The challenge of persistent physical symptoms

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Background

Persistent physical symptoms (PPS) for which no medical explanation has been found are challenging for patients, families, and their doctors. A multidisciplinary conference,[1] and a subsequent article in a national UK newspaper, highlighted the long and painful health journey of a patient with complicated symptoms called Maureen who was searching for a diagnosis.[2] The wave of correspondence that followed from others detailed longstanding unresolved health issues that were characteristically sad and diverse, united by a sense of frustration and hopelessness.

In most advanced health systems, common medical issues such as cancer, heart disease, and stroke are subject to evidence-based guidelines and fast-track treatments. These initiatives are supported by specialists, dedicated funding, and research. By comparison, people like Maureen are poorly served; it could be argued that their management represents a major public health issue yet to be addressed. While the topic generates increased discussion, resources remain unavailable to most patients beyond a few specialist centres. Is this because the issue is too big, diverse, and complicated to be a recognised entity? Perhaps there is a sense of futility among healthcare professionals (HCPs) and governments that patients with complex PPS will always be with us and a dedicated strategy would be too expensive? While traditional medical skills and available treatment can do much, we argue that an integrated and appropriately funded national approach will prove economically beneficial and help many.

The problem

While most physicians will recognise 'Maureen', PPS encompass a spectrum, from mild and transient to severe and persistent, with varying degrees of functional impairment and healthcare utilisation.[3] Common features in adults may include persistent/intermittent muscle pain, abdominal symptoms, back or chest pain, dizziness, palpitations, tiredness, and headaches, for which clinical examination and investigations have failed to find a cause.[4] These features are more than the vague aches, pains, and snuffles that most of us occasionally experience. While younger women are frequent presenters, all ages are affected. PPS can sometimes signify life-threatening disease or result in permanent impairment.[5]

It is estimated that there are >7000 rare diseases, 70% of which are associated with genetic abnormalities,[6] with 50% of patients remaining undiagnosed even in advanced diagnostic settings.[7] Screening in utero and at birth will pick up some of the better-known genetic and acquired diseases that, depending on penetrance, can lead to overt symptoms. Children may be diagnosed in their early years because of physical and developmental abnormities. The paediatric population is usually well served by interested physicians, meaning that some 70% of undiagnosed diseases are first recognised in childhood. By comparison, those in later life experiencing chronic and often complex multiorgan symptoms, notably pain, have no dedicated specialist to turn to as they attempt to navigate a fragmented system (Figure 1).[8]

For patients experiencing chronic symptoms, the explanations may broadly include undiagnosed 'organic disease', something 'unknown' or 'rare', an unusual presentation of a well-recognised pathology, 'mental health disorders', or a combination of factors.[9] Iatrogenic causation is often unrecognised. Current testing may be insufficient for diagnosis. In some patients the original stimulus may have resolved, yet their symptoms persist. The importance of central brain mechanisms, psychosocial factors, childhood adversity, and transgenerational effects are increasingly recognised, and may offer an explanation for many with PPS rather than a physical diagnosis.[9]

Box 1. Key messages

- Persistent physical symptoms (PPS) are common, complex, and carry significant personal and societal burdens that are underrecognised.
- Patients often face repeated tests and referrals, delays, disbelief, and a lack of empathy. A diagnosis, while it may not lead to a cure, can offer relief and hope.
- For doctors, managing PPS is challenging because of frequent attendances, time constraints, limited resources, siloed care, and a shortage of general physicians.
- