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Persistent physical symptoms: definition, genesis, and management

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Persistent physical symptoms (synonymous with persistent somatic symptoms) is an umbrella term for distressing somatic complaints that last several months or more, regardless of their cause. These symptoms are associated with substantial disability and represent a major burden for patients, health-care professionals, and society. Persistent physical symptoms can follow infections, injuries, medical diseases, stressful life events, or arise de novo. As symptoms persist, their link to clearly identifiable pathophysiology often weakens, making diagnosis and treatment challenging. Multiple biological and psychosocial risk factors and mechanisms contribute to the persistence of somatic symptoms, including persistent inflammation; epigenetic profiles; immune, metabolic and microbiome dysregulation; early adverse life experiences; depression; illness-related anxiety; dysfunctional symptom expectations; symptom focusing; symptom learning; and avoidance behaviours, with many factors being common across symptoms and diagnoses. Basic care consists of addressing underlying pathophysiology and using person-centred communication techniques with validation, appropriate reassurance, and biopsychosocial explanation. If basic care is insufficient, targeted psychological and pharmacological interventions can be beneficial. A better understanding of the multifactorial persistence of somatic symptoms should lead to more specific, personalised, and mechanism-based treatment, and a reduction in the stigma patients commonly face.

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Introduction

The term persistent somatic symptoms is used as a synonym for persistent physical symptoms, with the latter probably being more commonly used in the UK and USA and the former more commonly used in other countries. In the same sense, physical and somatic are used interchangeably in this Review. Persistent physical symptoms are distressing somatic complaints that last several months or more, regardless of their cause. These symptoms occur in the context of somatic diseases, functional somatic disorders, mental disorders, and undiagnosed conditions, and are a core problem in a wide range of medical disciplines.[1] Back pain, headache, abdominal symptoms, and fatigue are among the most frequently reported symptoms by patients in Western primary care, where they account for up to 50% of all consultations.[2] Approximately a third of persistent physical symptoms cannot be attributed to a recognised disease; however, their prevalence in chronic diseases is also high, with studies reporting, for example, that 70% of patients with chronic kidney disease have persistent fatigue;[3] 63% of patients with coronary heart disease have persistent pain in the arms, legs, or joints;[4] and 31% of patients with ulcerative colitis in remission have persistent gastrointestinal symptoms.[5] Often, persistent physical symptoms are not specific to the organ systems involved in the primary condition, and subjective symptom burden correlates poorly with the severity or stage of the underlying disease.[6,7] Unlike acute somatic symptoms, which are mostly associated with clearly identifiable biomedical causes such as infection, injury, or metabolic dysfunction, the association between persistent symptoms and their original biomedical cause typically becomes weaker as the condition persists or progresses.[8]

Irrespective of cause, persistent physical symptoms are a major determinant of quality of life, as these symptoms can severely impair patients' daily activities and are the most prominent factor limiting patients' ability to work.[9,10] These symptoms are an increasing global burden in terms of years lived with disability and disability-adjusted life years,[9,11,12] as well as high health-care costs.[13] This problem is aggravated by the fact that persistent physical symptoms are often accompanied by depression, anxiety, and sometimes by suicide attempts.[14,15] Persistent physical symptoms remain the major unmet need in the management of many chronic conditions.[16,17] This unmet need is a major challenge because medical treatment traditionally focuses on modifying disease progression rather than on symptom management. In many chronic

Search strategy and selection criteria

We performed a search in PubMed, Scopus, and PsycInfo for "persistent somatic symptom*" or "persistent physical symptom*" in titles or abstracts. No filters or language restrictions were applied, and grey literature was not excluded. We searched from database inception to Jan 27, 2024. This search was combined with keywords related to the individual topics of this Review. As the terms persistent somatic symptom and persistent physical symptom have only become established in recent years, PubMed, Scopus, PsycInfo, and reference lists of journal articles and book chapters were also searched for related terms. For the final reference list, we selected articles that were most relevant to the topics of the sections of our Review, prioritising systematic reviews and meta-analyses, randomised controlled trials, and prospective studies over cross-sectional studies and other types of publications. Disagreements over inclusion were resolved by discussion between BL, AT, and PH.

diseases, the course of disease and survival rates can be positively influenced by effective medication protocols, but these are often much less effective in alleviating the associated somatic symptoms and impairments.[18,19]

Causal mechanisms of persistent physical symptoms appear to be complex and multifactorial, and might vary between individuals with the same symptoms. Neither purely biomedical nor purely psychological models are sufficient, and both represent overly simplistic and outdated dualistic views.[1,20,21] Ignoring the role of psychosocial factors in persistent physical symptoms can lead to harm from unnecessary testing and treatment, and explicitly or implicitly attributing symptoms to a purely psychogenic cause leads to denial of the reality of the patient's experience and stigmatisation.[22,23] Over the last decade, new models for understanding risk factors and mechanisms of somatic symptom persistence have been developed,[1,21,24,25] representing promising starting points for mechanism-based approaches to alleviate persistent physical symptoms across multiple conditions.

In this Review, we aim to provide a comprehensive overview of the emerging understanding of persistent physical symptoms in medicine, including definition and clinical picture, genesis, and therapeutic options. Secondary aims are to increase clinicians' skills in treating patients with persistent physical symptoms, to combat stigma, and to contribute to the harmonisation of knowledge about the diagnosis and treatment of persistent physical symptoms across countries and health-care settings.

