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EPIDEMIOLOGY (JI SILVERBERG, SECTION EDITOR)

Epidemiology of Chronic Pruritus: Where Have We Been and Where Are We Going?

Nicholas K. Mollanazar · Savannah Dean Koch · Gil Yosipovitch

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Abstract Between 23 and 44 million Americans are estimated to suffer from chronic pruritus in the setting of both cutaneous and systemic conditions. Patients with chronic pruritus suffer extreme detriment to their ability to function, including but not limited to deranged sleep patterns, mood disturbances, increased levels of anxiety and depression, and reduced levels of overall quality of life. Indeed, chronic pruritus is now known to be as debilitating as chronic pain. For these reasons, chronic pruritus represents a serious public health concern that must be adequately addressed by clinicians. We present an up-to-date summary of the epidemiology of chronic itch in different cutaneous and systemic conditions. While we have endeavored to discuss some of the most common causes of chronic pruritus, this review does not encompass all of the myriad different diseases in which chronic pruritus can occur.

Keywords Chronic pruritus · Epidemiology · Prevalence · Psoriasis · Atopic dermatitis · Geriatric

Introduction

Itch (pruritus in Latin) is defined as an "unpleasant sensation that elicits the desire or reflex to scratch" [1]. Pruritus is a remarkably common complaint. A 2013 study by Shive et al. reported 77 million visits for itch in America over an 11-year period, with an average of 7 million visits per year, accounting for roughly 1 % of all physician visits [2••]. For comparison, 1.8 % of all physician visits in America were for low back pain [2••]. Moreover, the 1 % of all visits reported most likely is an underestimate, as several studies have demonstrated that only half of patients experiencing itch will visit a physician for that problem [2••, 3–5].

Clinically, itch can be separated into two broad categories: acute and chronic [6]. Chronic itch is defined as itch lasting more than 6 weeks and represents a veritable quagmire for clinicians, as it causes significant emotional distress in patients with negative effects on quality of life and sleep and is often difficult to treat [7–9]. From a quality of life perspective, it becomes increasingly important that the medical community be able to adequately describe the prevalence of this disease.

The prevalence of pruritus in the general population varies from 8 to 38 % worldwide [5, 10, 11]. While little is known regarding the incidence of chronic pruritus in the general population, one can generalize from the prevalence data that chronic itch is indiscriminate and is found across a variety of ages, ethnicities, and medical conditions [6, 12]. Interestingly, chronic itch does not only manifest in dermatologic conditions, but rather is associated with infectious, systemic, psychiatric, neuropathic, and psychosomatic diseases [13]. We will focus our discussion on the topic of chronic itch. More specifically, in this paper, we hope to shed light not only on the prevalence and incidence of chronic pruritus, but also on the commonalities and differences between populations.

Note on Table

The vast range of findings reported from numerous different studies often complicates the epidemiology of pruritus. For this reason, we have endeavored to grade the various findings from the cited studies in this review based on sample size. After careful consideration, we decided to organize previous findings into three categories: studies with more than 500

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N. K. Mollanazar · S. D. Koch · G. Yosipovitch (✉)
Department of Dermatology and Itch Center, Temple University School of Medicine, 3322 North Broad Street, Medical Office Building, Suite 212, Philadelphia, PA 19140, USA
e-mail: gil.yosipovitch@tuhs.temple.edu

subjects, studies with between 100 and 500 subjects, and lastly, studies consisting of less then 100 subjects. Please use Table 1 as a reference for the numbers discussed in the proceeding text.

