Published in final edited form as:
Dermatol Ther. 2013 ; 26(2): 92–103. doi:10.1111/dth.12029.

Advanced Aging Skin and Itch: Addressing an Unmet Need

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Keywords

pruritus; elderly; Willan's itch; xerosis

Introduction

Itch, or pruritus, is defined as an unpleasant sensation that elicits the desire to scratch. Itch is the most common skin disorder in the elderly and while often ignored, can have a major impact on the quality of life of in older patients [1]. The high prevalence of pruritus in the geriatric population has been partially attributed to the decline in the normal physiology of the advanced aging skin. Major changes in skin structure and its ability to regenerate, along with cumulative effects of the environment, diminish the barrier function and hydration status of the skin. These changes make the elderly more susceptible to entry of irritants and allergens through the skin, leading to inflammation and pruritus. Decline in normal immune function and age related changes in nerve fiber density, polypharmacy and the presence of other systemic diseases also contribute to the high rate of pruritus in the elderly. As the elderly population continues to grow, practitioners need to be aware of how to evaluate and manage pruritus. Pruritus in advanced aging skin may reflect primary skin disease, systemic disease or arise idiopathically. The approach to evaluate itch in older patients should be guided by history and physical exam, and requires recognition of physiological changes that occur as skin ages. Ultimately, management of pruritus will require an individually tailored approach that is guided by a patient's general health, severity of symptoms and the potential adverse effects of the treatments [2].

Prevalence of Pruritus and It's Impact on Quality of Life

Itch is the most common skin complaint in people over the age of 65 years [1]. One survey examining dermatologic conditions and skin care needs of 68 subjects aged 50 to 91 years (mean age of 74 years) found that two-thirds of the subjects reported one or more specific complaints about their skin with pruritus being the most common complaint, affecting at least 29% of the subjects [3]. Another study involving 1,556 patients from a skilled-nursing facility reported that the two most common dermatologic conditions were xerosis and pruritus, with nearly two-thirds of patients reporting pruritus as a major complaint [4]. Thus, pruritus has a high prevalence within the elderly population.

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Chronic pruritus, defined as itch lasting for longer than 6 weeks, poses a significant threat to overall quality of life (QoL). A recent survey of 73 patients with chronic pruritus and 138 patients with chronic pain (mean age of participants was 55 years old) which utilized directly elicited health utility scores demonstrated that chronic pruritus has an impact comparable to that of chronic pain on QoL [5], underscoring the significant burden of disease with which chronic itch patients suffer. Pruritus in the elderly can lead to sleep impairment and clinical depression. It has been suggested that depressive symptoms in chronic pruritus patients are partly mediated by the effect of itch on quality of sleep [6]. Separate studies in patients with uremic pruritus have suggested that itch, via it's impact on sleep, not only affects morbidity, but increases mortality [7]. Given the high prevalence of chronic itch in elderly populations and it's potential profound impact on QoL, physicians, both dermatologists and non-dermatologists, must be cognizant of how to diagnose and appropriately manage itch in elderly patients.

Pathogenesis of Pruritus in Aging Skin

Xerosis

Pruritus in the elderly is most commonly associated with dry skin or xerosis [8]. Epidemiological studies conducted in nursing homes populations have reported 30 to 75% prevalence of xerosis in the elderly [1, 9]. Additional studies examining individuals living in the community yielded similarly high prevalence rates, ranging from 55 to 85% [10, 11]. These results suggest that xerosis is a widespread condition regardless of individual living or care settings.

Xerosis in the elderly arises in part due to age-dependent physiologic changes in the ability of skin to produce and retain moisture. Skin from younger individuals has an ample supply of active sebaceous and sweat glands which promote and maintain moisture in their local environment, whereas these glands are less active in aged skin. [12, 13] In addition, the most superficial layer of the skin, known as the stratum corneum, is saturated with lipids, proteins and amino acids that are vital to it's ability to retain moisture and maintain the skin's barrier function. These structural components are reduced in the elderly, impairing its water retention and thereby leading to xerosis [14]. A recent study identified aquaphorin-3 (AQP3), a membrane channel which allows passage of glycerol and water, as a critical element in maintaining skin hydration via its regulation of glycerol concentration within the cornified layer. AQP3 deficient mice have relatively dry skin and delayed recovery of barrier function. Interestingly, AQP3 gene expression is significantly reduced in human skin from individuals older than 60 years of age, suggesting that AQP3 reduction may also be contributing to the relative challenges of maintaining proper hydration in elderly skin [15].

