Pruritus in the Elderly

Clinical Approaches to the Improvement of Quality of Life

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Case Report

J. D., an 85-year-old female resident of a long-term-care facility, was recently evaluated for generalized pruritus. Her medical history includes dementia, diabetes mellitus, peripheral vascular disease, hypertension, congestive heart failure, chronic obstructive pulmonary disease, osteoarthritis, gastroesophageal reflux disease, and a recurrent urinary tract infection.

Over the clinical course of her disorders, she was taking multiple medications off and on, including acetaminophen, fluticasone/salmeterol inhaler, albuterol inhaler, ipratropium inhaler, docusate sodium, ferrous sulfate, flunisolide nasal spray, furosemide, lovastatin, insulin, omeprazole, and enalapril.

These medications were discontinued to determine whether they were the cause of the patient's pruritus. The discontinuations had no effect on her condition.

Systemic hydroxyzine, diphenhydramine, and prednisone; oral amitriptyline; and topical betamethasone dipropionate ointment were used to treat her pruritic symptoms.

A review of the patient's organ systems proved unremarkable. On physical examination, she was noted to be in no distress. Her cognition was unchanged from her admission status of mild disorientation, which was consistent with her dementia.

The remainder of her examination was significant only for mild excoriations on her stomach and extremities and an erythematous rash across her buttocks.

Laboratory assessments were within normal values except for a white blood cell (WBC) count of 11,500 mcL with a normal differential; a random blood glucose level of 278 mg/dL; and a blood urea nitrogen (BUN) of 42 mg/dL.

The patient's pruritus has remained moderately symptomatic; only occasional relief was achieved with medications.

The cause was never determined. The purpose of the review was to present the possible causes of the pruritus to assist clinicians in individualizing treatment.

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INTRODUCTION

Pruritus is the most common skin disorder in the geriatric population.[1] It is defined as an unpleasant cutaneous sensation that provokes the desire to scratch.[2] Acute itch (lasting less than 6 weeks) may provide a protective function, but chronic itch (lasting more than 6 weeks) is mostly a nuisance.[3] The prevalence of pruritus increases with age and can be partially attributed to a decline in the normal physiological status of the skin (Table 1).[2,4]

In a French study, a survey was sent to 10,000 randomly selected households.[5] Of 7,500 respondents, 87% reported skin problems since birth and 43% experienced these problems over the 2 years preceding the survey. In addition, 29% of the respondents described their symptoms as burdensome. Of those individuals, more than half indicated that chronic skin disorders, with pruritus as the primary symptom, impaired daily activities.

Moreover, in a study of skin disorders in 68 noninstitutionalized persons, two-thirds of the group and 83% of octogenarians reported medical concerns regarding their skin, with pruritus the most frequent complaint.[6] In a study conducted in Norway, itching was the predominant skin complaint in subjects ranging from 30 to 76 years of age.[7]

Chronic pruritus can have a significant effect on quality of life, because therapies for acute pruritus often do not ameliorate chronic disease.[8] In many people, itching is not just an occasional problem; it can have debilitating effects, such as sleep impairment, that can result in clinical depression. In fact, many people with chronic itching can become so depressed that they would rather live a shorter life free of symptoms than a longer life with pruritus.[8] Studies have shown

Table 1 Decline of Skin Function in the Geriatric Population

- Cell replacement
- Barrier function
- Chemical clearance capacity
- Sensory perception
- Mechanical protection
- Wound healing
- Immune responsiveness
- Thermoregulation
- Sweat production
- Vitamin D production

Data from Tycross R, et al. *Q J Med* 2003;96:7–26;[2] and Fenske NA, Lober CW. *Geriatrics* 1990;45:27–35.[4]

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that the detrimental effect of chronic pruritus on quality of life is comparable with that of chronic pain.[8,9]

INCIDENCE AND PREVALENCE

As noted, chronic pruritus is one of the most common dermatological complaints of patients, especially in the elderly. In the study by Beauregard and Gilchrest,[6] two-thirds of geriatric patients reported pruritus as their major skin complaint. The condition is more prevalent in women than in men.[7,10]

In an analysis of hospital-based patient registry records, 11.5% of hospital admissions in elderly patients were attributed primarily to pruritus.[1] In patients older than 85 years of age, this incidence rose to nearly 20%. In another study, pruritus was present in two-thirds of approximately 1,500 elderly patients in skilled-nursing facilities.[11]

PATHOPHYSIOLOGY

The sensation of itching is closely associated with the sensations of touch and pain.[12] Pruritus is stimulated by the release of neurostimulators, such as histamine, from mast cells and other peptides. The resulting sensation of itch is carried on A-delta and C fibers, through the dorsal horn of the spinal cord, and across the anterior commissure to the spinothalamic tract, ultimately terminating in various brain centers, including the cortex and thalamus.[10,12–14]

Aging skin is susceptible to pruritic disorders because of the cumulative effects that the environment has on the skin and because of changes to the skin structure that occur as we age.[15] Loss of skin hydration, loss of collagen, impaired immune system responses, and impaired function of the skin as a barrier to pathogens are also involved. Impaired blood circulation, leading to decreased perfusion to the skin, may also occur.[3] The presence of comorbid conditions, the lack of mobility, and the increased use of medications may also contribute to the prevalence of pruritus in elderly individuals.[16]