Prevalence in the General Population

One of the first comprehensive dermatology-focused population-based studies was published in 1976 and took place in the central London district of Lambeth (n=614). The point prevalence of pruritus was found to be 8.2 %; however, this study failed to differentiate between acute and chronic forms of pruritus [14]. A more recent population-based study from France (n=25,441) reported that the 2-year prevalence of chronic pruritus was 14.4 %; unfortunately, the authors did not include their definition of chronic itch [5]. In a population-based study from Oslo, Norway (n=18,747), 8.4 % of those surveyed reported suffering from acute pruritus in the past 2 weeks [10]. The point prevalence of chronic pruritus in a German study (n=11,730) of employees was 16.7 % [4]. In a 2009 pilot study of 300 subjects (response rate 59 %), the point, 12-month, and lifetime prevalences of chronic pruritus were 13.9, 16.5, and 22.6 %, respectively [15]. In a follow-up cross-sectional population-based cohort study of 1190 participants (response rate 57.8 %), the point, 12-month, and lifetime prevalences of chronic pruritus were, respectively, 15.4, 18.2, and 25.5 % [16]. Most recently, in a phone survey of 1075 veterans, Carr et al. documented a point prevalence of chronic pruritus of approximately 38 % [17•].

Table 1 Graded prevalence

	Percentage (%)		
(Study size)	>500	100–500	<100
Prevalence in the general population			
Point	13–38	–	–
12 months	17–18	–	–
Lifetime	23–26	–	–
Age			
>60	12–20	7–38	–
	Prevalence (%)		
(Study size)	>500	100–500	<100
Dermatologic conditions			
Atopic dermatitis (Eczema)	58.1	87–91	–
Contact dermatitis	78.1	–	–
Psoriasis	64–79	80–98	85
Chronic urticaria	–	68	–
Cutaneous T-cell lymphomas	–	–	68–93
Folliculotropic MF	–	–	68
Lichen planus	–	–	97
Seborrheic dermatitis	25	–	13
Connective tissue disorder			
Dermatomyositis			63–85
Systemic sclerosis	43	45	
Systemic disease			
Uremic pruritus (CKD-aP)	42–73	66–72	22–90
Chronic liver disease	25–70	15–31	–
Malignancy			
Hodgkin's lymphoma	19	30	
Endocrine disorders			
Hyperthyroidism	–	60	–
Diabetes	–	18	–
Infectious			
Scabies	–	–	–
HIV	31	25–28	6
Other			
Neuropathic	30–58	5	27
Psychogenic	–	36–42	–
Drug induced	17		

Key Points

- Much of the earlier epidemiologic studies of pruritus failed to differentiate between acute and chronic itch.
- The point prevalence of chronic pruritus ranges from 13 to 38 % (see Table 1); with lifetime prevalence ranging from 23 to 26 % [3, 4, 16].

Patient Characteristics

Age—a Factor of Chronic Itch

Acute itch is more associated with younger age, while there is a positive association between chronic pruritus and age [4, 15, 18]. The literature is replete with studies documenting that the greater the age, the greater the risk of chronic pruritus [15, 19, 20•]. In a large cross-sectional study of 11,730 working Germans, the point prevalence of chronic pruritus in subjects aged 16–30 was 2.3 versus 20.3 % in those aged 61 to 70 [4]. More recently, in a study of 302 Hispanic geriatric (age >65) subjects, Valdes-Rodriguez et al. reported a point prevalence for chronic itch of 25 % [20•]. The prevalence of itch in geriatric patients seems to vary based on geographic location. Indeed studies from Nepal (7.3 %), Turkey (11.5 %), Italy (18.9 %), Iran (22 %), Mexico (25 %), the USA (29 %), and India (37.5 %) all demonstrate varying prevalences [20•, 21–24]. In total, the literature suggests a point prevalence of chronic itch in the geriatric population that ranges from 7 to 37.5 % [21–26].

Key Points

- Acute itch is associated with younger age.
- There is a positive association between chronic pruritus and age.
- The point prevalence of chronic pruritus in geriatric patients ranges from 7 to 37.5 %.

Ethnicity

The racial and ethnic differences regarding the prevalence and clinical characteristics of itch are well documented in the literature [27]. Previous reports have postulated differences in genetic polymorphisms, receptor expression, and/or dermal innervation as possible mechanisms to explain this phenomenon [27, 28]. Itch is more common among Black and Asian patients, with elderly Asian patients being 3 times more likely to visit physicians for itch compared to whites or blacks [2••]. Chronic pruritus is associated with ethnic background in urban populations in Western Europe, with individuals from the Middle East, North Africa, and the Indian subcontinent reporting significantly more itch [29].