Definition and clinical picture

Description and symptom patterns

Somatic symptoms are a subjective experience.[26] A patient's experience of their symptoms is typically the basis for diagnostic testing and treatment. The definition of persistent physical symptoms is nominal, based on the duration and frequency of symptoms and distress, and is independent of the genesis of the symptoms (panel 1).[1] Accordingly, the term persistent physical symptoms is used as an umbrella term to describe distressing somatic complaints, regardless of cause, that are present on most days for at least several months.[1] This timeframe takes into account that different time limits—usually between 3 and 6 months—are used to distinguish between non-persistent and persistent symptoms in different medical conditions, and is consistent with both the timeframe used in the International Classification of Diseases, 11th Revision (ICD-11) to distinguish between acute and chronic pain and the definition of persistent in the context of bodily distress disorder.[27] Persistent physical symptoms are evaluated by repeated assessments of the patient's subjective somatic symptom severity. Crucially, this definition of persistent symptoms is not restricted to so-called medically unexplained symptoms, where no disease can be found after appropriate medical investigation.

Any physical symptom can become persistent. Six stable clusters of interrelated symptoms are repeatedly described in clinical and general population samples,

Panel 1: **Persistent physical symptoms at a glance**

Definition

Persistent physical symptoms (synonymous with persistent somatic symptoms) is used as an umbrella term to describe distressing somatic complaints, regardless of cause, that are present on most days for at least several months. Persistent physical symptoms are measured by repeated assessments of the patient's subjective somatic symptom severity.

Frequent persistent physical symptoms

- General symptoms: fatigue, insomnia, sleep problems, loss of energy, concentration difficulties, impairment of memory, headache, and pruritus
- Cardiopulmonary symptoms: chest pain, precordial discomfort, heart pounding or racing, light-headedness, and breathlessness
- Gastrointestinal symptoms: nausea, constipation, diarrhoea, bloating, abdominal pain, and epigastric burning sensation
- Musculoskeletal symptoms: back pain, neck pain, arthralgia, and myalgia
- Nervous system symptoms: paralysis or localised weakness, numbness or tingling sensations, and impaired coordination or balance
- Genitourinary symptoms: burning with urination and pelvic pain

Contexts in which persistent physical symptoms might occur

- Somatic diseases (eg, fatigue in multiple sclerosis or chronic kidney disease)
- Functional somatic disorders (eg, diarrhoea in irritable bowel syndrome)
- Mental disorders (eg, headache in major depressive disorder)

Rationale for a transdiagnostic view

For the transition from acute to persistent physical symptoms, evidence consistently shows that cross-disease biopsychosocial mechanisms play a role in addition to disease-specific mechanisms. These mechanisms provide promising starting points for mechanism-based transdiagnostic treatment of persistent physical symptoms.

namely clusters of general, cardiopulmonary, gastrointestinal, musculoskeletal, nervous system, and genitourinary symptoms (panel 1).[28–30] Although some individuals have persistent symptoms in only one of these clusters, many develop symptoms in different clusters. Accordingly, patients can present persistent symptoms to a wide range of medical disciplines, but because these are usually studied in isolation, treatment is often fragmented. Although persistent physical symptoms occur in all cultures, sociocultural factors affect how individuals experience, interpret, communicate, and manage their symptoms.[31]

The question arises as to whether persistent physical symptoms should be considered as a common diagnostic category, irrespective of their cause and specific presentation. Disease-specific mechanisms play a determining role in the initial development of most somatic symptoms and influence their course, and these pathophysiological mechanisms should be addressed, wherever possible, on the basis of scientific evidence. In addition to the disease-specific mechanisms of symptom development, particularly in the progression from acute to persistent symptoms and in their maintenance, similar cross-disease mechanisms appear to be relevant across a range of symptoms. These commonalities, and the resulting potential for effective and mechanism-based treatment across conditions and disciplines, suggest the use of a transdiagnostic—and broad and inclusive—term for persistent physical symptoms.

Persistent physical symptoms in somatic diseases, functional somatic disorders, and mental disorders

The division into somatic diseases, functional somatic disorders, and mental disorders is artificial, given the many overlaps between diseases, and promotes a misleading mind–body dualism; however, as this division is the basis for current diagnostic systems in medicine (eg, ICD-11), it is used here.

Somatic diseases

Persistent physical symptoms are a core feature of many somatic diseases. In some cases, the original pathophysiological cause still exists, such as paralysis in stroke with destruction of brain tissue. In other cases, the symptoms have a clear precipitating cause at the time of onset and might persist for a long time despite the original condition being controlled. For example, in patients with primary biliary cholangitis, fatigue is a common distressing symptom that is not satisfactorily relieved by drug therapy with rituximab[18] and often persists even after liver transplantation.[32]

Functional somatic disorders

Persistent physical symptoms are also a diagnostic feature of functional somatic disorders,[30] such as irritable bowel syndrome; however, the diagnostic criteria for functional somatic disorders usually do not require that the symptoms cause distress. For example, the Rome IV criteria for irritable bowel syndrome describe only clear patterns of abdominal pain and altered bowel habits, whereas a core feature of persistent physical symptoms as defined here is the inclusion of symptom-related distress.[33]

Mental disorders

Persistent physical symptoms can also be a feature of a mental disorder, such as headaches associated with major depressive disorder or heart palpitations associated with panic disorder. In current psychiatric classifications, somatic symptom disorder (as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision)[34] and bodily distress disorder (as defined by the ICD-11)[27] are diagnoses in which the presence of distressing persistent physical symptoms is a central diagnostic criterion. These diagnoses also require disproportionate and persistent thoughts about the seriousness of one's symptoms, considerable anxiety about health or symptoms, or excessive energy or time spent on these symptoms or health concerns.[35] Although some people with persistent physical symptoms might meet these criteria, others might not. Additionally, these diagnoses are rarely used outside of specialist mental health services. Compared with the predecessor diagnoses in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition and the International Classification of Diseases, 10th revision (ie, somatoform and related disorders), the criterion of the medical unexplainability of symptoms has been abandoned because the reliability of assessing whether or not there is a pathophysiological explanation for a particular symptom is very low.[36] As a result, these newer diagnoses allowed for much greater diagnostic reliability and validity.[35] For the same reason, the term medically unexplained symptoms is now considered obsolete.[36]