Environmental factors that deplete the skin's moisture also exacerbate xerosis in the elderly. Cold air with low humidity or excessive exposure to water are common causes of dry skin, especially in the winter months [16, 17]. The frequent use of harsh soaps and drying personal care products such as powders and gels also contribute to pruritus. Given the challenges of retaining moisture in elderly skin, these environmental insults are much more detrimental to epidermal structure and function in older individuals.

Impaired Barrier Function

Altered epidermal barrier function is another major factor that contributes to pruritus in the elderly. An intact external barrier prevents the intrusion of allergens and pathogens which may otherwise induce inflammatory cascades that trigger itch. A complex interplay of proteins, lipids and enzymes are involved in the establishment and maintenance of skin barrier homeostasis. Many of the enzymes required to process the lipids involved in maintaining epidermal barrier, function at an acidic pH. The surface pH of the epidermis becomes less acidic with age, thereby impairing the function of these crucial enzymes and their ability to promote barrier repair and homeostasis [18]. Consistent with these observations, levels of stratum corneum ceramides and lipids are reduced in aged human and mouse skin [16, 19]. In addition, electron microscope studies in aged skin have revealed focally decreased number of lamellar bodies, membrane-bound granules which deliver lipid precursors into the extracellular space at the interface of the stratum granulosum and stratum corneum [20]. The increase in the pH, from acidic to more neutral or basic pHs, also promotes activation of serine proteases in the stratum corneum that degrade important integrity and cohesion proteins such as desmoglein 1 [21]. Protease-mediated degradation of proteins necessary to maintain adequate barrier homeostasis and epidermal integrity may contribute to or aggravate itch in the elderly.

Impaired barrier repair and decreased clearance of transepidermally-absorbed materials from the dermis promote conditions that result in pruritus [22, 23]. For example, an altered barrier allows for epidermal penetration of potential antigens, allergens and pathogens, stimulating the immune system to release proinflammatory cytokines. Moreover, a shift in the Th1 to Th2 balance or an exaggerated Th2 response has been observed in the aging immune system, these changes may contribute to the development of different pruritic conditions, such as allergic or irritant contact dermatitis

Medication Side Effects

Due to the high prevalence of comorbid medical diseases such as diabetes, hypertension, hyperlipidemia and others, elderly patients often take multiple prescription medications as well as non-prescription vitamin and herbal supplements. Numerous medications have been implicated in causing pruritus, and it is not uncommon for elderly patients to be taking multiple potential offenders at one time, making it challenging to identify one causative agent. An abbreviated list of drugs that commonly cause pruritus in the aging population is provided in Table 2.

The mechanisms by which different medications induce pruritus vary widely. Pruritus may result from an allergic reaction to an active medication or to the preservatives present in the drug’s preparation [24]. Medications can also cause pruritus indirectly by affecting kidney and/or liver function, particularly in patients who already have some baseline renal or hepatic insufficiency. Certain medications such as angiotensin-converting enzyme (ACE) inhibitors may induce pruritus by inhibiting the breakdown of bradykinins and substance P by the angiotensin-converting enzyme [25]. Opiates are increasingly used in the elderly for management of pain, and may precipitate itch via stimulation of mast cells in the skin as well as itch-sensing neurons in the central and peripheral nervous system [26].

Certain medications can exacerbate xerosis or eczema in the elderly by interfering with skin barrier function, thus initiating or worsening pruritus. For example, HMG-CoA reductase inhibitors (statins) have been demonstrated to induce xerosis cutis mimicking asteatotic irritant dermatitis. Barrier dysfunction in this case is believed to be a consequence of inhibition of cholesterol biosynthesis and the resultant decrease in the production and distribution of lipids in the skin that are essential for maintaining the barrier [27]. Calcium channel blockers (CCBs), another commonly encountered medication in this population, are frequently implicated in causing itch. The mechanisms by which CCBs cause itch remain unclear. One case-controlled survey demonstrated that elderly patients with eczema are more likely to be taking CCBs than those without eczema[28], however whether this is due to a direct effect on skin barrier, inflammatory cascades or simply a non-causal association is unclear.