In older people, pruritus is often associated with dry skin resulting from decreased skin-surface lipids, reduced production of sweat and sebum, and decreased perfusion.[17] Collagen is also reduced and is less soluble in geriatric populations. Moreover, because of skin folding, less surface area is able to interact with water.[18] This can result in impaired immune function and diminished barrier repair. Altered skin pigmentation and increased skin fragility also increase the likelihood of pruritus in elderly adults.[18]

NEUROTRANSMITTERS

The release of histamine from mast cells is believed to be the primary mediator of itching.[19] This release may also cause a vascular response that results in erythema and swelling of the affected skin. However, because not all patients with pruritus respond to antihistamine therapy, other mediators appear to be involved as well.[19] For example, serotonin (5-HT) is released when platelets aggregate and stimulate serotonin receptors. 5-HT_3 antagonists have been shown to reduce itching.[20]

Acetylcholine, a neurotransmitter, is also involved in pruritus, particularly in patients with atopic dermatitis.[21] These patients have dry, thickened skin and an increased sensitivity to acetylcholine.

Prostaglandins (lipid compounds produced in cells by the enzyme cyclooxygenase) are involved in the chemical cascade created by histamine and may potentiate pruritic symptoms caused by histamine and possibly other agents.[22]

Nerve fibers containing substance P, a neuropeptide, congregate around sweat glands and blood vessels and can lead to neurogenic inflammation.[23] In addition, vasoactive intestinal peptide (VIP) can produce itching.[23] High levels of substance P, VIP, somatostatin, and neuropeptide Y occur in pruritic skin lesions.[23,24] In addition to histamine, activated mast cells release chymase, tryptase, leukotrienes, and interleukins, which can lead to pruritus.[23]

CLASSIFICATION AND ETIOLOGY

The classification of pruritus begins with the disorder's etiology.[13] The origin can be both dermal and neuropathic. Pruritus can also originate centrally, or the cause can be psychogenic.[2]

Dermatological Causes

The most common dermatological change that occurs in elderly people is xerosis, or dry skin.[25] Environmental conditions or excessive loss of moisture from the epidermis may result in xerotic lesions, which can crack and split. This in turn can cause pruritus and bleeding, possibly leading to infection. Other causes of dry skin include weather extremes, such as cold air or low humidity, and excessive exposure to water, especially in colder climates.[25–27]

Excessive exposure to the sun can also lead to a variety of skin irritations, including sunburn, or it can exacerbate further drying of xerotic skin lesions.[26,27]

Scabies, an extremely pruritic skin disorder, commonly occurs in the elderly, especially those confined to long-term-care facilities.[28] Scabies results from infection by the host-specific mite *Sarcoptes scabiei* var *hominis*. Each year, more than 300 million cases of scabies occur worldwide, and the infection is highly contagious in institutional settings.[28] The disorder is diagnosed by microscopic examination of skin scrapings under mineral oil.[29]

Atopic dermatitis, or eczema, is a recurring inflammatory skin condition that is often associated with allergic disorders, such as asthma and allergic rhinitis.[30] Exposure to an allergen provokes the release of histamine, which can result in pruritus.

Pruritus is also associated with contact dermatitis. Detergents used in institutional bedding and clothing, as well as the materials used in the manufacturing of these garments, have been implicated. Other irritants include fiberglass and environmental cleaning agents.

Infection (e.g., tinea, candidiasis, and herpesvirus) is another important cause of pruritus. Patients with certain viral infections, such as measles or rubella, commonly experience intense itching.

Bacterial infections can also cause pruritus; this usually occurs after scratching has damaged the skin, which allows bacteria to colonize the affected area. Fecal bacteria may be transferred to the skin from contaminated hands, or dermal bacteria, such as streptococci or staphylococci, may grow in open wounds.[29]

Neuropathic and Neurogenic Causes

Damage to nerve fibers or to the brain can lead to a particular form of pruritus known as "itch without rash."[31] This type of neuropathic itching is processed in the thalamus after the stimulation of dorsal horn neurons. The itching can be caused by a variety of nerve-related disorders, including multiple sclerosis and brain tumors.[31]

After a stroke, damage to the central nervous system (CNS) can lead to neurogenic pruritus.[32,33] In these cases, the sensation of intense itching arises from lesions in the thalamus or parietal lobe without localized skin irritation.

