\)) that regulates the transport of organic compounds, including bile salts.\(^{56,57}\) Bile acids produce a local pruritic response when intracutaneously injected in healthy participants, but bile acids most likely are not the cause of pruritus in the cholestasis of PBC because results show that pruritus is not always directly related to the level of bile acids present in the afflicted patient. Some patients experience itching with no concomitant increase in serum bile acid levels, while others experience frank hepatic failure with maximum levels of bile acids and no pruritus.\(^{56}\) Thus, bile acids are not considered to be the primary pruritogens associated with cholestasis.

Evidence suggests that pruritus is related to increased neurotransmission mediated by endogenous opioids, particularly methionine and leucine enkephalins.\(^{55,56}\) This theory of increased opioidergic tone is due to the observation that the pruritus of cholestasis can be relieved by naloxone hydrochloride, and administration of morphine can induce opiate antagonist–reversible pruritus.\(^{57}\) \(\mu\)-Opioid receptor antagonists such as naloxone hydrochloride and naltrexone hydrochloride have been widely studied with good results.\(^{58-63}\) Opiate withdrawal syndrome is a potential side effect of the opioid antagonists and naloxone is hepatotoxic, which may limit its use in some patients. Nalmefene hydrochloride has been successful as an antipruritic treatment but was dismissed in initial studies for long-term therapy because of poor oral bioavailability.\(^{54,57}\) Despite good efficacy, opioid antagonists generally are not recommended as first-line agents because of unfavorable side effects and high cost. The antidepressants sertraline hydrochloride,\(^{65,66}\) paroxetine hydrochloride,\(^{67}\) and mirtazapine\(^{68}\) all have been studied with success and generally are well tolerated. Sertraline hydrochloride has been recommended as a potential first-line therapy.\(^{66}\) Cholestyramine is a bile acid–binding resin that is widely used, has low toxicity, and appears to have an antipruritic effect despite the lack of rigorous clinical trials.\(^{69,70}\) Ursodeoxycholic acid, a choleretic agent, may decrease cholestasis but has not been consistently shown to relieve pruritus.\(^{71}\) The antibiotic rifampicin has been evaluated in several well-designed studies and meta-analyses and has been shown to effectively relieve pruritus, though patients must be monitored for hepatotoxicity.\(^{70,72}\) Dronabinol also has been
studied and found to improve intractable cholestatic pruritus in a small group of patients as well as aid in sleep. While it may prove to be a novel approach to antipruritic therapy in the future, it is not currently recommended. Phototherapy and plasmapheresis generally also are thought to be successful but require fairly extensive treatment regimens and recurrence tends to be a problem. Treatment generally is initiated with cholestyramine and advanced to naltrexone hydrochloride or rifampicin in the event of continued pruritus. 

End-stage Renal Disease—Patients with end-stage renal disease are afflicted with multiple cutaneous manifestations of the disease, including pruritus, pallor, sallow yellowish skin tones, hyperpigmentation, and elastosis. Pruritus (uremic pruritus) is the most frequently occurring symptom of end-stage renal disease, affecting 58% to 90% of patients on dialysis. The prevalence is similar among patients on either hemodialysis or peritoneal dialysis. Okada and Matsumoto found that the prevalence was higher in men and postulated that this increased prevalence in men may be due to women using emollients more frequently.

Zucker et al defines uremic pruritus as pruritus that appears shortly before the onset of dialysis or at any time after dialysis without any other explanation. The following criteria must be met: (1) at least 3 episodes of itch during a period of 2 weeks or less, or (2) the appearance of an itch in a regular pattern during a period of 6 months.

Patients with uremic pruritus present with frequent paroxysmal episodes of severe itch that occur most commonly at night (possible relation to diurnal rhythms) and adversely affect sleep. Pruritus can be generalized or localized, with most episodes located on the back (70%) and abdomen (46%). Patients also can develop complications from scratching, including excoriations, lichen simplex chronicus, and prurigo nodularis. Furthermore, the presence of pruritus appears to be associated with poor outcomes in patients undergoing chronic hemodialysis.

The exact mechanism of uremic pruritus is unknown, but the pathogenesis is thought to be multifactorial. Numerous theories have been proposed, including uremic skin developing xerosis; secondary hyperparathyroidism (refuted by Cho et al); divalent ion abnormalities, particularly calcium and iron deficiency anemia; increased levels of mast cells in the skin leading to increased histamine release; angiotensin-converting enzyme inhibitor use; neuropathy and neurologic changes; and retention of urochrome and other toxins in the skin. Retained toxins in the skin have been proposed to cause pruritus by stimulating cutaneous nerve endings. Cho et al proposed that uremic pruritus may be mediated by the release of substance P and other neuropeptides from the cutaneous sensory neurons in response to the toxin.

A correlation between higher Kt/V values, a measure of the clearance of small molecules such as urea, and increased pruritus has been described. The work of Dimkovic et al suggests that larger-sized toxins that are not accounted for in the Kt/V value also may be responsible for uremic pruritus.

Uremic pruritus has been palliated with hydration, topical lubricants, keratolytics, antihistamines, and many new novel agents. The current gold standard of therapy for this condition is UVB phototherapy. According to Ada et al, UVB phototherapy works by inducing apoptosis of dermal mast cells and reducing the release of substance P by decreasing epidermal nerve fibers. This therapy is effective, but recurrence is a problem. Maintenance therapy may prevent relapse. Novel treatments that have been utilized include gabapentin, UVA, μ-opioid receptor agonists, cholestyramine, active charcoal, and thalidomide. Conflicted studies on the utility of the opioid antagonist naltrexone hydrochloride have been reported, but it may be useful in a subset of patients. Nalfurafine, a relatively new κ-opioid receptor agonist, also has been found to be effective in preliminary reports, but further studies are necessary. Among second-line agents, gabapentin usually is preferred in the treatment of uremic pruritus because of safety and efficacy. The definitive cure for uremic pruritus is renal transplantation.

Comment

Pruritus is a common symptom of connective tissue and other common systemic disease states that often proves to be the most bothersome symptom for many patients. A search of the literature using PubMed and the terms pruritus and itching did not reveal reports of an association between the inheritable connective tissue diseases Marfan syndrome and Ehlers-Danlos syndrome, or rheumatoid arthritis and pruritus, aside from pruritus reported as an adverse drug reaction. To discuss each potential drug of interest is beyond the scope of this article. While it can be difficult to identify the cause of pruritus in many of the diseases discussed, medications are important sources and should be considered in the etiology. The conventional mainstays in the treatment of pruritus include topical agents and antihistamines, which often are ineffective. The widespread use of novel agents has great potential for patients, and treatment now can be directed at both central and peripheral mechanisms.
of pruritus. Further study of the pathophysiology of pruritus has great promise to produce new targeted antipruritic therapies.

REFERENCES

Pruritus in Common Disease States