Comorbidity

Often, patients might fulfil the criteria for several diagnoses at the same time, such as somatic, functional, or mental disorders, or a combination of these. In this case, all applicable diagnoses should be used simultaneously to best describe the patient's problems. The principle should be inclusive of all diagnoses rather than considering only one. This perspective best reflects the extensive literature on interactions between body and mind.[37,38] Importantly, the term psychosomatic is often misunderstood to mean psychogenic or imaginary, whereas the overall aim of psychosomatic medicine is to integrate psychological and somatic aspects of illness, focusing on the interactions between somatic and psychological processes.[39]

Assessment of persistent physical symptoms

Assessment of persistent physical symptoms depends primarily on the clinical history. Guiding questions should address the onset, course, severity, distress, and impairment caused by the symptoms. Assessment can be

supported by a range of validated scales, including both symptom-specific measures (such as the International Association for the Study of Pain scales for pain severity, pain-related distress and interference[40]) and generic scales. The range and severity of symptoms can be assessed using, for example, the well validated Patient Health Questionnaire-15 (PHQ-15),[41,42] or its short version, the Somatic Symptom Severity Scale (SSS-8).[43] Symptom intensity and interference can be assessed using simple numerical rating scales as recommended by the European Research Network to Improve Diagnosis, Treatment, and Health Care for Patients with Persistent Somatic Symptoms (EURONET-SOMA).[44] These scales can be used in verbal and written form and have high face validity. The well validated Somatic Symptom Disorder B-Criteria Scale (SSD-12)[45] or the Whitely Index (WI-7)[46] can be administered to assess the cognitive–emotional processing of somatic symptoms. An evaluation of the health-related quality of life is also recommended. In addition to assessing the extent of active organ pathology, a careful clinical examination could identify features indicative of somatic diseases, functional somatic disorders, or mental disorders.[47]

Genesis

General principles

An understanding of the genesis of persistent physical symptoms is necessary for planning targeted treatment. Many of the risk factors described herein are routinely assessed as part of the medical history. Other risk factors specific to persistent physical symptoms can be assessed as part of an extended history. The investigation of these risk factors also serves to develop a biopsychosocial explanatory model for the persistent physical symptoms, which itself often has beneficial therapeutic effects.

Multiple biological, psychological, and social risk factors contribute to the persistence of somatic symptoms, either individually or in combination.[1,48,49] The contributions of the different risk factors appear to depend on the underlying disease and its chronicity, and on individual and contextual predispositions. Although biomedical factors are usually, but not always, central to the development of short-term symptoms, psychological factors (such as the patient's beliefs or expectations) and social factors appear to be more important for the long-term persistence of somatic symptoms.[50] Although the development of persistent physical symptoms in functional or mental disorders has long been studied,[51] the scientific evidence for persistent physical symptoms in chronic somatic conditions is just beginning to emerge.[52–54] Given that the risk factors identified to date at least partly overlap between conditions, a comprehensive description of common risk factors seems justified at this stage.[48,55–58]

Current evidence on the development of persistent physical symptoms is best represented by biopsychosocial vulnerability–stress models, which distinguish between