Comorbid medical disease

Numerous systemic diseases have been implicated in causing chronic pruritus, many of which are more frequently observed in older populations [23]. Due to the extensive nature of this topic, we refer interested readers to a review that focuses the impact of medical disease on chronic itch. [29] We limit our discussion here to some of the more common causes encountered in aging populations.

Chronic renal and liver insufficiency represent common causes of intractable itch, regardless of the primary pathology leading to end-organ dysfunction [30]. Although the exact pathogenesis of how chronic renal failure or liver insufficiency lead to itch is still not clear, it has been hypothesized to result from several contributing factors including altered clearance of metabolites, abnormal activation of proinflammatory cytokines, and dysregulation of opiodergic signaling, all of which culminate in activation of itch-sensitive pathways in the peripheral or central nervous system [30, 31]. The hypothesis that altered metabolites initiate the itch-inducing cascade is supported by observations that symptoms improves in renal patients after hemodialysis, and that patients suffering from itch due to renal or liver disease, achieve resolution of their symptoms after organ transplantation [31, 32] Iron-deficiency anemia may induce intractable pruritus by promoting either epithelial or neurologic dysfunction [33], while thyroid function abnormalities provoke pruritus mainly by impacting skin hydration [34]. Similar to neuropathic pain, neuropathic pruritus may also arise in the setting of poorly controlled diabetes, spinal stenosis or injury [29-32]. Finally, paraneoplastic itch in the setting of low grade lymphomas, multiple myeloma and other myelodysplastic syndromes, is not infrequently observed in this patient cohort [30]. The pathophysiology of itch in the setting of malignancy remains unclear but inflammation is thought to be a key mediator [35]. The precise pathophysiology of pruritus associated with many of these systemic diseases remains poorly understood.

Differential Diagnosis and Clinical Features of Pruritus in Elderly Patients

When evaluating an elderly patient with pruritus, it is crucial to obtain a thorough history and physical exam. The presence of a primary cutaneous eruption as well as the distribution

and frequency of symptoms will help narrow down the differential. Table 3 lists common conditions that lead to pruritus in elderly patients. These are described in more detail below.

Xerosis Cutis

The most common cause of pruritus in the elderly is xerosis [36]. Interestingly, xerosis is an equally common finding on physical exam regardless of whether patients offer subjective complaints of dry skin [11]. As a result, we recommend always including xerosis cutis in the differential for pruritus in elderly patients even if they are unable to identify the severity of skin dryness. According to a cross-sectional study examining 756 French patients older than the age of 65 in an ambulatory primary care setting, potential risk factors associated with xerosis include increasing age, female gender, certain medications, pruritus during sweating, and a history of atopic dermatitis [10]. Xerosis can occur secondary to underlying medical conditions such as human immune-deficiency virus (HIV) infection, thyroid disease, diabetes or malignancy. These additional diagnoses should be explored if other historical or physical findings raise clinical suspicion [37]. In addition, medications can be reviewed for agents that promote xerosis, including diuretics, lipid lowering agents, anti-androgens, and cimetidine [38]. While it is important to identify medications that may contribute to xerosis, it is equally important to recognize that many of these medications are medically necessary and often cannot be discontinued except in the most severe and refractory cases of dryness.

Systemic Disease

In addition to skin barrier changes and the influence of immunosenescence, elderly patients are also at increased risk for pruritus due to the higher prevalence of underlying systemic conditions. These conditions generally present without primary cutaneous lesions. Because of the potential morbidity and mortality of many of these systemic diseases, it is critical that the following conditions remain on the differential in patients presenting with generalized, chronic or intractable pruritus.

Renal pruritus, also referred to as uremic or nephrogenic pruritus, is a form of generalized pruritus that arises most often in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). The exact etiology of this condition has not yet been confirmed. Currently, 20-50% of ESRD patients experience pruritus [31, 39]. In addition, studies have suggested that patients can be at risk for pruritus as early as CKD stage 3, with one group reporting pruritus in up to 18% of stage 3, 26% of stage 4, and 40-60% of stage 5 patients [40]. As a result, even patients without overt symptoms of renal failure should have their creatinine and BUN levels tested if they present with generalized pruritus of unknown etiology. The pruritus of renal failure tends to have a variable and nonspecific presentation. Pruritus may vary in severity and appear as seldom as once per month to occurring daily [41]. Itch may be widespread, however patients report most frequent involvement of the back, scalp, arms, and abdomen [42]. Another historical finding supporting this diagnosis is that many ESRD patients report improvement following immediately after dialysis. On physical examination, the condition presents without any obvious primary lesions, although there is usually evidence of secondary changes such as excoriations or keratotic and lichenified nodules due to repeated scratching [26].

