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CLINICAL PRACTICE

Chronic Pruritus

Gil Yosipovitch, M.D., and Jeffrey D. Bernhard, M.D.,

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

An otherwise healthy 55-year-old man reports that he has been itchy all over for 6 months. The itch interferes with falling asleep and wakes him repeatedly during the night. Initially, there was no rash, but during the past 4 months, itchy nodules and plaques have developed on his back, arms, and legs. Treatment with sedating and nonsedating oral antihistamines and topical glucocorticoids has had no effect. How would you evaluate and manage this case?

THE CLINICAL PROBLEM

Chronic pruritus, which is defined as itch persisting for more than 6 weeks,¹ is common. It may involve the entire skin (generalized pruritus) or only particular areas, such as the scalp, upper back, arms, or groin (localized pruritus). The incidence of chronic pruritus increases with age.^{2,3} The condition is more common in women than in men and is diagnosed more frequently in Asians than in whites.^{4,5} Chronic pruritus is associated with a markedly reduced quality of life. In a recent study, chronic itch was shown to be as debilitating as chronic pain.⁶ Deranged sleep patterns and mood disturbances, including anxiety and depression, are common and may exacerbate the itching.⁷⁻¹¹

Chronic pruritus is characteristic of several dermatologic diseases (e.g., atopic eczema, psoriasis, lichen planus, and scabies) but also occurs in a variety of non-cutaneous disorders. The causes of chronic pruritus can be broadly categorized into four major groups^{1,12}: dermatologic causes, systemic causes (e.g., cholestasis, chronic kidney disease, myeloproliferative disorders, and hyperthyroidism), neuropathic causes (e.g., notalgia paresthetica [a distinctive itch of the upper back] and brachioradial pruritus [a characteristic itch of the arms, probably caused by spinal-nerve impingement^{13,14}]), and psychogenic causes. Itching of any type may elicit secondary skin changes as a result of scratching, rubbing, and picking, so the presence of skin findings does not rule out a systemic cause. Excoriation and nonspecific dermatitis can camouflage both cutaneous and noncutaneous causes of itch. In some cases, the underlying cause is unclear (pruritus of undetermined origin).

The mechanisms underlying the various types of chronic pruritus are complex. A number of mediators are involved in the itch sensation (Fig. 1). The itch signal is transmitted mainly by small, itch-selective unmyelinated C fibers originating in the skin. Histamine-triggered neurons and nonhistaminergic neurons may be involved. They form a synapse with secondary neurons that cross over to the contralateral spinothalamic tract and ascend to multiple brain areas involved in sensation, evaluative processes, emotion, reward, and memory. These areas overlap with those activated by pain.^{15,16} Patients with chronic itch often have peripheral as well as central neural hypersensitization. In this state, sensitized itch fibers overreact

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KEY CLINICAL POINTS

CHRONIC PRURITUS

- Chronic pruritus (itching that persists for more than 6 weeks) may be caused by inflammatory skin diseases, systemic diseases, neuropathic conditions, and psychogenic disorders.
- The presence of a rash does not necessarily indicate a primary skin disease; lichenification, prurigo nodules, patches of dermatitis, and excoriations result from rubbing and scratching.
- The initial evaluation of a patient who has pruritus of undetermined origin should include a complete blood count with a differential count, a chest radiograph, and tests of hepatic, renal, and thyroid function. Patients with itch of undetermined origin should be reevaluated periodically.
- In the initial treatment of symptoms, the use of mild cleansers, emollients, topical anesthetics, and coolants may be helpful.
- Sedating antihistamines may be used, primarily to help the patient sleep.
- Anticonvulsants, antidepressants, and mu-opioid antagonists appear to be helpful in some forms of chronic itch.

to noxious stimuli that usually inhibit itch, such as heat and scratching. Misinterpretation of non-noxious stimuli also occurs: touch may be perceived as itch.¹⁷ It is not unusual for patients to report that just taking off or putting on their bedclothes triggers a bout of itching. Strange symptoms like this, combined with the extreme distress of chronic itch, sleep loss, and visits to many physicians, may lead to the erroneous diagnosis of psychogenic itch.