Pruritus has also been associated with neuralgia following a herpes infection.[34]

Psychiatric Causes

Pruritus can result from a number of psychiatric disorders. In one study, 70% of patients with chronic pruritus had at least one of six psychiatric diagnoses, including dementia, schizophrenia, primary depressive disorders, personality disorders, and behavioral disorders.[35]

The French Psychodermatology Group proposed three compulsory criteria for a diagnosis of psychogenic pruritus:[36]

- localized or generalized itch without skin lesions
- chronic itch (lasting more than 6 weeks)
- absence of a somatic cause

In addition, at least three of the following seven criteria should be present:

- a chronological relationship with an event that could have psychological repercussions
- stress-related variations in the intensity of the itching
- nocturnal variations in symptoms
- predominance of the itching during rest or inaction
- presence of a psychological disorder associated with itching
- itching that can be improved with psychotropic drugs or psychotherapy

Pruritus Associated With Systemic Diseases

Systemic diseases often lower the itch threshold. In this setting, a mild stimulus can trigger an exaggerated pruritic response in some patients. Comorbid xerosis resulting from decreased skin hydration may exacerbate pruritus in older patients with systemic diseases. This is especially true for institutionalized geriatric patients or for individuals with dementia whose general inactivity allows them to be distracted by pruritic stimuli.[37]

Patients with liver disease often experience pruritus.[38–40] Itching is a presenting symptom in 25% of those with jaundice from biliary obstruction or other causes, such as cirrhosis, pancreatic cancer, or hepatitis.[38] It has been hypothesized that pruritus in these patients might be the result of an accumulation of bile in nerves or skin cells, but this remains unproven.[38]

Increased levels of plasma lysophosphatidic acid (LPA) and of serum autotoxin have been observed in patients with cholestatic pruritus.[39] Autotoxin is involved in the conversion of lysophosphatidylcholine to LPA. High concentrations of bile salts or of endogenous opioids have been implicated as well.[40] Other causes of neurogenic itch associated with cholestasis include the release of intrinsic opioids or the extrinsic administration of opiate drugs.[41] The symptoms of cholestatic pruritus are usually more pronounced at night.

Pruritus occurs in up to 90% of patients with renal failure or uremia who are receiving maintenance dialysis.[42] The most common cause is xerosis secondary to dialysis, which affects the balance of calcium, magnesium, and phosphorus. In addition, the patient's uremic condition acts as a chronic inflammatory process, causing the releasing of proinflammatory cytokines and histamine.[43] Itching does not occur in patients with acute renal failure.[44]

The presence of pruritus is one of the four diagnostic hallmarks of diabetes mellitus (i.e., polyuria, polydipsia, polyphagia, and pruritus), although early studies found that itching was present in only 7% of patients with diabetes.[42] The cause of the intense itching experienced by diabetic patients is unclear, but it may be related to secondary conditions, such as xerosis or infections.[45] Interestingly, the control of elevated blood glucose levels often leads to a marked reduction in symptoms.

Several case studies have identified generalized pruritus as a symptom of thyroid disease. In these patients, the most common cause of pruritus was the presence of antithyroid antibodies.[46] Pruritus in patients with hyperthyroidism may be caused by the warm, moist skin that accompanies this disorder, although the exact cause is unknown.[47] Hyperthyroidism can also cause cholestatic jaundice, which has been associated with pruritus.[48] In patients with hypothyroidism, pruritus is usually the result of xerosis.[47,49] Treatment of the underlying condition usually results in the resolution of pruritic symptoms in patients with thyroid disease.[38,47,49]

Hematological disorders can also cause pruritus.[47] For example, the onset of Hodgkin's disease is often preceded by an intense, burning itch.[50] Moreover, generalized pruritus occurs in 25% to 50% of patients with polycythemia vera (a bone marrow disease associated with an abnormal increase in the number of blood cells).[51] Adult-onset eczema has been identified as a marker for leukemia.[50]

Drug-Induced Pruritus

Drug-induced pruritus typically results from an allergic reaction to an active medication or to the fillers or preservatives used in the drug's preparation.[52] Drugs can also cause pruritus indirectly by affecting the liver or kidneys, which leads to itching owing to liver failure and jaundice or to renal failure with uremia.[52] Some medications, such as angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors, mediate the release of bradykinins, resulting in pruritus.[52]

Pruritus may occur as a secondary response to systemic side effects involving the liver or kidney after treatment with amiodarone (Cordarone, Wyeth/Pfizer), ticlopidine (Ticlid, Roche), some antibiotics (e.g., macrolides and carbapenems), and psychotropic agents (e.g., tricyclic antidepressants and neuroleptics).[53,54] Statins (HMG–CoA reductase inhibitors), antimicrobials, chemotherapeutic agents, and antiseizure medications, such as phenytoin (Dilantin, Pfizer), carbamazepine (Tegretol, Novartis), and topiramate (Topamax, Janssen), may

cause a rash or skin lesions, with resulting pruritus.[54–56]

Opioids can cause pruritus, most likely as an adverse effect rather than as an allergic reaction. Pruritus occurs in 2% to 10% of patients who have been treated with opioids; the mechanism is thought to be related to the release of histamines or to a centrally mediated process.[57]

Some drug reactions that result in pruritus can be severe and potentially life-threatening. The appearance of acute urticaria and angioedema, for example, should be considered a medical emergency, requiring the immediate discontinuation of the offending agent, followed by treatment with parenteral antihistamines and prednisone.[58]

Toxic epidermal necrolysis (TEN), also known as Lyell's syndrome, is one of the most serious drug-related skin reactions. It involves the initial development of erythema, followed by large vesicles and mucosal erosions. The exposure of underlying tissue, with fluid loss, can lead to systemic infection and, potentially, fatal septic shock. Phenytoin, barbiturates, penicillin, and sulfonamides are known to cause TEN.[58]

EVALUATION

Although it can be difficult to identify the cause of pruritus, therapy is a fairly straightforward process after the origin has been determined. Treatment consists mainly of removing or avoiding the offending agent or allergen in conjunction with the use of topical or systemic drugs.