Pruritus of cholestasis should also be considered for persistent, generalized pruritus, particularly if the pruritus is severe. Patients struggling with cholestatic pruritus often experience worsening at night. Cholestatic pruritus can arise from both intra- and extrahepatic biliary diseases, along with hepatocellular injury [13]. These conditions should be evaluated with liver function panel testing. Similar to renal pruritus, patients present with excoriations, hyperpigmentation, lichenification and other secondary skin changes due to trauma from scratching. Other clinical symptoms of hepatic insufficiency or failure, such as scleral icterus, jaundice, telangiectasia, palmar erythema, caput medusa on the abdominal wall or gynecomastia and testicular atrophy in males may also aid in making this diagnosis.

Generalized pruritus may also be observed as part of a paraneoplastic syndrome associated with hematologic malignancies, or more common solid tumors including lung, colon, breast, stomach, and prostate cancer [43]. In particular, hematologic diseases such as Hodgkin's disease and polycythemia vera (PCV) have a strong association with pruritus [29]. Pruritus is reported in approximately 30% of Hodgkin patients and nearly 50% of PCV patients [43]. PCV-associated pruritus is generally characterized as worsening after contact with water, followed by stinging or burning sensations that last for minutes to hours after contact. A complete blood count as well as age-appropriate cancer screening are advised for all patients with generalized pruritus without a primary eruption. Finally, pruritus can also be a symptom of HIV infection, hyper- or hypothyroid, iron-deficiency anemia or connective tissue diseases such as dermatomyositis or scleroderma. In addition, seborrheic dermatitis can also be an important cause of pruritus, especially in patients with Parkinson's or Alzheimer's disease. Elderly patient's with non-melanoma skin cancers may suffer from localized pruritus within those lesions. While these conditions will not be a focus of this review, it is important to consider the possibility of these diagnoses in the elderly patient.

Drug-induced pruritus

As mentioned above, drug-induced itch must be considered in the differential diagnosis of any individual struggling with chronic pruritus. When approaching this concern in the elderly, it is crucial that the evaluating physician recognize several of the following features of drug-induced pruritus. First, clinical presentation may vary widely and some patients might experiencing severe itch even without an identifiable rash [44] [40]. Second,,drug-induced pruritus may occur after 10 or more years of being on a particular agent. Moreover, in some cases it can take up to one year after discontinuation of the offending medication for pruritus or eczema to completely resolve [28]. Finally, depending on the mechanism by which itch is caused, medications within the same class often trigger the similar itch side effects, whether due to allergic cross-reactivity or simply common biologic function. Unfortunately, this limits the types of agents that can be used when considering alternatives therapies for a particular medical condition.

Neuropathic Itch

Neuropathic itch, which arises in the setting of altered nerve function due to damage or inflammation, must also be considered when evaluating elderly patients with chronic pruritus without primary skin lesions. According to the published experiences of one major academic center, 8% of elderly pruritic patients were found to have a primary manifestations

of scratching including excoriations, hyperpigmentation and lichenification are focal in nature.

Notalgia paresthetica (NP) can be considered for patients who complain primarily of a focal area of unremitting, unilateral pruritus on the back that resides within a dermatomal distribution. NP is a sensory radiculopathy that is thought to arise due to radicular nerve compression. Indeed, a radiologic follow-up study has suggested that 80% of patients with a clinical diagnosis of NP have radiologic evidence of spinal abnormalities in the affected dermatomes, such as degenerative changes or a herniated nucleus pulposus [46]. Similarly, brachioradialis pruritus may cause focal, unremitting pruritus localized to the dorsolateral forearm overlying the proximal head of the brachioradialis muscle. Involvement of the upper arms and shoulders is also common. This condition is also believed to arise from radicular compression, and radiologic follow-up has suggested an association with cervical spine pathology [47].

Older patients are also at higher risk for herpes zoster, which can result in a chronic post-herpetic itch. This condition is analogous to post-herpetic neuralgia, except that it affects nerve fibers that mediate itch rather than pain [48]. An epidemiologic study has suggested that this post-herpetic condition affects from 33% to 50% of zoster patients and may be more common on the face and neck [49]. The condition is characterized by causing pruritus in a dermatomal distribution that is mild to moderate in severity. Eliciting a past history of shingles, including affected location, is key to making the diagnosis.