STRATEGIES AND EVIDENCE

EVALUATION

The first step in the evaluation of chronic pruritus is to determine whether the itch can be attributed to a dermatologic disease or whether an underlying noncutaneous cause is present. The evaluation should start with medical history taking and physical examination. A detailed review of systems (with attention to constitutional symptoms that may point to an underlying systemic illness¹⁸) should be performed and a thorough drug history (with attention to agents that cause itch, such as opioid analgesics) obtained. Such a review should be repeated at follow-up visits if the diagnosis remains elusive; pruritus is sometimes the first manifestation of a systemic disease, such as Hodgkin's disease or primary biliary cirrhosis, antedating other symptoms by months.

The skin should be examined carefully for primary lesions. Excoriations, nonspecific dermatitis, prurigo nodularis, and lichen simplex chronicus

are secondary lesions for which an underlying cause should be sought (Fig. 2). In some patients — for example, those with scabies, pemphigoid, or dermatitis herpetiformis — subtle primary lesions may be masked by secondary changes or may be nondiagnostic (e.g., patients with scabies may present with urticarial features, scattered secondary patches of dermatitis, nodules on genitalia, and interdigital dermatitis). Patients with excessively dry skin (xerosis) usually present with minimally detectable changes, but erythematous and scaly inflammatory patches may develop.

In addition to a history taking and physical examination, screening laboratory and imaging studies are suggested (Fig. 3).

MANAGEMENT

Treatment of chronic pruritus should be directed at the underlying cause when possible. Itch that is caused by hyperthyroidism or cutaneous T-cell lymphoma, for example, resolves with effective treatment of these conditions. In the absence of a definitive diagnosis, symptomatic treatment is required. Data from randomized, controlled trials of agents for itch treatment are scarce, and in practice, the treatments that are used have variable and often suboptimal effectiveness (Table 1).¹⁹

TOPICAL THERAPY

Emollients and Soaps

For mild or localized itch and for xerosis (e.g., winter itch), topical emollients are the first-line therapy. Such agents probably reduce itch by soft-