Dermatologic Conditions

Atopic Dermatitis (Eczema)

Atopic dermatitis (AD) is the most common variant of inflammatory skin diseases. Pruritus is the defining feature of AD, and its presence is an essential diagnostic feature. Indeed, itch is so pervasive in atopic disease that eczema is frequently referred to as "the itch that rashes" [30]. In a recent web-based questionnaire of 304 individuals with AD, 91 % reported suffering from pruritus at least once daily [8]. In a 2002 study of Chinese patients (n=102) with atopic dermatitis, 87 % of those surveyed suffered from daily pruritus [7]. In a cross-sectional study of working German adults (n=11,730), 58.1 % of participants with atopic eczema suffered from chronic pruritus [4]. Importantly, the aforementioned German study asked specifically about chronic pruritus.

Contact Dermatitis

Contact dermatitis is a common complaint that results from exposure to allergens or irritants. One of the most common forms of contact dermatitis is hand eczema. Indeed, in any given year, 10 % of the general population will suffer from dermatitis of the hand [31]. In a recent cross-sectional analysis of 1051 patients with diagnosed chronic hand eczema (CHE), 78.1 % (n=819) reported itching [32].

Psoriasis

In America, the prevalence of psoriasis approaches 2.2 % [33]. Psoriasis has a major negative impact on health-related quality of life (HRQoL) scores that is comparable to that of cancer, heart disease, and diabetes [34, 35]. Pruritus is known to be one of the most embarrassing and distressing symptoms for patients with psoriasis [36, 37]. Accordingly, in a questionnaire mailed to 40,350 psoriasis patients (response rate 43 %), 79 % of those surveyed reported itch, making it the second most frequent symptom [38]. Similarly, a 2002 study (n=100) reported that 80 % of psoriasis patients suffered from pruritus [39]. A 2004 Italian study of patients hospitalized for psoriasis (n=936) documented that 63.8 % of participants experienced pruritus [40]. Interestingly, a 2009 Italian study in patients with moderate to severe chronic plaque psoriasis (n=90) reported that 85 % of patients suffered from itching [41]. In patients with extensive psoriasis (n=101), 84 % reported suffering from generalized pruritus, with 77 % reporting symptom occurrence on a daily basis [42]. In the previous study, the average duration of generalized itch in patients with extensive psoriasis was >9 years [42]. In patients with chronic plaque psoriasis (n=109), 80 % reported suffering from pruritus [43]. Data from a psoriatic clinical trial (n=157) noted that 97.5 % of all patients had pruritus [44]. In a more recent large, multinational, population-based survey of psoriasis patients in North America and Europe (n=3426), 67 % of participants reported current itching [45••].

Chronic Idiopathic Urticaria

Chronic idiopathic urticaria (CIU) is defined as the daily, or almost daily, occurrence of wheals and pruritus lasting for 6 weeks or longer, with no discernable cause. To date, there is limited data regarding the epidemiology of CIU. In a study of 100 patients with CIU, 68 % reported pruritus on a daily basis, with most patients experiencing symptoms during the evening and at night [46].

Cutaneous T-Cell Lymphomas

Cutaneous T-cell lymphomas (CTCL) represent a heterogeneous group of lymphoproliferative disorders. Mycosis fungoides (MF), a rare, extranodal, non-Hodgkin's lymphoma with several histologically and clinically distinct variants, is the most common type of CTCL [47]. Pruritus is the most frequent and often the earliest presenting feature of CTCL and can occur in the absence of skin lesions [48, 49]. Folliculotropic MF (FMF) and erythrodermic MF, when compared to the pagetoid reticulosis variant, are defined by severe pruritus [50]. In a case-control study of patients with FMF (n=43), 68 % suffered from severe pruritus that required separate treatment [51]. In a phase 2 clinical trial of oral vorinostat for

refractory CTCL (n=33), 93 % of participants reported symptomatic pruritus [52].