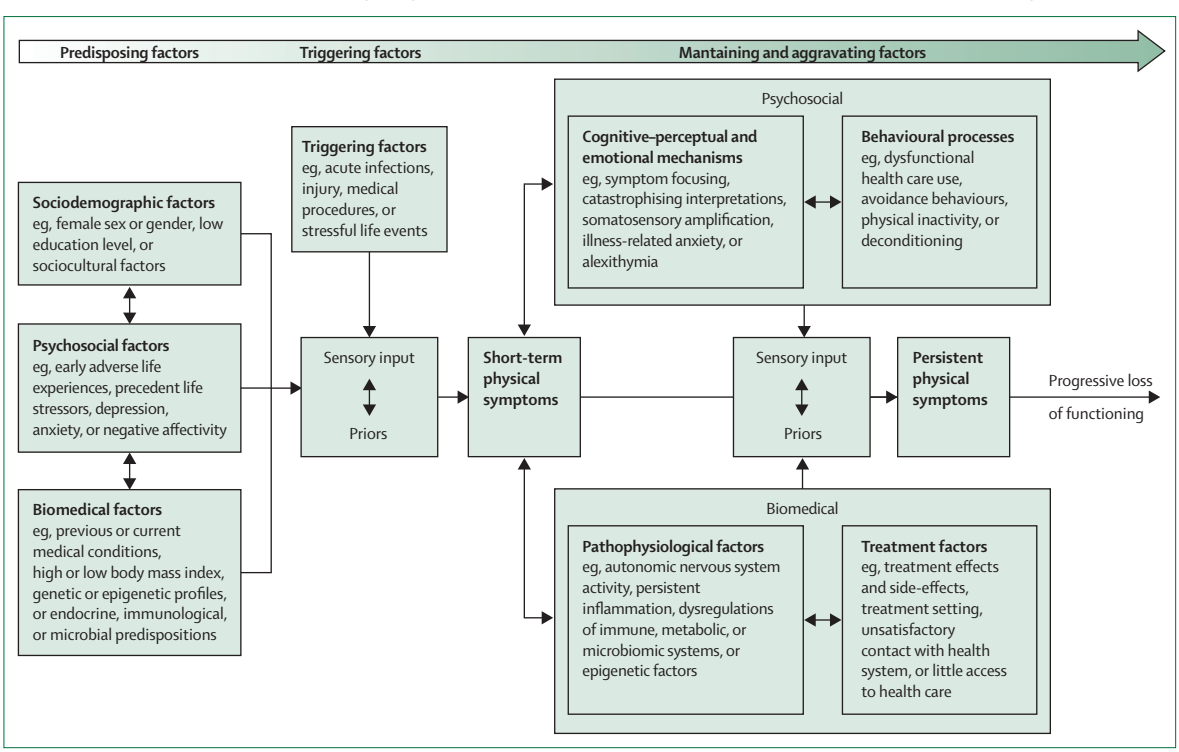

Figure 1: **Conceptual working model of risk factors and mechanisms currently under discussion for the persistence of somatic symptoms**
This working model is an updated version based on previous versions by Henningsen and colleagues[25] and Löwe and colleagues.[1] Risk factors are not exclusive and can also apply in parallel Sociodemographic factors should be interpreted with caution, taking into account their intersectionality and the ways in which societal disadvantage influences access to health care.

predisposing, triggering, and maintaining or aggravating factors.[1,25] Embedded in these models are recent findings about perceptual processes related to persistent physical symptoms.[24,59] Figure 1 summarises the risk factors and mechanisms described in the following text into an empirically based and verifiable conceptual working model for the persistence of somatic symptoms. The outlined factors are known to increase the risk of developing persistent physical symptoms across a range of medical conditions.

Factors associated with the persistence of somatic symptoms

The most commonly described predisposing socio-demographic factors associated with the transition from short-term to persistent physical symptoms include female sex or gender, lower socioeconomic status, lower education level, and culture-specific factors (eg, culturally determined ways of expressing distress and of explanatory models for symptoms).[31,60–62] These factors should be interpreted with caution, however, taking into account their intersectionality and the ways in which societal disadvantage influences access to health care. Biomedical predisposing factors that appear to be relevant across diseases include chronic medical conditions, previous somatic symptom burden, sleep disturbance, elevated body mass index, and certain genetic or epigenetic risk profiles.[48,51,57,58,63] Early adverse life experiences, negative affectivity, neuroticism, depression, and anxiety have been identified as psychological predisposing conditions for persistent physical symptoms.[48,61,63–70] Acute infections or injuries, medical or surgical procedures, or recent stressful life events are typical triggers associated with the initial onset of short-term somatic symptoms, which might persist depending on the individual's predisposition.[48,61]

Maintaining and aggravating factors can be difficult to disentangle from predisposing factors. Common biomedical factors, such as persistent inflammation and dysregulation of the immune, autonomic, metabolic, and microbiome systems, as well as genetic and epigenetic factors, can cause somatic symptoms to persist or intensify.[51,69,71–73] Cognitive–perceptual and emotional processes considered to be maintaining and aggravating factors in the development of persistent physical symptoms across diseases include selective attention to and heightened perception of bodily sensations, catastrophising interpretations, dysfunctional health behaviours, and somatosensory amplification.[25,50,51,63,74,75] Alexithymia, a deficit in the perception and regulation of emotions, is considered an affective risk factor.[76,77] At the cognitive–behavioural level, learning processes and avoidance behaviours such as physical inactivity and subsequent deconditioning also play a role in maintaining and amplifying somatic symptoms.[63,78,79] For example, evidence suggests that in stroke patients with fatigue, depression and avoidance of physical activity amplify poststroke fatigue.[80] Other maintaining or aggravating factors for persistent physical symptoms might be negative treatment experiences, treatment side-effects, unsatisfactory contact with treatment providers, illness-related anxiety, little access to health care, low health literacy, social inequality, and stigmatisation.[1,25]

Current understanding of symptom perception

Evidence increasingly suggests that symptoms are imprecise representations of body states. This inaccuracy can lead to overestimation or underestimation of the activity of disease processes. Central to a contemporary neuroscientific account of symptoms is the process of predictive coding,[24,59] a computationally efficient process by which the brain integrates complex information, including information about body states. Predictive coding involves resolving differences between unconscious predictions of the body's state and incoming ascending sensory signals using error minimisation, in which the predictions act as Bayesian priors.

Predictive coding has been shown to underpin a range of symptoms, including chronic pain and breathlessness,[81,82] and can also be applied to existing concepts such as central sensitisation,[83,84] nociplastic pain,[81] and somatosensory amplification.[59] In the case of persistent physical symptoms, evidence suggests that priors, which are based on implicit learned experiences of symptoms or explicit beliefs, have a dominant effect, and the effect of ascending signals is diminished.[24,59] Thus, predictive coding models explain how somatic symptoms can persist long-term in the absence of sensory input, provided that strong priors are present.[85] In contrast, short-term symptoms are not usually associated with strong priors from implicit expectations, so ascending sensory input plays a greater role in these symptoms, thus contributing to the bidirectional connectivity between the brain and the body.[86]

Placebo and nocebo effects (ie, positive or negative treatment effects that cannot be attributed to the active treatment components[87]) can also be explained by predictive coding processes. In this case, expectations acquired through personal experience, implicit learning, or explicit information from physicians or other sources might lead to strong priors about the effect of treatment on symptoms, which in turn contribute to the placebo or nocebo response in the absence of increasing sensory input from the active treatment components.[88] Placebo and nocebo responses provide a good example of the importance of patients' beliefs and expectations in the perception and management of their symptoms. Predictive coding models allow for the observed variation in the relationship between subjective symptoms and pathophysiological dysfunction, as each individual's previous prediction processes are unique.[24,59] Importantly, although predictive coding involves expectation, this process is primarily unconscious, not something that a person consciously expects to happen. Figure 2 illustrates the perception of somatic symptoms as conceptualised in predictive coding models.