Finally, an often overlooked, yet potentially very common cause of neuropathic itch is diabetic polyneuropathy. Diabetic neuropathy presents as pain and/or itch in a symmetric distribution that usually affects the lower extremities initially with subsequent proximal extension. Patients may ultimately experience chronic truncal pruritus [50]. Localized neuropathic pruritus of the scalp has also been described in diabetic patients. Complete resolution of scalp symptoms can be achieved with improved control of diabetes. [48, 49] Neuropathic itch may also arise following cerebrovascular accidents (CVA). Although not widely recognized, post-stroke pruritus has been reported to develop in the days to weeks after suffering CVA. Patients usually present with excessive pruritus, which may be localized or generalized, but primarily involves skin contralateral to the stroke lesion [51]. Trigeminal Trophic Syndrome (TTS), which may result from stroke or peripheral damage to the trigeminal nerve, is also associated with localized neuropathic itch [42]. TTS is characterized by unilateral, self-induced facial ulceration from scratching because of underlying neuropathic sensory abnormalities. It is believed that the loss of sensory small-fiber innervation leads to intractable itch, which in the setting of loss of protective pain sensation leads to painless self-mutilation from scratching. These lesions are commonly located at the nasal ala, and are often confused for basal or squamous cell carcinomas, infection or granulomatous skin disorders [52]. Although both stroke induced pruritus and TTS are rare, they should always be considered in elderly patients with the appropriate clinical history.

Infestation

While often overlooked, infestations with mites or lice are not infrequently the cause of pruritus in the elderly. Mite infestations are commonly spread among those living in group or long-term care facilities, and may disproportionately affect the elderly because of frequent residence in institutionalized settings [53]. Classically, the history will reveal a sudden onset of intense pruritus that does not abate over time. In younger patients, scabies usually presents as intractable, widespread itching limited to the body and sparing the face and scalp. In older patients, particularly those that are chronically ill or immunosuppressed, the presentation may be atypical in that it involves the scalp or face. In most cases, patients will complain of worsening pruritus at night. A report of multiple individuals in a household or nursing home experiencing pruritic symptoms should place scabies high on the differential. On physical examination, a scabies infestation can present with a variety of morphologies depending on the host's immune reaction to the mite, including papules, vesicles, pustules and nodules, eczematous patches or lichenified plaques [35]. The finger web spaces, thenar and hypothenar eminences, wrists, feet, and genitals should be closely examined for burrows, vesicles or crusted nodules. Given the increased likelihood of atypical presentations in the elderly, one should also look for lesions on the scalp or the presence of nodular scabies, which appears as violaceous nodules in the groin or axillae that result from hypersensitivity to mite antigen [54]. Patients who are immobilized or suffering from dementia are also at risk for crusted scabies, which presents as intensely pruritic scaly and crusted plaques, usually centered on the hands and feet. Because the average institutional outbreak of scabies affects up to 18 patients and last an average of 14.5 weeks, early identification of a scabies infestation in the acutely itchy elderly patient may bear a tremendous public health impact [55].

For elderly patients who are bed-ridden, or those unable to bathe or wash their clothes regularly, head or body lice may induce an intensely pruritic, erythematous papular dermatitis. The patients may describe widespread or localized, intense itch and a prickling or biting sensation along the neck, upper back, neck, axillae, flanks and waistline in response to body lice. On examination, erythematous or excoriated papules observed in a widespread distribution outlining areas of contact with the patient's clothing should raise suspicion for body lice. This type of presentation has been described as a "louse blouse" [56]. Clothing must be examined closely for the presence of lice or nits, particularly along the seams of clothing. Pet exposure may also contribute to eczema or pruritus from fleas or mites. Thus, a detailed living and exposure history along with physical exam is needed to rule out infestation as a cause of itch.

Additional Diagnoses to Consider

As in any age group, primary pruritic skin conditions such as atopic dermatitis, allergic contact dermatitis, dermatitis herpetiformis or lichen planus, may affect the elderly and must be considered in the differential diagnosis of chronic itch. As a review of these conditions is beyond the scope of this review, we only make mention of bullous pemphigoid (BP) and transient acantholytic dermatosis (TAD), which are relatively common in the elderly.