Medical History

A detailed medical history should be obtained if the primary cause of the patient's pruritus is to be identified. The following factors must be considered:[59]

1. ***Initiation of symptoms.*** Understanding when the pruritus started and its relationship to the introduction of a new environmental factor, detergent, soap, or food is important. It should also be determined whether the itching is generalized or localized, and its location should be pinpointed; this information may point to a primary cause of the disorder. For example, an itch that is localized to the groin or to the anal area may have a specific cause, such as a fungal or parasitic infection, or it may be secondary to another disorder, such as hemorrhoids.

2. ***Presence or absence of lesions.*** The presence or absence of a lesion can help point to the cause. For example, a pruritic rash that waxes and wanes may indicate an allergic reaction.

3. ***Time of day when symptoms are worst.*** Knowing when symptoms are most severe may guide the diagnosis toward a primary cause, such as mites or other parasites, which tend to be more active at night. Pruritus that is worse at bedtime could also be related to irritation from bedding.

4. ***Identifying what makes the condition better.*** Some circumstances may improve the condition, such as immersing the affected area in cold water or avoiding certain clothes or soaps.

When seeking a secondary cause, the clinician must consider the presence of other disorders. For example:[60]

- Polyuria, polydipsia, and polyphagia may indicate the presence of diabetes mellitus.
- A history of anxiety, palpitations, or hair loss may indicate that the pruritus is associated with hyperthyroidism.
- A pruritic patient who is chronically fatigued may have concomitant hypothyroidism.
- Generalized pruritus accompanied by dark brown urine, abdominal pain and bloating, and yellowing of the skin and eyes may point to a hepatic origin.
- Pruritus accompanied by weight loss may signify an occult neoplasm.[61]
- The presence of diabetes mellitus, liver disease, a thyroid imbalance, or neoplasia may indicate that the pruritus is a secondary condition.[62]

Other important aspects of the patient's medical history include:[63,64]

- ***Surgery.*** Determining whether the patient has had surgery for a chronic biliary disorder or has had cancerous tissue removed can help pinpoint a secondary cause of the itching.
- ***Medications.*** Drugs can be a primary cause of chronic pruritus, and a detailed history of their intake must be obtained. Noting a relationship between the start of drug treatment and the beginning of itching could be the key to identifying its cause. Conversely, a history of improvement after the withdrawal of a drug is also significant.
- ***Allergies.*** Understanding medication allergies and cross-sensitivities is helpful. Well-known cross-sensitivities, such as penicillin and cephalosporin, can be quickly resolved. Lesser-known cross-reactions should be investigated, especially if the timing of the beginning of the itching coincides with the introduction of a new drug. The clinician should also investigate the patient's use of over-the-counter medications and the cross-reactivity of those drugs with prescribed agents.
- ***Social history.*** A history of social behaviors, including the use of illicit drugs and alcohol, can also assist the clinician. The recreational use of illicit drugs, such as opiates, amphetamines, and cocaine, may indicate that a generalized pruritus is secondary to this behavior.
- ***Family history.*** A family history of medical conditions associated with secondary pruritus is important. The occurrence of diabetes mellitus, thyroid disease, or liver disease in other family members may assist the clinician in reaching a diagnosis.[63]
- ***Review of systems.*** A review of the patient's organ systems, besides the skin, is an important part of the medical history, as accompanying complaints may guide the clinician toward a diagnosis of secondary pruritus. Symptoms associated with other organ systems should be considered, and a further workup should be performed to exclude specific conditions, based on findings from the initial review.[64]

Physical Examination

The physical examination of a patient with pruritus should start with a general evaluation.

Vital signs must be assessed. The presence of fever (i.e., a temperature of more than 100.8°F) may indicate that the pruritus has been caused by an infectious process.

Assessment of the skin, of course, is the most important part of the physical examination.[65] The clinician must check the skin's coloration. The presence or absence of erythema in the areas affected by the itching can help in diagnosis, especially infection. Hemorrhage may signify a secondary cause of pruritus, such as neoplastic disease. Jaundice may indicate itching related to liver disease.

During the skin examination, the clinician must also look for lesions. Pruritic vesicles on the skin are a hallmark of viral infections, such as varicella (chickenpox). Larger lesions (bullae) could be the result of bacterial infections, such as impetigo, or autoimmune disorders. Excoriations in the affected areas signify the intensity of the itching as well as the possibility of secondary infection, because the barrier properties of the skin might have been jeopardized. Scaling and cracks in the skin are hallmarks of xerosis. Localized, itchy macules or papules may indicate an atopic reaction to an allergen.[59]

A simple touch of the skin to assess the warmth of the affected area helps in identifying an infection. The clinician may palpate the skin for fluctuance when an abscess is suspected of causing pain and itching. Subcutaneous or subepidermal lesions should be assessed to determine the need for a biopsy.