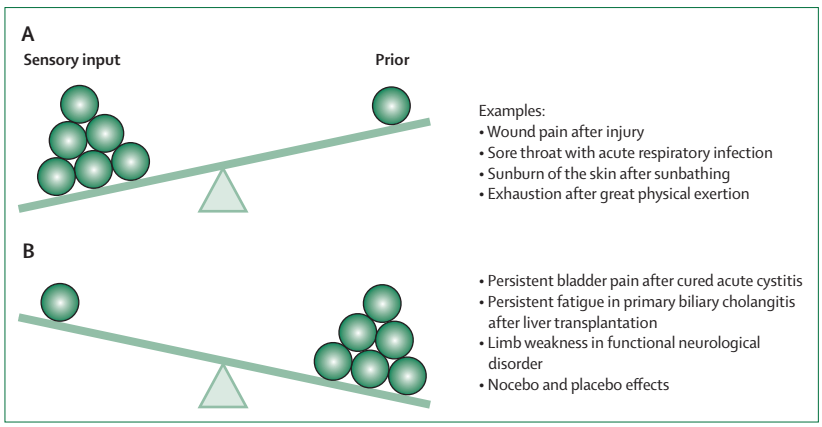

Figure 2: **Illustration of the predictive coding model in symptom perception**
(A) Situation with strong sensory input and low precision prior; here, posterior symptom interpretation is mainly shaped by sensory input. (B) Situation with weak sensory input and high precision prior; here, posterior symptom interpretation is mainly shaped by the prior.

Cross-disease processes

Evidence suggests that at least some of the risk factors and mechanisms leading to the transition from short-term to persistent physical symptoms are common to a variety of conditions,[8,55,63] albeit to varying degrees. Additionally, the perceptual processes described previously are of a generic nature, and there is no convincing reason why these should not be involved across different diseases. Parallels also exist between the risk factors described previously for many different types of symptoms and those specific to chronic pain, such as persistent inflammation or heightened perception of bodily sensations.[21,81] These parallels support the hypothesis of a generalisability of risk factors and mechanisms. The assumption that multifactorial biopsychosocial processes contribute to symptom persistence offers a potential opportunity to overcome the artificial separation between somatic and mental illness in the diagnosis and treatment of persistent physical symptoms and between pain medicine and psychosomatic medicine. Importantly, many of these generic mechanisms are modifiable, such as attention to symptoms, dysfunctional expectations, avoidance behaviour, and limitation of physical activity. These mechanisms represent starting points for transdiagnostic, symptom-focused treatment approaches.

Treatment

Summary of the evidence

The first step in the management of persistent physical symptoms is, whenever possible, providing diagnosis-specific treatment of the underlying pathophysiological processes. We do not discuss these disease-specific treatments here; however, in many cases, these treatments address the underlying disease without resolving the symptoms. The following is an overview of the effectiveness of treatments for persistent physical symptoms that might be considered when treatment of the underlying disease is not sufficiently effective to improve clinical symptoms, distress, or impairment. Traditionally, many of these treatments have focused on functional somatic disorders or so-called medically unexplained symptoms, but studies are also increasingly being conducted on somatic diseases.

Psychological interventions

A 2023 meta-analysis concluded that psychological interventions have a small, statistically significant effect on reducing somatic symptoms.[89] Most of the interventions investigated for the treatment of persistent physical symptoms include cognitive behavioural therapy (CBT) techniques.[89] Trials of CBT for persistent physical symptoms, delivered face-to-face or via the internet with therapist support, have taken a transdiagnostic approach, with small-to-moderate positive effects on somatic symptom severity.[90,91] Results from an earlier randomised controlled trial in patients with unexplained persistent physical symptoms showed that both standard CBT and CBT augmented with emotion regulation training can have effects on somatic symptom severity and secondary outcomes such as symptom coping.[92] Encouragingly, the results of a recent randomised clinical trial suggest that the statistically significant positive effect of CBT on fatigue in multiple sclerosis was sustained over 12 months.[93]

Other psychological therapies have been tested, including short-term psychodynamic psychotherapy, for which an earlier meta-analysis had suggested that it could have beneficial effects on somatic symptoms in a range of medical conditions, with medium effect sizes.[94] For functional somatic symptoms, a meta-analysis concluded that short-term psychodynamic psychotherapy statistically significantly improves somatic symptoms, with a large effect size that was maintained at long-term follow-up.[95] Similarly, a meta-analysis on the effectiveness of mindfulness-based and acceptance-based CBTs for persistent physical symptoms indicated that these interventions were more effective than inactive and non-specific control conditions in reducing the severity of somatic symptoms.[96] Systematic reviews of more specific interventions or patient groups, such as interventions for fatigue in inflammatory bowel disease,[97] psychological interventions for children and adolescents with so-called medically unexplained symptoms,[98] or self-help for adolescents with persistent physical symptoms,[99] found uncertain or weak evidence of their efficacy.