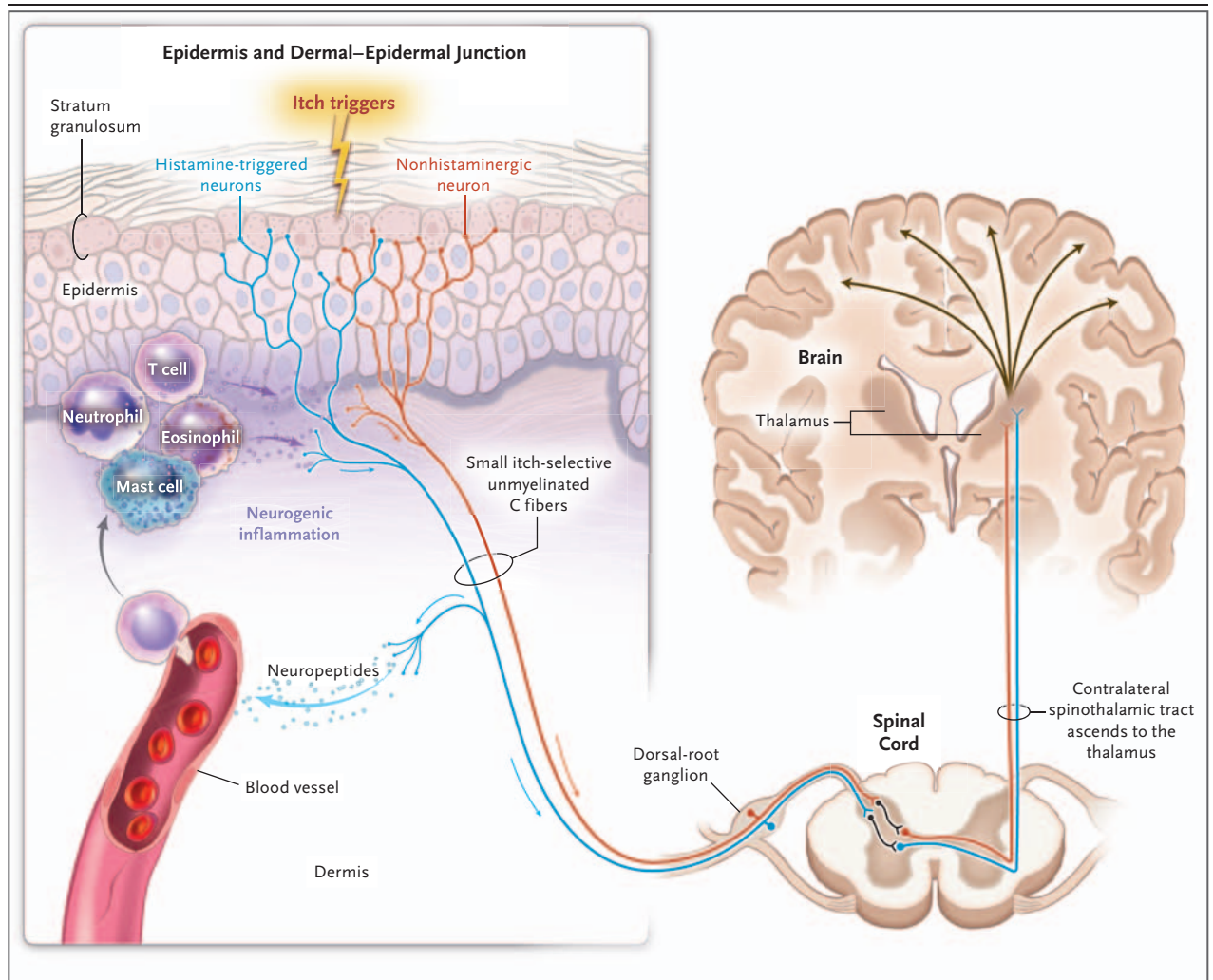


Figure 1. Pathways of Itch from Skin to Brain.

Itch originates in the epidermis and dermal–epidermal junction and is transmitted by itch-selective C nerve fibers. Some of these fibers are sensitive to histamine, but the majority are not. A complex interplay among T cells, mast cells, neutrophils, eosinophils, keratinocytes, and nerve cells (along with increased release of cytokines, proteases, and neuropeptides) leads to exacerbation of itch. The C fibers form synapses with second-order projections in the dorsal horn, and the itch signal ascends in the contralateral spinothalamic tract, with projections to the thalamus. From the thalamus, itch is transmitted to several regions of the brain that are involved in sensation, evaluative processes, emotion, reward, and memory.

ening the sharp edges of the outermost layer of dry skin (stratum corneum) and by improving skin-barrier function. Cutaneous-barrier insufficiency is common in inflammatory skin diseases and is exacerbated by repetitive scratching, which facilitates the entry of irritants. “Wet pajama” treatment can be helpful and soothing when extensive inflammation is present, as in severe atopic dermatitis.^{20,21} In this technique, the patient first applies an emollient and a low-potency topical glucocorticoid to the affected area and then dips

a pair of cotton pajamas in water, wrings them out, and wears them overnight. This treatment should be limited to short courses (≤ 1 week at a time) because of the associated risks of folliculitis and excess absorption of topical glucocorticoids.

Since solutions with a high pH such as alkaline soaps increase the secretion of serine proteases that may induce itch, their use should be avoided in favor of moisturizers and cleansers with a low pH (4.5 to 6.0).²² If secondary infection is present, it should be treated.



Figure 2. Prurigo Nodules on Lichenified Skin in a Patient with Chronic Pruritus.

Anesthetics

Capsaicin, which acts locally by desensitizing peripheral-nerve fibers,²³ has been used as an antipruritic agent in various localized disorders. In a randomized, vehicle-controlled trial, topical capsaicin showed efficacy in patients with notalgia parasthetica.²⁴ Clinical experience suggests that higher concentrations of capsaicin (up to 0.1%) may be more effective than lower ones.²⁵

Preparations of topical anesthetics such as pramoxine 1% or 2.5% cream and the eutectic mixture of lidocaine and prilocaine 2.5% cream have been reported in case series to have short-term beneficial effects for neuropathic, facial, and anogenital itch,²⁵ although data from randomized trials that support their use are limited. In one randomized trial involving patients with pruritus caused by chronic kidney disease, pramoxine 1% cream significantly reduced pruritus, as compared with vehicle alone.²⁶ The safety of long-term use of these agents or use over a large area of skin is unknown.