Lichen Planus

Lichen planus (LP) is a relatively rare disorder of unknown origin that most commonly occurs in middle-aged adults and may affect the skin, oral cavity, genitalia, scalp, nails, or esophagus. Patients with LP often complain of itching. In one study of 30 patients with LP and 76 subjects with psoriasis, 96.7 % of patients with LP experienced pruritus [53]. Of note, the itching experienced by patients with LP was significantly more severe than the pruritus experienced by psoriasis patients [53].

Pityriasis Rosea

Pityriasis rosea (PR) is defined as an acute, self-limited rash that begins with a single lesion (herald patch). The cause of PR is unknown, though it is thought to be infectious in etiology. Itch is a frequent complaint of patients with PR, though not all PR patients experience itch. There are no good data regarding the prevalence or severity of chronic pruritus in PR.

Seborrheic Dermatitis

Seborrheic dermatitis (SD) is a chronic and relapsing dermatitis that occurs in areas rich with sebaceous glands. Patients with SD often complain of itching and scaling ("dandruff" or "flaky skin"). There are few, if any studies that directly assess the epidemiology of chronic pruritus in SD. Since SD often occurs on the scalp and is frequently itchy, inferences can be made from scalp itching. In one representative study of 1011 French participants, 25 % of subjects with "sensitive scalps" reported itching [54]. In a study of 75 patients with chronic idiopathic pruritus, 13 % of subjects reported scalp involvement [55].

Skin Infections

Common skin infections, such as folliculitis and tinea pedis, can be itchy, but there are no epidemiologic data documenting this.

Bullous Disorders

Dermatitis Herpetiformis

Dermatitis herpetiformis (DH) is a subepidermal bullous disease characterized by the presence of erythematous-grouped vesicles distributed symmetrically on the extensor surfaces, buttocks, and back [56]. DH is associated with celiac disease [56]. While no formal epidemiologic studies exist regarding the prevalence of chronic pruritus in DH, the clinical presentation is defined by severe and intense itching [57]. Indeed, some argue that all patients with DH experience chronic pruritus. More often than not, patients with DH suffer from such intense itching that they scratch off the cardinal vesicles and present with only erosions and excoriations [57].

Bullous Pemphigoid

Bullous pemphigoid (BP) is a chronic blistering autoimmune disease of the skin that is commonly seen in the elderly [58]. The initial presenting symptoms of BP are often nonspecific and include pruritus, eczematous like rash, or urticarial eruption [58]. The initial nonspecific eruption often persists and progresses to tense blisters and bullae. Throughout the course of the disease, pruritus remains a characteristic component of BP [58]. Several case reports (14 patients in total) have presented an unusual prodromal manifestation of BP characterized by generalized pruritus in the absence of primary skin lesions wherein an underlying diagnosis of BP was subsequently made [59]. Given this unusual occurrence of pruritic pemphigoid, immunofluorescence testing may be warranted to exclude BP in any elderly patient with unexplainable severe or persistent generalized pruritus [59]. A recent German study demonstrates that all forms of autoimmune dermatoses (including BP) are associated with intense pruritus and have a significant negative effect on quality of life [60].

Connective Tissue Disorders

Dermatomyositis

Dermatomyositis is a rare inflammatory disease of the skin that can also involve muscle, though not always. In a recent study of dermatomyositis in patients from the USA and Singapore (n=34), pruritus was the most common initial symptom reported, with 63 % of American patients and 80 % of patients from Singapore reporting itch as their initial clinical symptom [61]. In a different study (n=26), 85 % of participants reported pruritus [62].

Systemic Sclerosis

Systemic sclerosis (SSc) is a chronic connective tissue disorder that is characterized by fibrosis of the skin with internal organ involvement. Pruritus is a common complaint in patients with SSc. In a cross-sectional multicenter study of 400 SSc patients in Canada, 45 % of patients reported suffering from pruritus [63]. In another large cross-sectional multicenter

study of 578 SSc patients, 43 % of patients reported pruritus on most days [64].