Interventions delivered in primary care

Trials of psychological interventions delivered in primary care, although largely focused on so-called medically unexplained symptoms, have been small and shown little evidence of benefit.[89] A 2023 review indicated that improvement in persistent physical symptoms also depends on the treatment setting, with the best results in specialist care, followed by secondary and primary care.[100] Training and supervision of clinicians are clearly needed in the management of persistent physical symptoms

to reduce barriers to treatment.[101,102] In this regard, a 2023 Norwegian two-arm cluster randomised trial provided promising evidence that the implementation of a structured communication tool in primary care statistically significantly improved functioning, symptoms, sick leave, and quality of life of patients with medically unexplained physical symptoms.[103] Another randomised controlled trial showed that one to four consultations with a general practitioner with an extended role during an 8-week period led to a statistically significant reduction in Patient Health Questionnaire-15 scores at 52 weeks. In this intervention, which was delivered in person or online via a symptom clinic, general practitioners actively listened to participants about their illnesses and proposed and negotiated explanations and actions. This randomised controlled trial excluded participants with severe persistent physical symptoms and participants with evidence in their medical records of a previous or current major illness likely to cause symptoms.[104] Overall, these randomised clinical trials indicate the potential of appropriate communication techniques in the management of persistent physical symptoms.

Pharmacological interventions

There have been few transdiagnostic trials of pharmacological interventions for persistent physical symptoms. For somatoform disorders (a specific subgroup of persistent physical symptoms), an early Cochrane review concluded that there was very low-quality evidence for the effectiveness of new-generation antidepressants when compared with placebo.[105] A 2017 randomised trial for functional somatic disorders showed that imipramine resulted in statistically significantly greater patient-rated global health improvements than placebo.[106] Some antidepressants have been shown to be effective for specific persistent physical symptoms (eg, selective serotonin reuptake inhibitors and tricyclic antidepressants for gastrointestinal symptoms in irritable bowel syndrome and tricyclic antidepressants and serotonin and norepinephrine reuptake inhibitors for pain in a number of somatic and functional disorders).[107,108] The presence of any comorbid depressive or anxiety disorders adds additional justification for their use.

Target variables for treatment

To refine treatments, understanding which potentially modifiable risk factors and mechanisms involved in the persistence of somatic symptoms to target is important. Expectation optimisation (ie, influencing the conscious expectation of symptom development and treatment effects in a realistic direction) was found to be a promising method for treating clinical symptomatology in patients with a variety of medical conditions.[54] Other CBT trials reported that improvements in catastrophising and

***Panel 2:* Treatment principles for persistent physical symptoms**

Basic care for all patients

- Diagnosis-specific treatment of the underlying condition or pathophysiology
- Person-centred communication techniques with appropriate reassurance, validation, and explanation: providing a biopsychosocial explanatory model, explaining the perception of persistent physical symptoms as a long-term process with the possibility of changing this process, avoiding induction of dysfunctional expectations about symptom development or treatment effects

Additional treatment when basic care is not sufficient

- Person-centred psychological treatment of persistent physical symptoms when basic care does not result in satisfactory improvement of persistent physical symptoms, when the underlying pathophysiology is unknown, or when a disease-specific therapy is not possible
- Antidepressant (or other neuropsychiatric) medication might be considered for the treatment of comorbid depressive or anxiety disorders or for the relief of persistent physical symptoms when no other treatment is successful
- In severe cases, multimodal integrative treatment including symptomatic medication treatment, psychotherapy, psychoeducation, physiotherapy, and body-oriented and relaxation therapies; treatment of comorbid mental disorders

Potential targets for person-centred treatment

- Modifying dysfunctional symptom and treatment expectations
- Addressing illness-related anxiety
- Modifying catastrophising interpretations, symptom focusing, and somatosensory amplification
- Reducing symptom-related disability
- Providing a biopsychosocial explanatory model
- Treating comorbid depressive disorders, anxiety disorders, and sleep disturbances
- Increasing emotion regulation skills
- Processing early childhood trauma

Probable predictors of poor treatment response

- Somatic symptoms and impairment: longer reported symptom duration; high pretreatment symptom intensity; or lower physical, emotional, and social functioning
- Psychological variables: comorbid depressive or anxiety disorders, symptom focusing, catastrophising interpretations and worrying, somatosensory amplification tendencies, low symptom acceptance, or self-efficacy
- Social factors: low educational level, low socioeconomic status, or little access to appropriate health care

symptom focusing,[109] depression, symptom-related disability, health-related quality of life, early childhood trauma, health anxiety, and emotion regulation skills predict treatment response in patients with persistent physical symptoms.[110] In a qualitative study, patients and therapists perceived the alternation of psychosocial conversations and body-oriented exercises to raise awareness of the interaction between body and mind as the working mechanism for successful treatment of persistent physical symptoms.[111] Finally, two meta-analyses identified factors associated with less favourable CBT outcomes in the treatment of persistent physical symptoms. These factors included comorbid depressive and anxiety disorders; symptom catastrophising and worry; somatosensory amplification tendencies; low symptom acceptance; low self-efficacy; higher symptom intensity; lower physical, emotional, and social functioning; and longer reported symptom duration at baseline.[112,113]

Clinical management of persistent physical symptoms

The clinical management of persistent physical symptoms, derived from the current scientific evidence, is summarised in panel 2. Clinical management should include diagnosis-specific, disease-oriented treatment when an underlying pathophysiology or disease is present, in parallel with management of symptoms. In addition, consultations should be person-centred (ie, the person should be considered as a whole in their biopsychosocial context), with the aim of reaching a common understanding between the physician and the patient about the personal experience of and concerns about the illness.[114] Consultations about persistent symptoms can be psychologically informed[115] and still follow the norms of a medical consultation. A 2023 model for consultations for general practitioners with an extended role about persistent physical symptoms included recognition and validation, explanation of symptom processes, action to manage these processes, and learning what works.[116] Explanations should be grounded in a biopsychosocial model based on current knowledge of the multifactorial genesis of persistent physical symptoms and adapted to the individual patient. Together with the patient, an individual biopsychosocial explanatory model for their persistent physical symptoms should be developed.[101,117,118] Focusing on persuading the patient that they do not have a disease and making presumptions about psychogenic factors[47] are usually not helpful to the treatment process. Counselling should avoid inappropriate pessimism about outcomes and overemphasis on rare treatment side-effects, as this type of counselling can have nocebo effects.[119] Avoiding nocebo effects is also important in more acute conditions, because appropriate, reassuring communication is a preventive factor for the later development of persistent physical symptoms.[120]

