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REVIEW

Psychodermatology of Chronic Pruritus: An Overview of the Link Between Itch and Distress

Bárbara R. Ferreira · Olivia M. Katamanin · Mohammad Jafferany · Laurent Misery

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ABSTRACT

Chronic pruritus (CP) is defined as an unpleasant sensation causing a desire to scratch and lasting > 6 weeks. It has a multifactorial etiology but is more frequently associated with chronic inflammatory dermatoses and systemic disorders. Psychogenic pruritus and neurological disorders are other less common etiologies, while, in some patients, it is idiopathic. CP appears to be processed by non-histaminergic pathway, contributing to its complexity and therapeutic challenge. Moreover, regardless of the etiology, it is multidimensional, including cognitive, motivational and affective components. There is a close link between psychological distress and pruritus, with particular clinical expression in chronic inflammatory dermatoses, involving the activation of the hypothalamic-pituitary-adrenal axis (and its cutaneous equivalent), the sympathetic nervous system, the release of hormones and peptides, the role of immune cells (T and B cells, macrophages) and immune-related cells in the skin (mast cells, dendritic cells and keratinocytes). Moreover, there is strong evidence that psychological factors influence the experience of pruritus. CP can also cause psychiatric disorders, including but not limited to anxiety and depression, and also lead to significant quality of life (QoL) impairment. Thereby, although a psychodermatological assessment should ideally be carried out in the context of a specific psychodermatology consultation, a brief mental health assessment could be part of the general dermatological approach to these patients. Considering that mental health, QoL and pruritus are closely linked, psychotherapeutic interventions and/or psychotropic drugs should thus be considered in some patients as an adjunct to the pharmacological treatment of CP.

Keywords: Pruritus; Chronic pruritus; Psychodermatology; Psychological distress; Mental disorders; Quality of life

B. R. Ferreira (✉) · L. Misery
Univ Brest, LIEN, Brest, France
e-mail: barbara.roqueferreira@gmail.com

B. R. Ferreira
Department of Dermatology, Algarve University Hospital Centre, ULS Algarve, Faro, Portugal

O. M. Katamanin
Chicago Medical School, Rosalind Franklin University, North Chicago, IL, USA

M. Jafferany
College of Medicine/CMU Medical Education Partners Saginaw, Central Michigan University, Mt Pleasant, MI, USA

L. Misery
Department of Dermatology, Brest University Hospital, Brest, France

Key Summary Points
Chronic pruritus is defined as pruritus lasting for at least 6 weeks and can be idiopathic, psychogenic, neuropathic or, more frequently, linked with primary dermatoses or systemic disorders
Itch is processed by two main neuronal pathways: acute itch involves the histaminergic pathway, while chronic itch is processed by the nonhistaminergic pathway
The mechanisms which explain chronic pruritus include the concepts of peripheral and central sensitization
Mast cells have a key role in the understanding of the link between distress and pruritus through the activation of the central and the peripheral hypothalamic-pituitary-adrenal axes, with relevance in psychodermatological diseases
The experience of chronic pruritus can be modulated by psychological factors and can be associated with psychiatric comorbidities and significant impact on quality of life, which should be addressed in clinical practice

INTRODUCTION

Pruritus is the most common cutaneous symptom and is defined as an unpleasant sensation that causes a desire to scratch [1–3]. It is multidimensional, including cognitive, motivational and affective components [4]. Remarkably, several other aspects that can modulate pruritus are sleep, jet-lag and, consequently, circadian rhythm perturbations, and diet [5–7]. Pruritus can also be a marker of drug response [8]. Pruritus has complex etiopathogenesis that can involve histaminergic and non-histaminergic pathways [1, 9].