Bullous pemphigoid is an immunobullous condition that predominantly affects older patients, with a median age of 80 years [57]. This diagnosis should be considered in any older patient with a history of bullae or erosions, or even urticarial or eczematous papules or plaques as these findings may represent an early stage of BP. Pruritus associated with BP can range from mild to severe, with some patients presenting with only faintly erythematous patches but with innumerable erosions due to deep excoriation. Although a presumptive diagnosis may be made on clinical examination alone, a skin biopsy is usually required to make a definitive diagnosis.

Transient acantholytic dermatosis, also known as Grover's disease, is an intensely pruritic eruption that predominantly affects older men [58]. The condition is more common in the winter months [59]. The clinical presentation characteristically begins with few erythematous papulovesicles or keratotic papules of the trunk, but lesions may become more widely distributed over time. The eruption typically spares the palms, soles, and scalp. There are generally no constitutional symptoms, although there are reports of TAD erupting subsequent to a fever or systemic illness [60]. While a clinical diagnosis of TAD may be rendered, skin biopsy demonstrates hallmark findings of acantholysis. Patients often report pruritus out of proportion to the clinical findings. Although the condition can be extremely uncomfortable, it is benign. Individual lesions are self-limited and spontaneously resolve over weeks to months, however the eruption recurs frequently.

Psychogenic itch is a diagnosis of exclusion that should be considered if all other investigations have been exhausted. The condition is characterized by excessive scratching or picking at normal skin in the absence of a primary eruption. In these patients, it will be important to work with patients to break the itch-scratch cycle, whether by treating the underlying condition or using other approaches such as wraps or an Unna boot. In some patients, however, there may be some underlying psychiatric condition that is causing self-mutilating behavior, such as depression, obsessive compulsive disorder, anxiety, or psychosis [61]. If screening questions regarding sleep, mood, or self-perception raise concerns, the patient may benefit from a referral to a psychiatrist or psychologist.

TREATMENT OF PRURITUS IN THE ELDERLY

The management of pruritus in the elderly can be challenging because of the physical and/or cognitive limitations.. The elderly patients are frequently unable to apply topical treatments and therefore compliance becomes a major issue. In addition, comorbid conditions and polypharmacy increase the risk of adverse drug reactions especially with systemic therapy. When deciding how to treat pruritus in the elderly, the physician must tailor a treatment plan that takes into consideration the patient's general health, living situation, severity of symptoms, and the adverse effects of available treatment(s).

Patient education plays a paramount role in the management of pruritus [62]. Patients need to be educated on how to identify and avoid exacerbating factors. It is important to implement strategies to break the "itch-scratch" cycle. Simple measures such as keeping fingernails short or using Unna boots can help interrupt this injurious cycle.

TOPICAL TREATMENTS

Enhancing Barrier Function of the Skin

Preserving the integrity of the skin barrier is crucial for all elderly patients, not just those with overt xerosis, in order to reduce water loss and minimize exposure to irritants and allergens. Fortunately, there are a number of simple and effective ways to help improve the integrity of the epidermal barrier. First, patients should be encouraged to eliminate use of harsh soaps and detergents, and rather use mild or no cleansers on the skin except to the axillae and groin. They should also limit showers to 10 minutes or less and use only warm water. In addition, patients should apply moisturizers immediately after bathing, and up to 3 times per day as needed to adequately hydrate the cornified layer of the skin.

Moisturizers function by rehydrating corneocytes and by restoring the structure of the lipid bilayer of corneocytes in the lower straum corneum. Contained in all commercial moisturizer formulations, humectants such as glycerol, lactate, and urea help to attract and hold water in the skin. In addition, occlusives such as petrolatum and mineral oil prevent evaporation, while emollients such as sterols and lanolin spread across the skin to provide elements of both occlusion and hydration [63]. While no specific moisturizer formulation has consistently proven superior to others for improving skin barrier function [31], we recommend ointments or thick creams for their high lipid content over lotions or gels.