If these basic psychologically informed communication strategies are not sufficient to achieve sustained improvement in distressing persistent physical symptoms and associated impairment, specific psychotherapeutic interventions should be offered as a next step. These should

Panel 3: Patient aged 44 years with ulcerative colitis and persistent physical symptoms

Medical history, symptoms, and diagnostic measures

A male bank employee, aged 44 years, was first diagnosed with ulcerative colitis at the age of 23. Since then, he has had several flares of colitis of moderate severity, confirmed endoscopically and histologically. 4 years ago, his gastroenterologist commenced him on treatment with the TNF antibody infliximab, to which he responded well. For the past 3 years, the patient has had no evidence of inflammation, faecal calprotectin was normal, and colonoscopies including random biopsies showed mucosal healing; however, he continued to have troublesome gastrointestinal symptoms associated with highly urgent bowel movements. These symptoms varied from day to day but consistently included several urgent bowel movements with small amounts of loose stools every day. These bowel movements were associated with bloating and the feeling of abdominal cramps. His stools did not contain blood or mucus, and he had no other notable symptoms apart from moderate fatigue. His gastroenterologist ruled out small intestinal bacterial overgrowth by hydrogen breath testing and reassured him that there was no sign of active colitis or other pathology to explain his ongoing symptoms.

In the detailed biopsychosocial history, the patient stated that his father died of colon cancer at the age of 56. He described being worried about the possibility of developing colon cancer himself and stated that he spent many hours a day worrying about his symptoms, monitoring them very closely, and keeping a symptom diary. Dysfunctional symptom expectations were present in that the patient constantly expected his symptoms to worsen and new flares to occur, despite long periods of remission. He restricted his daily activities so that he could always find a toilet within walking distance. He was embarrassed by his symptoms and largely withdrew from social contacts. His mood was depressed, he no longer enjoyed work or sports, and his energy was reduced. Although he sometimes questioned his purpose in life, he credibly distanced himself from suicidal intentions.

Basic care

At diagnosis, the patient received high-dose (3 g/day) mesalazine orally as disease-specific treatment from his gastroenterologist and as additional mesalazine enemas for acute flares, as well as oral budesonide.

(Continues on next page)

(Panel 3 continued from previous page)

He was on maintenance treatment with low-dose mesalazine for years and was escalated to infliximab 4 years ago. In view of the histologically proven remission, infliximab therapy was stopped and the patient remained on maintenance monotherapy with 2 g of mesalazine daily. The gastroenterologist continued to keep him under review.

Using person-centred communication techniques, the general practitioner validated the patient's limitations related to his disease and his efforts to monitor and manage the disease successfully. She addressed the patient's fears about developing colon cancer in the context of his father's disease and provided information about the actual risk of developing colon cancer. Although this risk was somewhat increased relative to the general population (due to both the personal history of colitis and the family history of sporadic colon cancer), she explained that the absolute risk is still low and that the surveillance by his gastroenterologist is there to screen for precancerous changes before they become problematic. She developed an explanatory model of the symptoms with the patient, using descriptions and metaphors, such as: When your ulcerative colitis was bad, the inflammation sensitised the nerves in your gut (the autopilot) that control bowel function. What has happened now is that, although the inflammation has gone, the autopilot is still very quick to signal the need to go to the bathroom, even when there is not much stool in the bowel.

She and the patient discussed how this made sense and agreed that if that was the case, it would be safe to find ways to make the gut autopilot act more slowly.

Additional treatment

As a result of the ongoing specialist follow-up and person-centred consultations with his general practitioner, the patient was able to develop a much better way of managing his symptoms and a more realistic assessment of his risk of ulcerative colitis flares and of developing colon cancer. Dysfunctional symptom expectations were reduced. Using his individual explanatory model, he achieved better acceptance of his illness and a greater sense of control over his gastrointestinal symptoms; however, recurrent abdominal pain, urgent bowel movements, and depressive symptoms persisted, with social withdrawal and repeated limitations to his ability to work, leading the general practitioner to diagnose a moderate depressive episode. In a shared decision, the patient declined antidepressant medication but was keen to start psychotherapy to learn to cope better with his illness and improve his quality of life.

Longer-term course

Together with the patient, the psychotherapist developed an extended individual biopsychosocial explanatory model for the persistent gastrointestinal symptoms, in which chronic inflammatory processes, learning processes, symptom focusing, illness-related fears, dysfunctional symptom expectations, and avoidance behaviour all played a role. The psychotherapist addressed the anxiety associated with the disease and successfully introduced behavioural exercises to reduce avoidance and increase the patient's daily radius independent of the proximity of a toilet. His personal symptom diary was discontinued, gradual cognitive defocusing of gastrointestinal symptoms was achieved, and the patient was able to devote more time to his work, personal relationships, and sports. Social avoidance was reduced and the patient regained more confidence and trust in his body's ability to function. Towards the end of psychotherapy, the patient was aware that flares of ulcerative colitis could still occur, but he felt better prepared, had higher expectations of his coping skills, and had a substantial reduction in depressive symptoms, disease-related anxiety, and somatic symptoms. He remained on maintenance treatment with mesalazine and sees his gastroenterologist and general practitioner regularly.