The clinician should also examine the skin for tissue turgor to assess general hydration. In elderly patients, the elasticity of the skin tends to be lost, so the "tenting" that is typically seen in patients with low turgor may be the result of aging, not dehydration, in these individuals.[63]

Checking for dermatographism is an easy test to perform. The clinician strokes the patient's skin using the dull side of an object in a linear motion. If the line remains elevated and erythematous, the result is considered positive. A positive test indicates that the patient has overly sensitive skin and that histamines have been released in response to the mild trauma. This finding usually indicates that an antihistamine should be prescribed.

Thickening of the skin in a pruritic area can indicate the presence of chronic inflammation, which can result from continuous scratching or irritation.[66]

Laboratory Tests

Laboratory assessments may be helpful in identifying the cause of pruritus, but they usually play a supportive role in the physical examination. The complete blood count might show an increased white blood cell (WBC) count. A high neutrophil count, with a large number of immature neutrophils (left shift), would indicate the presence of a bacterial infection. An elevated WBC count showing an increased number of eosinophils may indicate an allergic reaction or the presence of a parasitic infection. A high lymphocyte count, by contrast, may indicate a viral infection. The presence of any abnormal WBC counts, as well as the presence of abnormal WBCs, should be reviewed and considered in terms of a neoplastic process.[67]

Chemistry panels may indicate the presence of a secondary cause of the itching. Elevated bilirubin levels confirm an observation of jaundice, and elevated alkaline phosphatase levels would pinpoint the cause of the jaundice. Elevated glucose levels might point to diabetes as a cause of the pruritus. Thyroid-function studies can identify abnormal activity in the thyroid gland, which may be manifested as pruritus.[46]

The erythrocyte sedimentation rate (ESR), although generally nonspecific, may be increased in autoimmune connective-tissue disorders or in infectious diseases, and it may be extremely high in the presence of neoplastic disease.[68]

TREATMENT

General Measures

In the elderly, the management of pruritus poses a unique challenge. Elderly patients with cognitive impairment may make it impossible for them to identify a cause-and-effect relationship between the pruritus and the routine activities of daily living, or physical impairments may prevent them from applying topical treatments.[59] The management of pruritus in this age group requires a patient-specific approach, in which treatments are tailored to the patient's mental and physical disabilities, as well as to concurrent disease states, the severity of the pruritic symptoms, and the potential adverse effects of available treatments.

Patient education is the first step in alleviating nonspecific pruritic symptoms in elderly individuals. Patients should be counseled to break the itch–scratch cycle. Scratching can cause increased cutaneous inflammation, thereby worsening the itch.[59] The cessation of scratching, therefore, may alleviate the secondary irritation caused by the scratching itself. Moreover, patients should keep their nails short to avoid further irritation of the skin if they are inclined to scratch.

Educating patients about the nonpharmacological measures that they can take to alleviate pruritic symptoms may decrease the need for continuous pharmacological intervention. For example, patients should be instructed to take short baths and to avoid hot water. Applying moisturizers immediately after bathing will ensure that the skin remains well hydrated. Ideally, moisturizers with a low pH should be used to maintain the normal acidic pH of the skin and to preserve the skin's barrier function.[59] Using a twice-daily emollient, especially one that contains 5% or 10% urea, may be beneficial, although trial and error is often the method used to determine which emollient works best.[3]

Patients should avoid alkaline cleansers and preparations containing alcohol, as these tend to dry the skin. Mild, moisturizing bar soaps, such as Dove (Unilever), and soaps containing lanolin and glycerin are preferred over commercially available pure soaps, such as Ivory (Procter & Gamble), because they cause less skin flaking after use.[69]

Wearing light, loose clothing while avoiding irritating fabrics, such as wool, will also benefit the patient.[70] To prevent excessive heat or perspiration, patients should maintain a comfortable air temperature in their homes, allowing less than 40% moisture content.[69] Using a humidifier in the winter and an air conditioner in the summer is recommended.

Topical Therapies

Corticosteroids

Although corticosteroids are not directly antipruritic, they are believed to produce their therapeutic effects by alleviating the inflammation associated with some skin conditions, such

as atopic dermatitis and psoriasis.[70] Corticosteroids should be used sparingly. Higher-potency steroid creams and ointments may provide an improved anti-inflammatory response, but they also put the patient at increased risk for adverse effects, including skin atrophy, telangiectasia, and suppression of the hypothalamus–pituitary axis.[70]

Topical corticosteroids should be used with caution in the elderly; these individuals may be particularly susceptible to the skin-thinning effects of these drugs.[70]

Topical Immunomodulators

The topical calcineurin inhibitors tacrolimus (Protopic, Astellas) and pimecrolimus (Elidel, Novartis) are commonly used in the treatment of atopic dermatitis. These agents are nonsteroidal selective inhibitors of the production and release of inflammatory cytokines in T cells and of other pro-inflammatory mediators in mast cells.[71]