Coolants

Topical menthol relieves itch by activating A-delta cold afferents, which transmit the sensation of cold by the activation of an ion channel called transient receptor potential cation channel subfamily M member 8 (TRPM8); the cool sensation appears to reduce itch.²⁷ Clinical experience suggests that topical menthol may be effective in low concentrations (1 to 5%); higher concentrations tend to cause irritation.²⁷ The long-term use of this agent for chronic itch has not been studied.

Glucocorticoids

Although topical glucocorticoids do not have direct antipruritic effects, they are antiinflammatory. In randomized, controlled trials, glucocorticoids (both those of high potency and those of moderate potency) have shown efficacy in inflammatory skin conditions, such as atopic eczema, psoriasis, lichen planus, and genital lichen sclerosis.^{25,28} Potent glucocorticoids are also used for secondary manifestations of chronic itch, such as prurigo nodularis and lichen simplex chronicus, although such therapy is largely based on clinical experience in the absence of controlled studies.

Other Agents

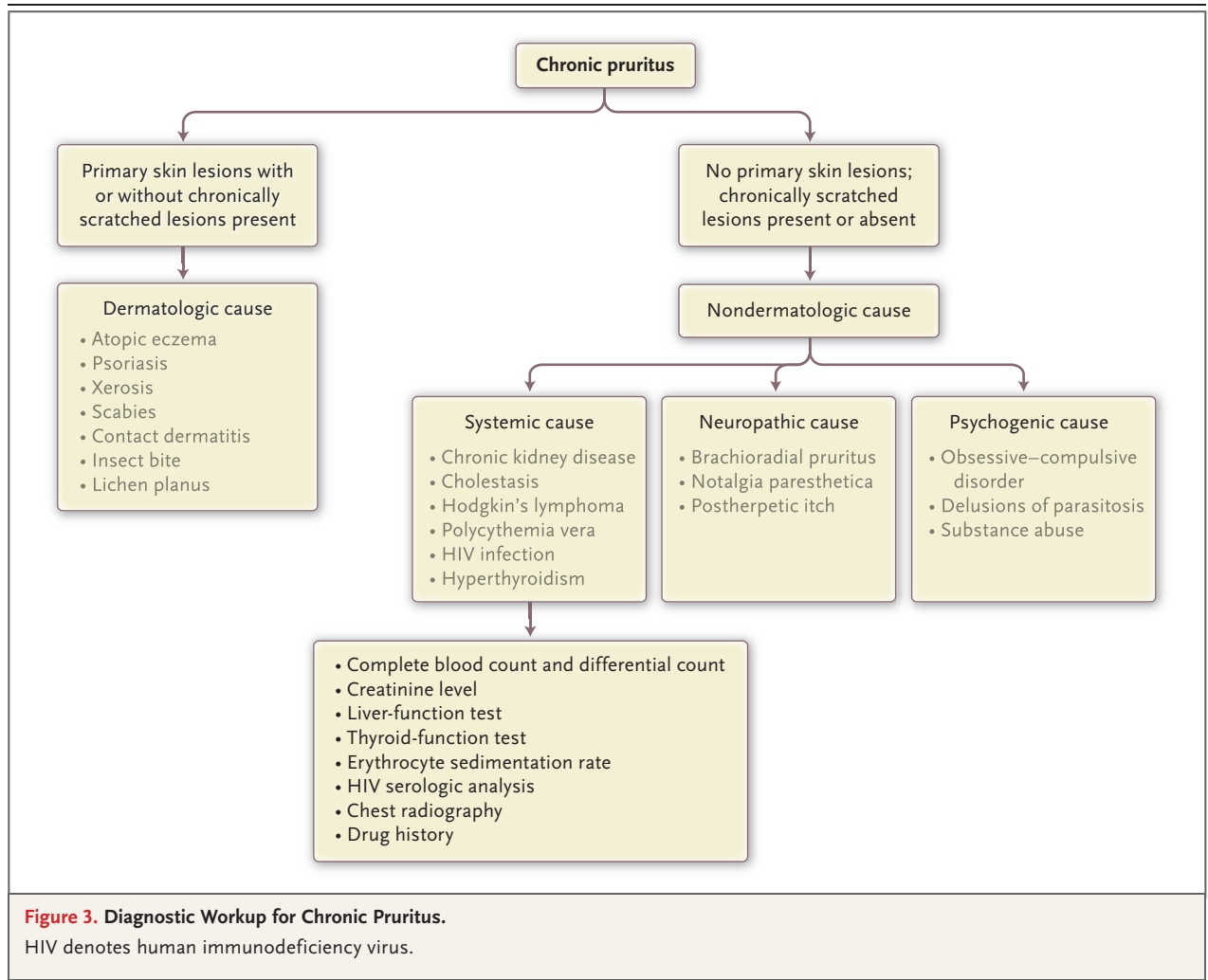
Randomized clinical trials have shown the efficacy of the topical calcineurin inhibitors tacrolimus and pimecrolimus in reducing itch in inflammatory skin conditions, including seborrheic dermatitis, psoriasis, and various types of eczema.²⁹ In a small controlled study, tacrolimus was effective for resistant anogenital pruritus.³⁰ The antipruritic effect of these agents may be mediated by the activation of transient receptor potential cation channel subfamily V member 1 (TRPV1). A common adverse effect of topical calcineurin inhibitors is a burning sensation that fades after a few days of repeated applications.