involve working on potentially modifiable risk factors for persistent physical symptoms, such as illness-related anxiety, symptom-focusing, catastrophising interpretations, somatosensory amplification, and avoidance of physical activity. Furthermore, as derived from predictive coding models, overly precise prior predictions and dysfunctional expectations should be addressed. Comorbid depressive or anxiety disorders, other potential mental disorders, or early childhood trauma might also need to be addressed with appropriate treatment. In the case of therapy-resistant persistent physical symptoms or the presence of comorbid depressive disorders, antidepressant or other neuropsychiatric medication can be considered. The goals of treatment in general are to reduce the severity of somatic symptoms and to improve quality of life, psychosocial wellbeing, and disease acceptance.[121] Psychological and somatic aspects of persistent physical symptoms must be managed simultaneously and equally, from diagnosis to specialised treatment, including interdisciplinary treatment. A case scenario illustrating the management of persistent physical symptoms is presented in panel 3. In very severe cases, integrated multimodal treatments provided in day care, rehabilitation hospitals, or inpatient settings might be needed, including symptomatic medication, psychotherapy, psychoeducation, physiotherapy, and body-oriented and relaxation therapies.[39,122] Any additional comorbid mental disorders can also be treated in these settings.

Given the still fragmentary evidence, the insufficient availability and effectiveness of treatment, and the little knowledge that treating physicians have, best practice models for the treatment of persistent physical symptoms are urgently needed. Personalised treatment models, stepped care, and collaborative care models should be developed and implemented to improve treatment

effectiveness. Given the need for transdisciplinary collaboration and multimodal treatment, and the high prevalence of persistent physical symptoms in many medical settings, this task is challenging but necessary and promising. In this context, the long duration of untreated illness,[123] the unclear cost-effectiveness of interventions,[124] and the risk of overtreatment, undertreatment, and mistreatment need to be addressed with a continued commitment to research.

Conclusions

Limitations

This Review has the limitation that it is largely based on the current state of knowledge on persistent physical symptoms, where the aetiopathogenesis is not yet fully understood. In addition, the list of exemplary described risk factors and mechanisms is clearly incomplete, and not every risk factor or mechanism has been studied in all symptoms and conditions. More prospective studies of the relevance of these risk factors and mechanisms in many conditions are needed, including those with a poorly understood pathophysiology such as post-COVID-19 condition. Even with this condition, however, evidence suggests that risk factors are not only of a biological nature, but also of a psychosocial nature.[125,126]

Future directions

We recommend that future studies should also include a focus on the social determinants of persistent physical symptoms, such as the intersections between sex or gender, race or ethnicity, education, and socioeconomic status.[127] To identify causal relationships and the specific contribution of individual risk factors to persistent physical symptoms as an outcome, these studies should be prospective and ideally examine biological, psychological, and social risk factors simultaneously. In addition, iatrogenic, systemic, and cultural risk factors for persistent physical symptoms deserve more attention,[128] as does increasing public knowledge about symptoms, causes, and treatment options.[129] More research is also needed to develop and test the efficacy of transdiagnostic therapies for persistent physical symptoms, involving patients and the public wherever possible.[130] Panel 4 summarises research gaps and promising future research directions.

A biopsychosocial understanding of persistent physical symptoms has great potential to provide a patient-centred focus on subjectively distressing somatic symptoms; to avoid simplistic binary thinking; to reduce unnecessary, costly, and potentially harmful medical interventions; and to provide reliable information for shared decision

Panel 4: **Research needs and future directions**

Definition and clinical picture

- More detailed description of the diagnostic commonalities of various persistent physical symptoms
- Identification of trajectories of specific somatic symptoms over the course of illness

Genesis

- Identification of disease-specific and cross-disease risk factors and mechanisms in various persistent physical symptoms
- Cross-validation of disease-specific and generic mechanisms across different medical conditions
- Investigation of the specific contribution of biological, psychological, and social risk factors to persistent physical symptoms in prospective studies
- Investigation of iatrogenic, systemic, and cultural risk factors for the persistence of somatic symptoms

Treatment

- Investigation of specific mechanisms of action in experimental studies
- Development of mechanism-based, tailored interventions
- Development of personalised treatment models, stepped care, and collaborative care models
- Investigation of the cost-effectiveness of interventions
- Implementation of best practice models for the management of persistent physical symptoms in health-care systems, involving patients and the public whenever possible
- Adaptation of management strategies to cultural and regional differences, ensuring relevance across diverse patient populations

Other

- Promotion of transdisciplinary collaboration and establishment of multimodal treatment settings for persistent physical symptoms
- Translation of the latest scientific evidence on persistent physical symptoms into clinical practice
- Investigation of the social determinants of persistent physical symptoms, such as the intersections between sex or gender, race or ethnicity, education, and socioeconomic status
- Implementation and evaluation of treatment and communication strategies for persistent physical symptoms into medical curricula
- Increasing public knowledge about symptoms, genesis, and treatment options
- Reduction of stigma associated with persistent physical symptoms
- Investigation of the potential for prevention of persistent physical symptoms through education, training, and early recognition

making in diagnostic and treatment processes. Greater awareness and understanding of the multifactorial dimensions of persistent physical symptoms might also lead to better prevention and reduce the feelings of ambiguity and stigma reported by many patients with persistent physical symptoms.

Contributors

BL and PH conceptualised the Review and wrote its outline. BL coordinated the research activities. BL and AT conducted the literature search and analysed the literature. All authors discussed the literature together and contributed substantially to its interpretation. BL wrote the original draft of the Review with input from AT. All authors discussed and critically reviewed the original draft of the Review, provided comments, revised the original draft, approved the final version of the manuscript, had full access to the literature for this Review, and accepted responsibility to submit the Review for publication.

Declaration of interests

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