In a randomized trial comparing pimecrolimus cream 1% with placebo in patients with atopic dermatitis, 56% of the pimecrolimus group experienced a significant reduction in the severity of pruritus compared with 34% of the placebo group within 48 hours after treatment ($P = 0.003$).[70]

In another study, Ständer et al. evaluated the efficacy of tacrolimus 0.1% and pimecrolimus 1% in patients with prurigo nodularis (pruritic nodules of an unknown etiology) and in patients with localized or generalized pruritus.[72] Of the 20 patients who received these medications, eight (40%) achieved a complete cessation of itching (a reduction of 70% to 90%). Adverse drug effects included stinging and burning at the application site.

If tolerated, topical immunomodulators might be a good option for elderly patients with pruritus, because thinning and atrophy of the skin are not a concern.

Coolants

Menthol and phenol are cyclic terpene alcohols that occur naturally in plants. They affect delta-A nerve fibers, which transmit the sensation of cold.[73] The cooling sensation provided by these agents may alleviate itching.

Although the optimal concentration of menthol has not been established, products containing 1% menthol are commonly used to relieve pruritus.[74] With favorable safety and toxicity profiles, menthol is a good option for relieving pruritus in elderly patients.

Local Anesthetics

Agents that contain local anesthetics, such as lidocaine (Lidoderm, Endo) and lidocaine/prilocaine (Emla, AstraZeneca), may relieve itching, especially when they are applied with occlusive dressings of cloth or nylon.[73]

A local anesthetic made by Abbott, pramoxine HCl (also known as pramocaine) has antipruritic properties and has been used in hemodialysis patients with uremic pruritus.[75] Prax Lotion (Ferndale) is another product that contains pramoxine.

Polidocanol is a non-ionic surfactant with moisturizing and local anesthetic properties, both of which help to ameliorate pruritic symptoms. In an open-label study, polidocanol lotion 3%, when combined with urea 5%, significantly reduced pruritus in patients with xerotic disorders, including atopic dermatitis, contact dermatitis, and psoriasis.[76]

Capsaicin

As the main capsaicinoid in chili peppers, capsaicin exerts its antipruritic effect by desensitizing sensory nerve fibers.[77] It is beneficial in the treatment of neuropathic, systemic, and dermatological pruritus. Adverse effects include pain, burning, and stinging at the application site, which may cause patients to stop treatment prematurely.

In a single-blind study involving healthy volunteers, the topical anesthetic cream EMLA (lidocaine 2.5%/prilocaine 2.5%) was applied 60 minutes before capsaicin cream 0.075% was applied on one forearm and before placebo was applied on the other forearm.[78] After 5 days of three-times-daily application, pretreatment with Emla significantly reduced the burning sensation from capsaicin, which may promote better adherence to capsaicin treatment.

Topical Cannabinoids

Cannabinoids act at peripheral sites and produce analgesia through their actions on CB_1 and CB_2 receptors. The local analgesic actions of agonists for CB_2 receptors, such as *N*-palmitoyl-ethanolamine (PEA), include the inhibition of mast-cell function and inflammatory pain.[79] PEA has been incorporated into topical analgesic preparations and has been shown to reduce pruritus in patients with atopic dermatitis, lichen simplex, and prurigo nodularis; it has also decreased itching associated with chronic kidney disease.[80,81]

Topical Antihistamines

Topical antihistamines, such as diphenhydramine and pyrilamine, are used primarily to treat urticaria and insect bites. These products are not usually used for other pruritic conditions, such as idiopathic local and generalized pruritus, because of the side effects of erythema and skin irritation.[73]

Doxepin (Sinequan, Pfizer), a tricyclic antidepressant, exhibits potent histamine receptor (H_1 and H_2) antagonism. In a double-blind study, Drake and Milikan compared the antipruritic efficacy and safety of doxepin HCl cream 5% (e.g., Prudoxin, Healthpoint) with a placebo vehicle in patients with lichen simplex chronicus, nummular eczema, or contact dermatitis.[82] Twenty-four hours after initiation of treatment and for the remainder of the 7-day study, almost all of the doxepin patients experienced significantly greater relief of pruritus compared with those receiving placebo ($P < 0.002$).

The most common side effects included a transient stinging sensation after application (20.7%) and drowsiness (15.5%) resulting from systemic absorption. Although the drowsiness subsided over time, this undesirable side effect may limit the use of doxepin cream in elderly patients.

Topical Aspirin

A double-blind placebo-controlled study in patients with lichen simplex chronicus (an intractable, itchy dermatosis) demonstrated a significant improvement in the symptoms of pruritus after treatment with an aspirin/dichloromethane solution.[83] This option may be helpful for elderly patients who are unable to tolerate long-term, high-potency steroids.