In one randomized, controlled trial,³¹ doxepin 5% cream, a tricyclic antidepressant with potent anti-H₁ properties, relieved localized itch in patients with atopic eczema and contact dermatitis. However, efficacy has not been shown in other conditions that cause chronic pruritus. Potential adverse events include drowsiness (from absorption through the skin) and allergic contact dermatitis.

SYSTEMIC THERAPY

Antihistamines

In clinical practice, sedating antihistamines (e.g., hydroxyzine, doxepin, and diphenhydramine) are often used as first-line treatment for pruritus. However, data from randomized trials are lacking to support the efficacy of antihistamines in pruritic conditions other than urticaria. It appears in practice that the observed benefits may be due to the drugs' soporific properties, which may help patients sleep and take the edge off itching during the day. Nonsedating H₁-receptor and H₂-receptor antagonists have at most a limited effect



in the treatment of chronic itch, since histamine does not play a major role in conditions other than urticaria.^{25,32}

Neuroactive Medications

Gabapentin and pregabalin, structural analogues of the neurotransmitter γ -aminobutyric acid, are effective for several types of pruritus. In controlled trials involving patients with pruritus caused by chronic kidney disease, low doses of gabapentin (100 to 300 mg three times a week) were significantly more effective in reducing itch than placebo.^{33,34} Case reports have described the use of these drugs in practice to reduce neuropathic itch (e.g., postherpetic itch, brachioradial pruritus, and prurigo nodularis), although there are no data from controlled studies of these conditions.^{15,35}

The mechanisms of action are unclear. The most frequent adverse effects are constipation, weight gain, drowsiness, ataxia, and blurred vision.

Antidepressants

Selective serotonin-reuptake inhibitors (e.g., paroxetine, sertraline, fluvoxamine, and fluoxetine) have been reported to reduce generalized pruritus of various types, including but not limited to psychogenic itch, in case series.³⁶ One small randomized trial showed a modest antipruritic effect of paroxetine, as compared with placebo.³⁷ A small double-blind trial demonstrated the efficacy of sertraline (at a daily dose of 100 mg) for cholestatic itch.³⁸ Case reports have also suggested that the oral noradrenergic and specific serotonergic antidepressant mirtazapine (at a dai-