Topical immunomodulators

For elderly patients experiencing pruritus due to moderate-to-severe but localized inflammatory skin diseases such as atopic or allergic contact dermatitis, we recommend the use of topical corticosteroids or calcineurin inhibitors. These topical immunomodulators may also be effective for treatment of individual pruritic lesions of BP or TAD [58]. We typically use medium strength (hydrocortisone valerate 0.2%, triamcinolone acetonide 0.1%) to ultrapotent strength (clobetasol propionate 0.05%, halobetasol proprionate 0.05%, fluocinonide 0.1%, etc.) steroid formulations, or tacrolimus 0.1% ointment, on a daily to twice-daily basis for up to three weeks in the affected areas. Therapy should be concurrently paired with gentle bathing habits and frequent moisturization to improve barrier function. The goal is to reduce inflammation with topical corticosteroids or calcineurin inhibitors while preventing future exposure to irritants or allergens through aggressive emolliation. Because of the increased fragility of skin in senescence, we would not recommend exceeding these limited treatment courses. Prolonged topical corticosteroids should be avoided in the elderly patient with systemic pruritus, however topical calcineurin inhibitors may be used indefinitely if patients report symptomatic relief.

Phototherapy

Patients with pruritus refractory to topical steroids may be treated with phototherapy. Ultraviolet (UV) light, including narrowband or broadband UVB, or less often UVA, is used to treat inflammatory skin conditions and primary pruritus in patients of all ages. Phototherapy has been shown to be effective in treating a variety of pruritic conditions that afflict elderly patients, including pruritus due to atopic dermatitis, renal failure, PCV, chronic liver disease, and Hodgkin’s lymphoma [64]. Phototherapy is especially appropriate

for elderly patients as it avoids the adverse effects of systemic immunosuppressive therapies [36]. In addition, it may be helpful in cases when elderly patients have cognitive difficulties that limit medication compliance, although it often requires coordination with the patient's family or care givers to ensure regular bi- or tri- weekly treatments. It is important to recognize that UV exposure, even when delivered therapeutically, is associated with increased risk of skin cancer. This risk is higher in lighter skinned individuals and in those who have already had a previous skin cancer. Thus, we recommend addressing this risk with all elderly patients prior to initiation of phototherapy and following patients with regular skin cancer screenings.

Systemic Treatments for Itch

If patients fail to improve with gentle skin care or topical therapy, systemic medications including oral antihistamines, immunomodulators, anticonvulsants or antidepressants, must be considered. The appropriate agent for a given patient must be chosen based on the clinical characteristics and presumed etiology of pruritus, e.g. immunomodulators for inflammatory conditions and neuromodulators for neuropathic conditions, and must take into consideration an individual's concurrent medical problems and other medications.

Oral antihistamine therapies should be considered for patients with acute or chronic urticaria. There has not been consistent evidence to support to the role of antihistamines in treating other forms of pruritus that are not mediated by mast cells [65]. It is best to use non-sedating formulations such as fexofenadine, certirizine or loratadine during the day. For patients whose sleep is disturbed by pruritus, however, more sedating antihistamines such as hydroxyzine may be used at bedtime.

Doxepin is a tricyclic antidepressant with activity at the antihistamine H1 receptor and exhibits potent antipruritic properties. Oral doxepin is tolerated very well by most patients with mild sedation being the most common side effect. It should be used with caution in the elderly, however, as the medication may induce hypotension and hyponatremia [66]. Moreover, because the anticholinergic effects of doxepin may be more prominent in the elderly, it is prudent to inform a patient's primary care physician about it's use and advise patients to have their intraocular pressure measured annually if being treated with doxepin for prolonged periods.

Use of systemic immunosuppression in the case of inflammatory pruritic conditions may be required. While we prefer to limit or avoid systemic steroids in the elderly population, short courses of oral steroids in the setting of severe flares of conditions like BP, atopic dermatitis or eczematous hypersensitivity reactions, may be required to improve symptoms while initiating other management strategies. Steroid-sparing immunosuppressive agents such as cyclosporine or mycophenolate mofetil may also be considered for longer treatment periods. Patients must be advised of potential side effects of these agents, including gastrointestinal upset, headaches, and neuropathy, which may be experienced more readily in this patient cohort due to medical comorbidities. Furthermore, risks associated with impaired immune surveillance, such as increased risk of infection or malignancy, re-activation of zoster, etc must also be considered when treating the elderly population.

Anticonvulsants including gabapentin or pregabalin, as well as selective serotonin reuptake inhibitors, have demonstrated some benefit for patients with neuropathic, paraneoplastic, uremic and cholestatic pruritus [67-73]. Both have also been reported to reduce itch in patients with aquagenic pruritus arising in the setting of polycythemia vera or other hematologic dyscrasias [74]. While these agents are tolerated relatively well, it is prudent to start with low doses and increase gradually due to frequent dose-dependent side effects such as dizziness, sedation, nausea or vomiting.