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Systemic Therapies

Antihistamines

Traditionally, the treatment of pruritus associated with various skin disorders has focused on medications that antagonize histamine receptors. It has been proposed, however, that the relief of itching achieved with these medications might be a result of their sedating properties and not necessarily the antagonism of histamine, especially in pruritic conditions such as eczema, psoriasis, and lichen planus.[84]

Pruritus that results from the stimulation of histamine receptors (as in urticaria) may be effectively treated with antihistamines, such as diphenhydramine (Benadryl, McNeil Consumer) because of their ability to antagonize histamine H_1 receptors.[13,75,84] The use of systemic antihistamines should be avoided in elderly patients because of the anticholinergic effects of these drugs.

Pruritus that is caused by the release of histamine is mediated by H_1 receptors. Therefore, the nonsedating H_2 receptor antagonists, such as loratadine (Claritin, Schering-Plough) and fexofenadine (Allegra, Sanofi), are generally not effective in the treatment of histamine-related pruritus.[13] These agents, however, have favorable side-effect profiles, are relatively safe in older persons, and may be an option for elderly patients with pruritic dermatoses accompanied by erythema and wheals.[13]

Serotonin Receptor Antagonists

The antidepressant mirtazapine (Remeron, Organon), a serotonin ($5\text{-}HT_2$/$5\text{-}HT_3$) receptor antagonist, is an effective therapy for pruritus, particularly in patients with advanced cancer, cholestasis, or hepatic or renal failure.[85] The drug's potential for causing drowsiness may be beneficial in patients with nocturnal pruritus.[86]

In an open-label study, patients with chronic pruritus received long-term treatment with the selective serotonin reuptake inhibitors (SSRIs) paroxetine (e.g., Paxil, GlaxoSmithKline) and fluvoxamine (Luvox, Abbott).[87] An antipruritic effect was observed in 68% of the patients. Paroxetine and fluvoxamine did not differ significantly in their efficacy. The best responses occurred in patients with atopic dermatitis, systemic lymphoma, or solid carcinoma.

Patients with cholestatic pruritus showed an antipruritic response after they were treated with the antiemetic agent ondansetron (Zofran, GlaxoSmithKline), a $5\text{-}HT_3$ receptor antagonist.[73]

The use of serotonin receptor antagonists in elderly patients may be limited by the occurrence of adverse effects, including excessive CNS stimulation, sleep disturbances, and increased agitation. It is important to consider the risk–benefit ratio of these agents in the elderly; they should be administered only as second-line or third-line therapy.[3]

Opioid Antagonists and Agonists

Opioid-induced pruritus occurs after activation of the mu-opioid receptors in the CNS. It is through this central process that mu-opioid receptor antagonists, such as the generic drugs naltrexone, nalmefene, and naloxone, are believed to have an effect in treatment-resistant pruritus.[88] These agents have been used successfully to treat uremic and cholestatic pruritus, chronic urticaria, atopic dermatitis, prurigo nodularis, and opioid-induced pruritus.[3,89]

The activation of kappa-opioid receptors is known to reduce pruritus. The kappa-opioid receptor agonists butorphanol (formerly Stadol, Apothecon) and nalfurafine (not available in the U.S.) have been beneficial in patients with intractable itching and uremic itching, respectively.[59,90]

Both opioid-receptor antagonists and agonists should be used sparingly with supervision and caution in elderly patients. These medications can put patients at risk for sedation and insomnia, and they have a potential for abuse.

Neuroleptic Agents

The antiepileptic drugs gabapentin (Neurontin, Pfizer) and pregabalin (Lyrica, Pfizer) decrease neuronal transmission. Gabapentin is effective in the treatment of neurological pruritus (including brachioradial pruritus and notalgia paresthetica) when used as a localized patch worn on the infrascapular area of the back.[91,92] Gabapentin is also effective in the treatment of uremic pruritus.[93]

Because it is chemically similar to gabapentin, pregabalin has been proposed as a therapy for chronic pruritus.[94] Both gabapentin and pregabalin are eliminated by the kidneys; therefore, they must be administered appropriately in elderly patients and in patients with impaired renal function to avoid an overdose and adverse side effects.

Other Treatments

Phototherapy

Narrow-band ultraviolet-B (NB–UVB) therapy is effective for uremia-related pruritus and has achieved dramatic improvements in patients with severe itching.[13] In a prospective study, NB–UVB was also effective in patients with generalized pruritus, although the therapy's mechanism of action was not entirely clear.[95] This approach may be a viable option, especially in elderly patients, because the barrier of nonadherence to topical treatments does not come into play.

Psychotherapy

A meta-analysis was conducted to determine the effects of psychological interventions in patients with atopic dermatitis.[96] Eight clinical trials were reviewed, and numerous interventions were evaluated, including aromatherapy, autogenic training, brief dynamic psychotherapy, cognitive–behavioral therapy, habit-reversal behavioral therapy, stress management, and structured education. The investigators concluded that psychological interventions reduced the severity of eczema or the intensity of itching and scratching in patients with atopic dermatitis.

Acupuncture

Acupuncture interferes with the central and peripheral transmission of itching through sensory nerve innervation, which may be beneficial in patients with neuropathic pruritus, prurigo nodularis, or uremic pruritus.[97] Undertaking a review of the literature, Carlsson et al. noted that pruritus had been successfully treated with acupuncture in several trials, although the patient cohorts were small.[97] Alternative modalities may show promise for the treatment of pruritus in elderly patients.