Chronic pruritus (CP), defined as pruritus lasting for at least 6 weeks [9], appears to be processed by non-histaminergic pathway [9], which may contribute to its complexity and therapeutic challenge. CP may arise from dermatological, systemic, neurological or psychosomatic disorders [4]. Primary dermatoses and systemic disorders are the most common etiologies. Examples of systemic disorders associated with CP include chronic kidney disease and cholestatic liver diseases, and examples of primary dermatoses associated with CP are atopic dermatitis, chronic urticaria and psoriasis. Prurigo nodularis is a separate diagnosis, associated with primary dermatoses, systemic disorders, psychopathology and/or neuropathic findings. Some patients with CP present with one or more etiologies, while, in few cases, the origin remains unknown (idiopathic pruritus) [3, 4, 10].

CP is a hallmark in psychodermatology, as it is a common characteristic shared by dermatoses which are worsened or triggered by distress [11]. Mental health factors, and individual personality characteristics, can modulate the experience of pruritus. For instance, mental health disorders are closely linked with itch intensity reported by patients in the setting of chronic dermatoses that can be worsened or triggered by distress [10]. Besides, psychogenic pruritus is a challenging example of CP, as it is linked with mental health features, with specific criteria that were previously suggested by the French group of psychodermatology [12, 13]. An interesting clinical finding of CP is that these patients may benefit from learning to disengage their attention away from pruritus. It was observed that focusing attention on the location of pruritus may aggravate it [2]. This finding reinforces the relevance of mind-body therapies as a potential adjunct treatment for the management of CP (and, as a consequence, the related dermatoses) [14]. Studies on the efficacy of psychotherapy for CP and related comorbidities suggest that psychotherapies may be useful as part of a multidisciplinary treatment [15].

This review provides an overview of the link between distress and pruritus and the mental health factors that affect the experience of pruritus along with the psychiatric consequences of CP. It highlights the relevance of the understanding and management of CP in psychodermatology and discusses how to manage the vicious cycle of pruritus and distress (and related

psychopathology), based on the biopsychosocial model [15].

Ethics

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

PSYCHOLOGICAL DISTRESS CAN WORSEN OR TRIGGER PRURITUS

1. General pathophysiological aspects of pruritus

Itch is processed by two main neuronal pathways: acute itch involves the histaminergic pathway, while chronic itch is processed by the nonhistaminergic pathway. In the skin, pruritus originates in the epidermis and in the dermoepidermal junction, and there is a crosstalk between the immune system, keratinocytes and the nonhistaminergic sensory nerves to originate CP, a characteristic of several psychodermatological disorders [10, 11, 16–18].

The etiopathogenesis of pruritus illustrates the connection between the brain and the skin and can be summarized as follows. After an itching stimulus, there is an activation of C nerve fibers, and the impulse is conducted to the dorsal root ganglion at the spinal cord, where it crosses to the contralateral spinothalamic tract and then ascends to the laminar nuclei of the thalamus and is afterwards transmitted to different regions in the brain (subcortical and cortical brain areas) that are involved in motor planning, sensory perception, attention, motivation and emotion [16]. It is important to note that nonhistaminergic and histaminergic pathways have different projections in the spinothalamic tracts; then, there is a different brain processing of these two pathways in association with many psychoneurological interactions with different brain areas.

The mechanisms which explain CP include the concepts of peripheral and central sensitization. Peripheral sensitization (PS) relates to a lower threshold for the perception of itch sensation and is associated with an increased activity of pruriceptors. In turn, central sensitization (CS) occurs as a result of neural plasticity, which means that non-pruritus stimuli may function as an itch stimulus and are thus perceived as a pruritus sensation [16]. Three descriptors for pruritus have been described: pruriceptive pruritus, whose origin is due to the activation of pruriceptors (including acute pruritus and CP), which can also lead to PS; neuropathic pruritus, whose origin is associated with lesions of the peripheral or central nervous system (CNS), leading to CP; pruriplastic pruritus, which involves a CS (observed in CP). An overlap of these different types of pruritus can also occur [19]. Central sensitization may be linked with inflammatory dermatoses such as psoriasis: neurokinin 1 receptors (NK1Rs) are highly expressed in the CNS and can be involved in this mechanism. For instance, a pilot observational open-label study showed that neurokinin 1 inhibitors can be useful in the management of psoriasis-related CP undergoing biologics [20].