Conclusion

Itch is highly prevalent in the elderly population and has an overwhelmingly negative impact on the quality of life of affected individuals. Decline in normal physiology of the skin, age-related changes in cutaneous nerve fibers, polypharmacy and other medical comorbidities all contribute to the high rate of pruritus in the elderly. In addition, these factors make the diagnosis and its management more challenging. Regardless of the severity of itch or it's cause, the foundation of all treatment must include appropriate skin hydration to improve barrier function. Control of cutaneous inflammation or neural dysfunction may ultimately require topical or systemic medications. When addressing the needs of the elderly, coordinated care with primary care physicians and family members is crucial to the success of any treatment plan.

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Table 1

Reasons for pruritus in the elderly

- Xerosis
- Diabetes Mellitus
- Seborrheic dermatitis
- Hepatic and renal diseases
- Drugs
- Neoplastic diseases
- Iron deficiency
- Autoimmune diseases
- Polycythemia
- Hypothyroidism
- Dermatitis herpetiformis
- Parasite infestation
- Psychogenic
- Neuropathic (peripheral and central)

Table 2

Drugs that can cause pruritus

Group of Drugs	Examples	Possible Mechanism
Antihypertensive Drugs	Calcium channel blockers	Xerosis, secondary to skin lesions
	Angiotensin receptor blockers	Cholestasis
	Angiotensin-converting enzyme inhibitors	Increase of bradykinin level
	Beta blockers	Secondary to skin lesions
Hypolipidemic Drugs	Statins	Xerosis
Plasma volume expanders	Hydroxyethyl starch (HES)	Deposition of HES in small peripheral nerves
Neurologic	Opioids	Central blockade of μ-opioid receptor
Antibiotics	Penicillins	Cholestasis or secondary to skin lesions
	Cephalosporins	Secondary to skin lesions
	Sulfonamides	Unknown or secondary to skin lesions
Antimalarials	Chloroquine	Unknown
Anti-cancer	Ipilimumab	Secondary to skin lesions, unknown
	EGFR inhibitors	Xerosis, secondary to skin lesions
	Bleomycin	Xerosis, secondary to skin lesions
	Tamoxifen	Sebostasis, xerosis
	Interferons	
Hormone modulators	Oral contraceptives	
	Androgens	Cholestasis
	Anti-androgens	
Psychotropic	Lithium	
	Tricyclic antidepressants	Cholestasis
Antiepileptic	Fosphenytoin	Secondary to skin lesions, allergic reaction, unknown
	Lamotrigine	Secondary to skin lesions, allergic reaction, unknown
Diuretics	Furosemide	Unknown or secondary to skin lesions
	Hydrochlorothiazide	Unknown or secondary to skin lesions
Other	Non-steroidal anti-inflammatory	Increased synthesis of leukotrienes, cholestasis
	Penicillamine	
	Aspirin	Mast cell degranulation
	Iodinated contrast medium	Allergic reaction, mast cell degranulation

Table 3
Pruritic Disorders to Consider in the Elderly

Disorder	Clinical Characteristics
Xerosis cutis	Extensive dry, rough skin with flaking scale. Lower extremities most often involved.
Scabies	Sudden onset of pruritus, nodular presentation or scalp involvement possible in elderly. Burrows easiest to visualize in finger webs and soles
Notalgia paresthetica, Brachioradial pruritus	Focal distribution of pruritus, excoriations; brachioradial pruritus relieved by ice
Diabetic polyneuropathy	Truncal pruritus
Renal failure, cholestasis, thyroid disorder	Persistent generalized pruritus. Patient may be asymptomatic otherwise without other symptoms of overt organ failure (i.e. chronic kidney disease stage 3)
Hematologic malignancy (i.e. polycythemia vera), solid tumor paraneoplastic syndrome	Extensive diffuse pruritus Polycythemia vera can present with aquagenic pruritus
Transient acantholytic dermatosis (Grover's)	Distribution centered on back and chest. May follow hospitalization or febrile illness.
Iron deficiency	Often asymptomatic; potentially symptoms of anemia such as pallor, weakness, fatigue, poor exercise tolerance
Psychogenic itch	Symptoms of depression, obsessive compulsive disorder, psychosis, or other mental illness
Bullous Pemphigoid	Extensive or localized bullae. Pruritus may precede bullae formation.