Systemic Disease

Uremic Pruritus

Uremic pruritus (UP), also known as chronic kidney disease-associated pruritus (CKD-aP), is a serious and frequent complaint in patients with advanced or end-stage renal disease (ERD) with significant effects on patient quality of life [65]. Uremic pruritus is rare in the setting of acute renal failure and is more common among those receiving hemodialysis than those undergoing peritoneal dialysis. Prior to modern hemodialysis technology, the burden of chronic pruritus in dialysis patients was as high as 85 % [66]. Since the advent of modern HD, the prevalence of chronic itch in these patients has precipitously declined [12]. Worldwide, the prevalence of chronic pruritus in patients with uremic itch varies from 22 to 90 % [66–72]. The wide range is due to the lack of standardized assessment tools, resulting in some studies reporting point prevalence and even others the rate of lifetime prevalence.

In a study to validate a standardized pruritus questionnaire in uremic patients, the point prevalence of chronic pruritus was 72 % [73]. A multicenter comprehensive study of 219 patients undergoing hemodialysis treatment reported a lifetime prevalence of chronic pruritus of 66 % (n=144) and a point prevalence of 48 % (n=105) [71]. The Observational Dialysis Outcomes and Practice Patterns Study (DOPPS), which assessed more than 29,000 HD patients in 12 countries, demonstrated that 42 % of patients suffered from moderate to severe pruritus [70]. In a Japanese study of 1773 hemodialysis patients, 73 % suffered from chronic pruritus, of which 35 % reported severe pruritus [69]. Of particular note, the prognosis of patients with severe pruritus was significantly worse than others [69]. Indeed, after adjusting for other clinical factors (diabetes mellitus, age, β-2-microglobulin, and albumin), severe pruritus was independently associated with death [69].

Key Points

- Uremic pruritus is a serious and frequent complaint in patients with ERD on HD.
- The worldwide prevalence is 22–90 %.
- Severe UP is a poor prognostic factor and seems to be independently associated with higher mortality rate.

Chronic Liver Disease

Chronic cholestatic pruritis (ChP) is a direct result of both cholestatic liver disease and various hepatobiliary disorders. It often emerges as the first clinical symptom of primary biliary cirrhosis (PBC) and is therefore an important diagnostic tool [74]. In those with PBC, presentation of the disease before the age of 50 was correlated to an increased likelihood of itch [75]. In the same study, pruritus of cholestasis was generalized, persisted throughout the disease, remitted with improving hepatic function, and worsened with declining function. Additionally, it has been noted that pruritus follows a circadian rhythm, with the most severe itching occurring in the evening hours [74]. It should be stated that this association is not unique to pruritus in the setting of chronic liver disease. Numerous studies have reported on the circadian pattern of chronic pruritus in a myriad disease states [1, 3, 12]. Indeed, for reasons that remain heretofore unknown, chronic pruritus appears to worsen during the late evening hours. Identification of the biochemical pathways responsible for this interesting finding may help further our understanding of the basic pathways that drive chronic pruritus. Previous studies reported that up to 70 % of patients with PBC (n=49), and 15–31 % of patients with hepatitis C (n=100), complain of chronic pruritus [76, 77]. In a more recent 2012 retrospective study of 60 patients with ChP, only 25 % of subjects experienced chronic pruritus before the diagnosis of an underlying liver disease [78].

Malignancy (Paraneoplastic Itch)

Chronic itching can be one of the earliest signs of Hodgkin's lymphoma (HL), presaging skin lesions, or any other stigmata of disease [12, 79]. Previous estimates (n=360) suggested that nearly 30 % of patients with HL experience chronic pruritus [80, 81]. In a more recent retrospective study of a tumor registry database from MD Anderson (n=88), the incidence of itch in HL was found to be 19 % [82]. In addition, the study found that in HL patients referred to a dermatology clinic, eczema and itching were the two most common complaints [82]. It should be stated, however, that the aforementioned MD Anderson study most likely underestimates the occurrence of chronic itch in patients with HL, as it is biased toward those with such distressing complaints that they were referred to a dermatology clinic. Interestingly, only 10 % of patients with non-Hodgkin's lymphoma are estimated to suffer from chronic itch. In a more recent systematic review and meta-analysis of targeted cancer therapies (n=20,532), the incidence of pruritus in solid organ malignancies was 19.2 %, while in hematologic malignancies, it was 13.0 % [83••].