2. Distress and pruritus: an overview of psychoneuroendocrinoimmunology

The stimulus from psychological stressors is first received by the brain. Afterwards, the information is transmitted to the periphery via several mediators through the activation of the hypothalamic-pituitary-adrenal axis (HPA), the sympathetic nervous system and the release of hormones and peptides that bind to their receptors on different cells. The cells involved include immune cells (T and B cells, macrophages) and immune-related cells in the skin (mast cells (MC), dendritic cells and keratinocytes) [21, 22]. Psychological distress stimulates the paraventricular nucleus of hypothalamus to produce corticotropin-releasing hormone (CRH), which stimulates the production and secretion of adrenocorticotropin (ACTH) in the anterior pituitary gland and then the production and release of cortisol from the cortex of the adrenal glands [23]. CRH is also involved in activating the sympathetic nervous system by stimulating the locus coeruleus. While acute stressors induce temporary activation of the HPA axis, chronic exposure to distress increases the central tone of this axis and interferes with its normal function [22]. The overstimulation of this axis leads to high levels of proinflammatory cytokines, including interleukin (IL)-1 β, IL-6 and TNF-α,

linked with depressive symptoms [23]. Moreover, the overstimulation of the HPA axis also occurs in chronic inflammatory dermatoses, worsened or triggered by distress, like psoriasis [22, 24]. The skin has an equivalent of the HPA axis, whose dysfunction was also observed in psychodermatological disorders that can be worsened by distress, including atopic dermatitis (AD), psoriasis, alopecia areata and acne, and which is directly activated by distress [24, 25].

Epidermal and hair follicle keratinocytes and MC can secrete CRH after a stressor. ACTH and α-melanocyte-stimulating hormone (α-MSH) and their receptors can be produced in the skin, while the release of these pro-opiomelanocortin (POMC)-derived peptides is controlled by CRH. They participate in the mechanisms of the link between distress and cutaneous inflammation. CRH is probably the most studied substance involved in the cutaneous HPA axis and has a variety of functions. These include skin barrier recovery and antimicrobial peptide production, the proliferation and differentiation of keratinocytes, neurogenic inflammation associated with effects on MC, impact on endothelial cells (vasodilation), *Propionibacterium acnes* function or sebum production, through effects on sebocytes. There is thus a crosstalk between the brain and the skin that is called the brain-skin axis, which involves the connection of the central and the peripheral HPA axes [22].

MCs have a key role in the understanding of the link between distress and pruritus through these two HPA axes, with relevance to psychodermatological diseases. Distress aggravates the itching sensation of inflammatory dermatoses through MC activation. For example, the production and secretion of CRH after psychological distress can activate MC and trigger premature catagen leading to hair loss, as observed in alopecia areata. Pruritus seems to be a common symptom in patients with alopecia areata, prior to hair loss, correlated with MC activity [11, 26]. The activation of HPA axes related to stressors activates MC through the receptors CRH-R1, MRGPRX2, NK-1R and VPAC2. Histamine, IL-3, the nerve growth factor (NGF) and tryptase are released from MC and activate their corresponding receptors H1R, IL-31RA, TrkA and PAR-2, respectively, that are present on C-fibers. MC themselves can also be activated through PAR-2 and TrkA, in an auto- or paracrine signaling. MC-derived mediators activate C-fibers, spreading the signal. NGF and IL-31 enhance the growth of C-fibers. Additionally, chymase is released from MC and, in CP, remains as inactivated chymase, that cannot inactivate substance P (SP). PAR-2 is able to sensitize the capsaicin receptor in C-fibers, increasing SP and calcitonin gene-related peptide (CGRP) release [27]. CGRP is expressed in both cutaneous sensory nerves and CNS. Higher serum levels of CGRP were described in chronic inflammatory dermatoses and associated psychiatric comorbidities, such as depression [11, 28, 29]. CGRP can induce a Th2-polarized T-cell response that can contribute to the sensitization of cutaneous sensory neurons in CP [30]. The connections between MC and C-fibers are still strengthened by the cell adhesion molecule-1 on MC and nectin-3 on C-fibers. These mechanisms are progressively amplified, in a vicious circle, leading to neurogenic inflammation and itch [27]. Another relevant neuropeptide is the pituitary adenylate cyclase-activating peptide (PACAP), which is widely expressed and is a key regulator in circuits of learning, distress and emotion [31], whose receptors are also expressed on MC, also contributing to cutaneous neuroinflammation.