Treatment of Pruritus Associated With Systemic Disease

Cholestatic Pruritus

Pruritus often develops in patients with hepatic disease. It has been theorized that the accumulation of bile in nerve and skin cells causes itching. Therapy in these patients should focus on the underlying disease.[38]

The bile-acid sequestrants cholestyramine (e.g., Questran, Par) and colestipol (Colestid, Pfizer) are used to treat cholestatic pruritus, and up to 80% of patients have shown a partial or complete response to these drugs within 2 weeks.[98] Because cholestyramine and colestipol can interfere with the absorption of many other drugs, they should not be administered within 4 hours before or after the use of certain agents. This schedule may be difficult for elderly patients who are taking multiple medications. Moreover, cholestyramine and colestipol are associated with potentially significant gastrointestinal side effects, such as bloating, diarrhea, and abdominal discomfort. Therefore, these drugs may need to be replaced with other bile-acid sequestrants, such as colesevelam (Welchol, Daiichi Sankyo).[98]

A double-blind, placebo-controlled study demonstrated the efficacy and safety of naltrexone (ReVia, Duramed), an oral mu-opioid receptor antagonist, in cholestatic pruritus.[99] Patients with intrahepatic cholestasis who received naltrexone (50 mg) showed a statistically significant improvement in daytime and nighttime itching ($P = 0.0003$ and $P = 0.001$, respectively) compared with patients given placebo.

Several other treatments, including rifampin (Rifadin, Sanofi), ursodeoxycholic acid (e.g., Actigall, Watson), propofol (Diprivan, AstraZeneca), phototherapy, SSRIs, and oral cannabinoids, have also relieved cholestatic pruritus.[98,100]

Uremic Pruritus

The cause of uremic pruritus is not completely understood. Treatment should be administered in a stepwise fashion using drugs with favorable side-effect profiles. Optimizing dialysis has been shown to improve pruritic symptoms in elderly patients.[100] Topical treatment with tacrolimus ointment (Protopic) reduces pruritus associated with chronic kidney disease and may be a safe option in elderly patients.[101]

A randomized, double-blind, controlled comparative trial was conducted to evaluate the benefits of an anti-itch lotion containing 1% pramoxine in patients with moderate or severe uremic pruritus who had received hemodialysis for at least 3 months.[75] Fourteen patients were treated with the pramoxine-based lotion, and 14 were given a control lotion. The pramoxine group experienced a significant reduction in the intensity of itching (a 61% decrease) compared with controls (a 12% decrease) ($P = 0.0072$).

In another study, gabapentin was effective in patients with uremic pruritus who had undergone hemodialysis for more than 3 months.[93] The patients received gabapentin (100 mg) after hemodialysis for 4 weeks. After a washout period of 1 week, they received placebo for another 4 weeks. On the Visual Analogue Scale (VAS), mean pruritus scores were 6.44 ($P < 0.0001$), 15.00 ($P < 0.001$), and 81.11 ($P < 0.001$) during the gabapentin, washout, and placebo periods, respectively.

Uremic pruritus has also been relieved with cholestyramine, activated charcoal, thalidomide, oral opioid antagonists, cannabinoids, capsaicin, phototherapy, pentoxifylline (Trental, Sanofi), and acupuncture.[100,101]

Hematological Malignancies

Pruritus that is directly associated with iron-deficiency anemia responds to oral therapy with iron salts, and symptomatic improvement is seen within 14 days after treatment.[100]

Pruritus is also a key clinical feature of polycythemia vera. Antihistamines, antidepressants, interferon-alpha, phlebotomy, phototherapy, iron supplements, and myelosuppressive medications have had mixed results when used to treat the pruritus associated with this condition.[102]

Many other malignancies are associated with itching, including Hodgkin's lymphoma, myeloma, lymphoma, leukemia, paraproteinemia, Waldenström's macroglobulinemia, and mastocytosis. Pruritic patients with these malignancies may experience relief after the underlying disorder has been controlled.[100]

Many adults with HIV infection also have skin conditions, including pruritus.[103] Clinicians must keep this in mind when treating elderly patients, and appropriate testing should be done.

CONCLUSION

The ultimate determination of the cause of the common complaint of pruritus remains a diagnostic dilemma and a challenge for any physician. Identifying the cause of pruritus in elderly patients with cognitive impairment can be even more difficult. Every effort must be made to identify primary and secondary causes of the disorder, and this can require excessive time and a meticulous history and physical examination. Careful attention must be paid to even the slightest detail that would lead the physician down the correct path.

When the cause has been determined, choosing the appropriate treatment is not always easy. The presence of comorbidities may make it difficult to select the correct treatment. In elderly or other impaired persons, using therapies that require a patient's attention to drug schedules or other details is rife with problems.

Physicians who treat patients with pruritus should consider the adverse effects of all medications; be aware of patient complaints early in the process; and act in the patient's best interest to improve quality of life and to eradicate discomfort.

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