Table 1. Commonly Used Topical and Systemic Medications for Chronic Pruritus.*

Medication	Common Dose	Side Effects	Medical Condition	Comments
Topical therapy				
Emollients	Many products with different ingredients	None	Atopic eczema itch, dry-skin itch, skin-barrier damage	
Glucocorticoids	Many products with various doses	Skin atrophy, telangiectasia, folliculitis	Atopic dermatitis, psoriasis, skin inflammation	Use low-potency agents in children and on face and in skin folds; avoid long-term use of very potent agents
Anesthetic agents				
Capsaicin	0.025% to 0.1%	Burning sensation for the first 2 wk	Neuropathic itch, itch caused by chronic kidney disease	
Pramoxine	1% to 2.5%	Skin irritation and dryness at the affected area	Facial eczema, genital itch, itch caused by chronic kidney disease, neuropathic itch	
Lidocaine and prilocaine mixture	2.5% to 5%	Methemoglobinemia	Neuropathic itch, postburn itch	
Menthol	1% to 5% cream	Skin irritation (including hypersensitivity and burning sensation) with higher concentrations	Itch that responds well to the application of an ice cube or to cold showers	
Calcineurin inhibitors	Pimecrolimus, 1% cream; tacrolimus, 0.03% to 0.1% ointment	Transient stinging or burning sensation	Atopic dermatitis, contact dermatitis, and particularly for facial or anogenital itch	
Systemic therapy				
Oral antihistamines				
Hydroxyzine	25 to 50 mg four times daily	Drowsiness, dry mouth; abrupt withdrawal may cause confusion	Chronic urticaria, nocturnal itch, drug-related itch; pruritic conditions in which drowsiness is desired effect	Should not be administered with antidepressants
Doxepin	10 to 50 mg orally one to three times daily	Same as for hydroxyzine; can prolong QT interval, so should be used with caution in patients with electrocardiographic abnormalities	Same as for hydroxyzine	May cause confusion in elderly, urinary retention
Diphenhydramine	25 to 100 mg orally four times daily	Same as for hydroxyzine	Same as for hydroxyzine	

Anticonvulsants			
Gabapentin	100 to 1200 mg orally three times daily	Drowsiness, constipation, leg swelling	Neuropathic itch (high dose, up to 3600 mg daily); pruritus from chronic kidney disease (low dose, 100 to 300 mg three times a week after dialysis)
Pregabalin	25 to 200 mg orally twice daily	Drowsiness, leg swelling	
Antidepressants			
Paroxetine	10 to 40 mg orally once daily	Insomnia, dry mouth, sexual dysfunction	Generalized pruritus, paraneoplastic itch, psychogenic pruritus
Mirtazapine	7.5 to 15 mg orally once daily	Drowsiness, dry mouth, increase in appetite, weight gain	Generalized pruritus, nocturnal itch
Amitriptyline	25 to 150 mg once daily or up to 3 divided doses	Drowsiness, dizziness, constipation, dry mouth, blurred vision	Neuropathic itch Urinary retention, heart palpitations, low blood pressure, confusion in elderly
Opioids			
Mu antagonist	Naltrexone, 12.5 to 50 mg orally once daily	Nausea and vomiting, abdominal cramps, diarrhea, hepatotoxicity	Intractable itch, cholestatic pruritus, possibly pruritus from chronic kidney disease
Kappa agonist and mu antagonist	Butorphanol, 1 to 4 mg inhaled at bedtime	Drowsiness, dizziness, nausea, vomiting	Intractable itch
Ultraviolet B radiation (broad and narrow band)	Three times a week	Burning sensation, initial pruritus; long-term risk of skin cancer	Atopic dermatitis, psoriasis, pruritus from chronic kidney disease

* Data are adapted from Yosipovitch and Patel.^{1,9}

ly dose of 15 mg) may relieve nocturnal itch of various types, including cancer-related itching.^{39,40} Improvement in intractable itch has been reported in a case series of patients with cutaneous T-cell lymphoma who were treated with a combination of low-dose mirtazapine and gabapentin or pregabalin.⁴¹ Tricyclic antidepressants, such as amitriptyline, are also occasionally used to treat chronic pruritus (e.g., neuropathic or psychogenic forms),^{14,25} although these agents have not been studied for this use in randomized trials.