Melatonin is another subject of interest for the comprehension of the link between distress and pruritus, through a dysfunction in the interplay between MC and melatonin [11]. Melatonin is a neurohormone mainly produced by the pineal gland but it is also produced by other organs, including the skin. A dysfunction of the melatonin system can induce neuroinflammation and subsequent changes in brain regions involved in emotional regulation, with relevance in depression [32]. As for the skin, MCs express melatonin receptors and melatonin affects T-cell and macrophage function [33]. A study showed that melatonin treatment reduced MC at the dermis in distress-induced skin diseases in rat models [34]. Beneficial effects of melatonin were reported for psychodermatological diseases where pruritus is a characteristic, namely, AD and seborrheic dermatitis [33]. Considering both the role of melatonin at the CNS and in the skin,

melatonin imbalance may be involved in cutaneous inflammation and contribute to CP related to psychological distress [11].

Increasing evidence indicates that the brain regulates peripheral immunity. A recent study showed whether and how the brain represents the state of the immune system by demonstrating that the brain's insular cortex (InsCtx) stores immune-related information. Neuronal ensembles in the InsCtx are activated during peripheral inflammation, and the reactivation of these neurons would be sufficient to retrieve the peripheral inflammation. Because InsCtx is known to be activated in case of psychological distress, this study provides a very interesting mechanism for the understanding of the role of distress in reactivating skin inflammation and pruritus [35]. Moreover, although the mechanisms are complex and still not clear, functional changes in the insula are observed in chronic pain [36]. Considering the pathophysiological correlates between pain and pruritus, InsCtx could play a role in the development of CP.

In Fig. 1, the pathophysiological mechanisms explaining the link between distress and chronic pruritus are illustrated.

3. Psychological aspects that influence pruritus

In a case-control study, patients with AD who had higher scores of public self-consciousness and lower scores of agreeableness showed a higher number of scratch movements [37]. In another study, with patients with AD, pruritus was positively correlated with anxiety trait (assessed by the Spielberger State-Trait Anxiety Index). Thus, in these two studies, personality traits were associated with increased pruritus intensity in AD [38].

Alexithymia is another psychological characteristic, of growing relevance in psychodermatology, also for the understanding and management of CP, although few studies have been published to date. Alexithymia corresponds to the difficulty in identifying and/or verbalizing one's own feelings and/or emotions and can be a dimension of personality or a coping mechanism to deal with a disease. Alexithymia was recently identified as a characteristic of psychogenic pruritus and may be a psychological feature that links different chronic skin disorders where psychological distress participates in the pathophysiology as a potential trigger [39, 40].

Finally, another relevant psychological feature of pruritus is its modulation by verbal suggestion. For example, increased intensity of pruritus was observed upon catastrophizing instructions. In another study, when patients with AD believed they had a pruritus-inducing solution on the skin, they experienced an increase in the severity of pruritus. This study also showed that this clinical finding was associated with brain activity changes. Thus, the expectations influence how mental pruritus stimuli are actually experienced, a finding that may have therapeutic relevance [15, 41].