Polycythemia Vera

Polycythemia vera (PV) is a myeloproliferative neoplasm characterized by clonal proliferation of myeloid cells. In a retrospective cohort study of 397 patients with PV, 48 % of patients had a documented history of pruritus, 17 % of which had pruritus at the time of diagnosis [84]. Interestingly, of

those patients without itch at the time of diagnosis, 36 % subsequently developed the symptom [84]. Historically, the occurrence of chronic pruritus in PV has been reported to be 50 % [85–87]. Multiple myeloma is another myeloproliferative disorder that is associated with itch. To date, there are no good epidemiological studies verifying this claim [88].

Endocrine Disorders

Hyperthyroidism

Hyperthyroidism, and particularly thyrotoxicosis of Graves' disease, is associated with generalized pruritus [89]. Additional information in regard to hyperthyroidism and pruritus is limited. In one study of 120 patients with hyperthyroidism, 60 % of participants reported generalized pruritus [89]. Historically, hypothyroidism has been described as a cause of chronic pruritus. Yet, no data exists to support such a claim. Clinically, we have never encountered a case of itching due to hypothyroidism.

Diabetes

In a study of 500 patients with diabetes, the incidence of pruritus was reported at 6.5 %; however, there was no control group. In a more recent study of 300 diabetics matched to 100 nondiabetics, localized itch was found to be more common in the diabetic group than in the controls (18.4 vs. 5.6 %, respectively) [90]. The frequency of generalized itch did not differ between these groups. In a 2010 large-scale survey (n=2656), truncal pruritus of unknown origin (TPUO) was found to be more common in diabetics than nondiabetics (11.3 vs. 2.9 %), while other types of pruritus had no significant difference between the two groups [91]. TPUO was also associated with other signs of diabetic polyneuropathy (DPN) and may therefore be a newly accepted symptom of DPN. These recent developments may give credence to the argument that diabetic pruritus is a type of neuropathic itch. In a recent study of Hispanic geriatric patients, chronic pruritus was significantly associated with diabetes mellitus [20•].

Infectious

Scabies

Scabies is a common parasitic infection characterized by generalized intense itching that typically spares the face [92]. As an obligate parasite that completes its entire life cycle in human skin, scabies represents a veritable scourge, occurring regardless of gender, age, ethnicity, or socioeconomic level [92]. The worldwide prevalence of scabies is estimated to be 300 million cases annually [93, 94]. Recent work suggests that the prevalence of scabies is increasing globally [93]. Primary (initial) infection requires a 3–6-week incubation period before symptom onset; in cases of reinfestation, symptoms can manifest in 1–3 days [92]. Scabies is the number one infectious cause of itch in terms of severity and is most prevalent in urban areas. Pruritus is the defining symptom of scabies. Indeed, except in cases of Norwegian scabies, a diagnosis of scabies is highly improbable in the absence of itch.

HIV

Chronic pruritus is a common symptom in HIV patients, even in our era of highly active antiretroviral therapy (HAART) [95]. In a study of 897 HIV-infected patients, the prevalence of itch was 6 %. A recent study from Spain (n=303) reported a much higher prevalence of pruritus in HIV patients (31 %), despite the fact that many patients were treated with HAART [96]. In African patients with HIV-1/AIDS (n=384), the most prevalent skin disorder is prurigo nodularis [97–100]. The prevalence of chronic pruritus in HIV patients with either hepatitis B or C (n=310) varies between 25 and 28 % [101]. More recently, in a large (n=201) cross-sectional study of HIV-positive patients in the southeastern USA, 45 % of participants reported pruritus, making it the most common skin complaint [95].