Opiate Agonists and Antagonists

Randomized, controlled trials have shown antipruritic effects of mu-opioid antagonists (e.g., naltrexone, nalmefene, and naloxone) in patients with chronic urticaria, atopic eczema, and cholestasis, findings that are consistent with the presumed involvement of endogenous activation of the mu-opioid receptor in mediating chronic itch (especially in systemic diseases such as chronic kidney disease and cholestasis).⁴² However, the results of studies of these agents for the treatment of pruritus in patients with chronic kidney disease have been inconsistent.^{43,44} Their use is limited by initial adverse effects, such as nausea, loss of appetite, abdominal cramps, and diarrhea.

In randomized, placebo-controlled trials, nalfurafine hydrochloride, a kappa-opioid agonist not currently available in the United States (but available in Japan), was shown to reduce itch significantly in patients with chronic kidney disease.^{45,46} The major adverse effect is insomnia. According to anecdotal reports, butorphanol, a kappa-opioid agonist and mu-opioid antagonist that is administered intranasally and has been approved by the Food and Drug Administration for the treatment of migraine, reduces intractable itch associated with non-Hodgkin's lymphoma, cholestasis, and opioid use.⁴⁷

PHOTOTHERAPY

Observational studies have suggested that broad- or narrow-band ultraviolet B (UVB) radiation, alone or combined with ultraviolet A (UVA) radiation, reduces pruritus caused by chronic kidney disease and improves itch in skin diseases such as psoriasis, atopic eczema, and cutaneous T-cell lymphoma.^{48,49} In a single-blind, randomized trial involving patients with refractory itch caused by chronic kidney disease,⁵⁰ there was no significant difference in efficacy between narrow-band UVB radiation and UVA radiation.

BEHAVIORAL THERAPY

Behavioral-modification therapies, including education of the patient regarding coping mechanisms and stress-reduction techniques that interrupt the itch–scratch cycle, may complement pharmacotherapy.^{51,52} However, data from randomized trials of such therapies are limited. In one randomized trial that assessed the addition of cognitive behavioral therapy and patient education to conventional dermatologic therapy in patients with chronic itch, there were short-term benefits in some outcomes, including a nonsignificant reduction in itch frequency and scratching (but not in intensity) and significant improvement in the use of coping mechanisms.⁵³

AREAS OF UNCERTAINTY

The pathophysiology of pruritus is only partially understood. The optimal evaluation strategy with respect to yield and cost-effectiveness has not been determined. Data from randomized, controlled trials of various pharmacologic and nonpharmacologic treatments for chronic pruritus are scarce.

GUIDELINES

European guidelines for the management of chronic pruritus have been published. The recommendations in our article are largely concordant with these guidelines, except that some medications are not currently available in the United States.²⁵

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette presented with chronic, severe, generalized pruritus of undetermined origin. He has prurigo nodules and lichenification (thickening of the skin); these are secondary to rubbing and scratching, not indicative of a primary dermatologic condition. In such patients, careful examination is needed to look for a dermatologic disorder. A complete medical history should be taken, and a physical examination and basic laboratory tests should be performed to look for evidence of systemic causes, such as chronic kidney disease, cholestasis, hyperthyroidism, or lymphoma. Periodic reevaluation is warranted if no cause is identified.

Since dryness of the skin may be subtle, and because dryness may aggravate pruritus of any

cause, emollients should be recommended; mild cleansers should be used to avoid further irritation. Trigger factors such as overheating from the use of excessive bedding should be avoided. Topical antipruritic agents (e.g., pramoxine) may be helpful.

In patients with severe pruritus that cannot be eliminated by identifying and treating an underlying cause (or pending effective primary treatment), topical therapy and lifestyle changes are unlikely to be sufficient, and systemic therapy should be considered. Given a paucity of data from randomized trials to evaluate various therapies, therapeutic choices are largely based on clinical experience and anecdotal reports. Sedating antihistamines are commonly used as first-line therapy but often have only modest efficacy in practice (largely attributable to their soporific

properties), and these drugs have not helped the patient described in the vignette. We would consider off-label treatment with gabapentin, starting at a low dose (e.g., 300 mg and increasing up to 2400 mg daily in divided doses). If this therapy is not adequate to control pruritus, we would consider adding off-label treatment with low-dose mirtazapine (7.5 to 15.0 mg at night), although data from randomized trials are lacking to support this approach.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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