PRURITUS AS A CAUSE OF PSYCHOLOGICAL DISTRESS AND PSYCHOPATHOLOGY

Many studies have demonstrated the significant negative impact that CP has on the quality of life (QoL), including but not limited to anxiety, sleep disturbances, depression and sexual dysfunction [10, 42]. This negative impact on patients' QoL has highlighted the importance of examining the relationship between CP and secondary psychiatric disorders. The following section will explore the multifaceted connection between CP and psychiatric comorbidities, with a focus on common specific skin disorders, namely, AD, psoriasis and acne. This perspective will additionally highlight the potential benefits of psychotherapeutic interventions in the treatment of CP, thereby lessening the burden of disease in these patients.

In AD, individuals not only face the social burden of visible disease but also the debilitating effects of CP, contributing to the increased prevalence of anxiety and depression induced by the discomfort of CP [43].

Psoriasis has also been reported to produce severe CP in > 70% of patients [11]. For many patients, the distress caused by CP extends beyond physical discomfort to significant social implications, including embarrassment from visible skin flaking and blood-stained clothes,

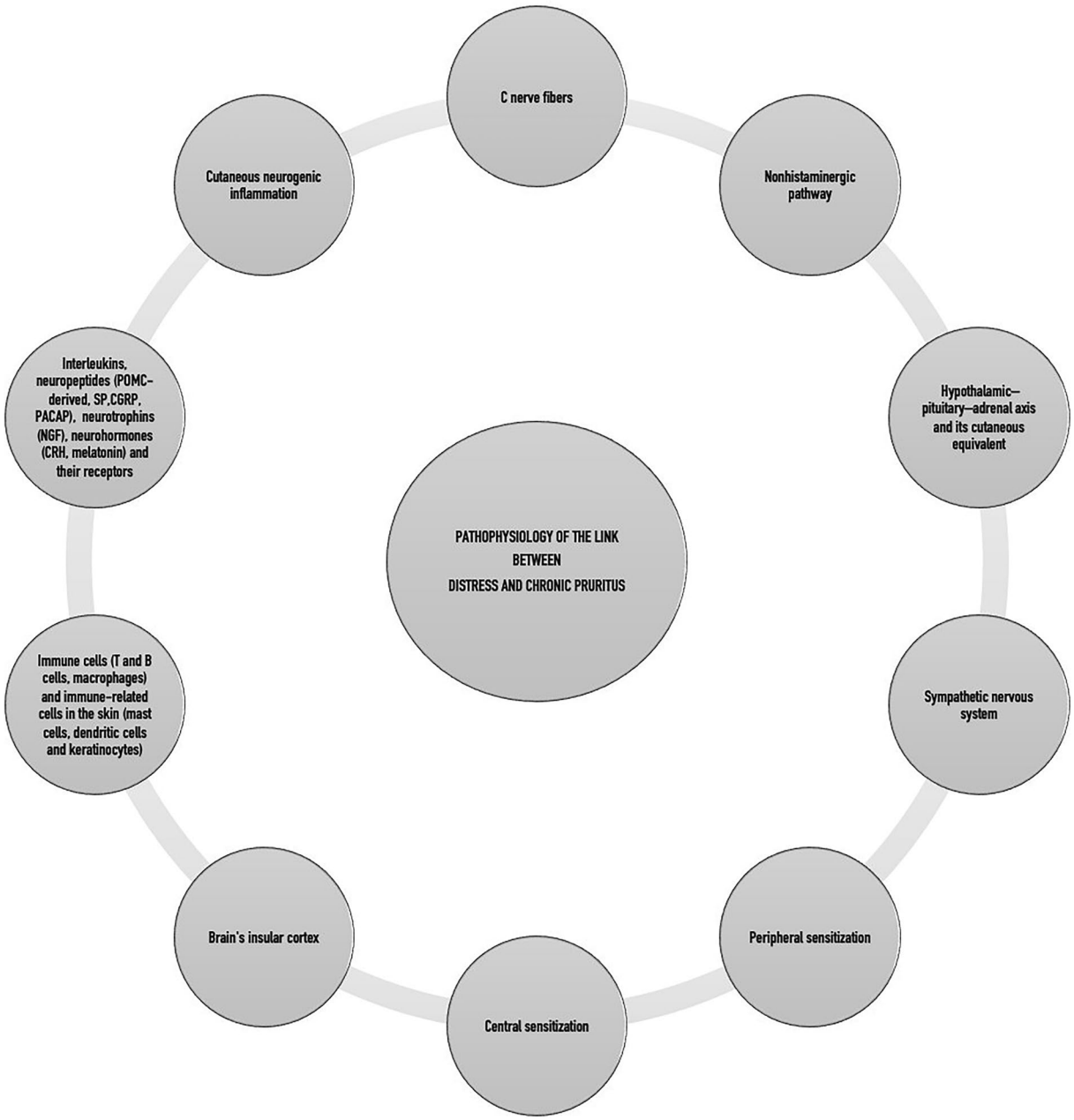

Fig. 1 Pathophysiological mechanisms involved in the link between distress and chronic pruritus. *POMC* proopiomelanocortin, *SP* substance P, *CGRP* calcitonin gene-related peptide, *PACAP* pituitary adenylate-cyclase-activating polypeptide, *NGF* nerve growth factor, *CRH* corticotropin-releasing hormone

contributing to the development of anxiety and depression. This distress is not only prevalent for patients themselves but extends to impact the lives of those whom they live with. Moreover, sexual function and desire were also demonstrated to be negatively impacted by the consequences of itchiness, further highlighting the profound effect on overall well-being in patients with CP. Irrespective of this demonstrated profound effect on the QoL, a study by Taliercio et al. revealed that the severity of itching is not always strongly correlated with