Other

Neuropathic

Neuropathic itch (NI) is the aberrant perception of itch in the absence of puritogenic stimuli due to dysfunction, damage, or disease at any point along the sensory pathway of the nervous system [102, 103]. For this reason, NI is best thought of as a broad general category of chronic pruritus secondary to neurologic disorder.

Lesions of the peripheral nervous system (PNS) are the most common cause of NI. Examples of peripheral NI include diabetic neuropathy, postherpetic neuropathy, brachioradial pruritus, notalgia paresthetica, scrotal itch, postburn pruritus, and postscar pruritus. Despite the fact that PNS lesions are the most common causes of NI, there are relatively few epidemiologic studies. One study (n=586) showed that 58 % of patients suffering from herpes zoster report itching, while only 30 % of patients with postherpetic neuralgia experience itching [103, 104].

Lesions affecting the neurons or axonal tracts responsible for the sensation and transmission of pruritus in the central nervous system (CNS) can cause central NI. Examples of central NI include MS, syringomyelia, traumatic brain injury

causing Brown-Sequard syndrome, Creutzfeld-Jacob disease, and cerebrovascular accident [102]. In a study of 377 MS patients, 4.5 % reported NI, though the study failed to assess chronicity [105]. Among 44 patients with aquaporin-antibody-positive neuromyelitis optica (NMO), 27 % of patients had NI that was attributed to spinal cord lesions [106]. Half of the 27 % of patients with NI reported continuous pruritus [106]. To date, there are scant epidemiological data on the prevalence or character of NI.

Psychogenic

Psychogenic excoriations are estimated to occur in 2 % of all dermatology clinic patients [107]. Previous studies demonstrated that between 20 and 70 % of itch patients have either a psychiatric comorbidity or psychosomatic cofactors [108]. Among the psychiatric inpatient population, 36–42 % of patients suffered from idiopathic itch [109, 110]. When pruritic dermatoses and systemic causes of itch were excluded, 17.5 % of psychiatric patients experienced pruritus [111]. Pruritus is intensified by emotional stress, psychological trauma, anxiety, depression, and psychoses. In addition, pruritus is associated with obsessive-compulsive disorder, substance abuse, and delusion of parasitosis which is a rather rare condition.

Drug Induced

Drug-induced itch represents just one of a myriad possible adverse cutaneous reactions. By definition, drug-induced itch results in generalized itching in the absence of skin lesions. Drug-induced itch can be either acute (<6 weeks) or chronic (>6 weeks). Acute drug-induced itch is most commonly due to opioids and usually resolves with drug cessation [112]. Interestingly, chronic drug-induced itch usually does not spontaneously resolve after withdrawal of the offending agent. The most commonly reported and documented culprit of chronic drug-induced itch is hydroxyethyl starch (HES), a volume expander used to prevent hypovolemic shock in the setting of severe blood loss [112].

In a study of 15,438 consecutive medical inpatients monitored for adverse drug reactions, drug-induced itch (defined as itch in the absence of rash) accounted for approximately 5 % of all adverse cutaneous drug reactions [113], while a study of 13,679 patients treated with antimicrobials in the ambulatory care setting reported that drug-induced itch accounted for 13.3 % of cutaneous drug reactions [114]. Importantly, this number represents patients with itch secondary to drug reaction. In a more recent meta-analysis of target cancer therapies (n=20,532), the incidence of all grade pruritus and high-grade pruritus were 17.4 and 1.4 %, respectively [83••]. The lowest incidence of pruritus occurred in patients treated with VEGFR inhibitors, while the highest incidence occurred in patients treated with CTLA4 inhibitors [83••].

Conclusion

Chronic pruritus research has made tremendous leaps and bounds in the past two decades. Nevertheless, chronic pruritus remains an important clinical topic in the assessment of the burden of skin morbidity in the community. More large-scale research is required to better identify the extent and severity of this distressing disease.

Compliance with Ethics Guidelines

Conflict of Interest NK Mollanazar, SD Koch, and G Yosipovitch all declare no conflicts of interest.

Human and Animal Rights and Informed Consent All studies by the authors involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

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