disease progression or severity [44]. As a result, despite the prevalence of itch in patients with psoriasis, patients may feel that their itchiness is not adequately addressed by physicians, who primarily focus on assessing the severity of psoriatic lesions during their clinic visits. Moreover, many patients struggle to find a cure for their CP, resorting to inappropriate methods such as using extreme water temperatures to drown out their need to itch. Thus, an emphasis on exploring pruritus severity and exploring alleviating treatment options should be made during clinic visits to lessen the burden of disease and provide resources and safe treatment options for patients with psoriasis experiencing CP.

According to the American Academy of Dermatology, acne is the most commonly experienced skin condition in the US [45]. Despite acne affecting a large proportion of the adolescent and adult population, few studies have assessed the psychological burden of itching in patients with acne. In a study aimed to investigate the prevalence, intensity and psychological burden of acne in patients, Szepietowska et al. [46] demonstrated that acne itching, regardless of acne severity, was shown to have a significant negative impact on patient QoL. In that study, the authors highlighted that similar to patients with psoriasis, patients with acne also regard itching as one of the most debilitating symptoms of their skin condition, contributing to the increased risk of anxiety and depression among patients with these diseases.

Although the prevalence of CP in various inflammatory skin conditions has been well documented in the literature, there is limited discussion regarding psychological management for CP. However, clinical evidence has demonstrated that interventions aimed at reducing distress levels in patients have proven effective in breaking the distress-itch cycle. These interventions include habit reversal training (HRT), relaxation therapy, cognitive behavioral therapy (CBT), contextual cognitive behavioral therapy (CCBT), meditation and hypnosis [47, 48]. In addition to non-pharmacological interventions, psychotropic treatment should be considered. This can include antidepressants, antipsychotics and anticonvulsants, which have been reported to simultaneously alleviate the urge to itch, depending on the associated psychopathology, to address psychological consequences, such as anxiety and depression [49].

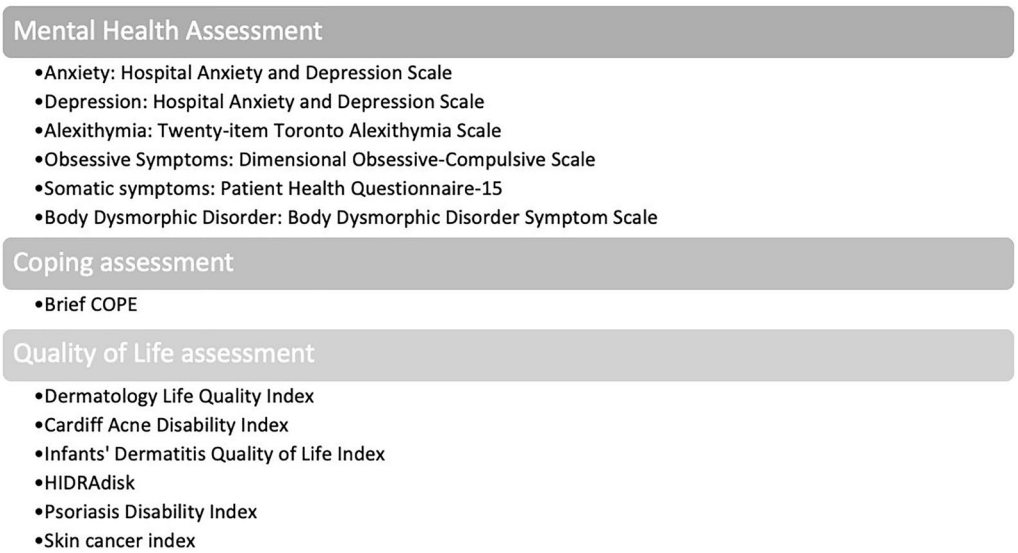

Fig. 2 Examples of specific questionnaires and scales to assess mental health, coping and quality of life in psychodermatology

Pruritus is one of the main determinants of QoL in dermatological disease [50]. A brief mental state examination can be performed in clinical practice to identify the most important aspects of mental health linked with the psychodermatological disorder associated with CP [51]. Useful questionnaires and scales are available to assess mental health, coping and QoL in psychodermatology, as illustrated in Fig. 2 [52–62]. They can be used as an adjunct to the clinical interview. Although a psychodermatological assessment should ideally be carried out in the context of a specific psychodermatology consultation, with the simultaneous participation of a dermatologist and a mental health specialist (psychologist or psychiatrist), there are some common and key psychosocial issues that should be part of the general dermatological approach, namely, the general assessment of symptoms of anxiety and depression and the impact of skin disorders on QoL.

CONCLUSION

Pruritus is multifactorial, and psychological distress can contribute as a trigger for certain chronic dermatoses that are associated with CP, such as AD or psoriasis, leading to an increase in the severity of pruritus as well. In addition, CP associated with chronic dermatoses and systemic diseases is associated with a higher prevalence of secondary psychopathological symptoms such as depressive symptoms, with a significant impact on the QoL of these patients. Moreover, some personality characteristics, such as alexithymia, can impact the coping strategies used by these patients.

Therefore, the overall management of patients with CP must consider the weight of underlying psychological and psychiatric aspects. Although it is still an underdiagnosed, undervalued and undertreated topic in general clinical practice in dermatology, addressing psychopathology, the patient's psychosocial context and the importance of certain personality traits (such as alexithymia) is also the mainstay of the treatment, along with specific therapeutic approach of the underlying dermatosis or systemic disorder, if present. A psychodermatological approach to CP could have an impact on decreasing the severity of pruritus and improving the patient's QoL, by reducing psychological distress as a potential trigger (in several chronic dermatoses), exploring psychosocial factors closely linked with CP (particularly, in psychogenic pruritus) and improving coping strategies used by these patients to deal with the underlying etiology and the burden of having CP.

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Declarations

Conflict of Interest. The authors (Bárbara R. Ferreira, Olivia M. Katamanin, Mohammad Jafferany and Laurent misery) have no competing interests to disclose for this article.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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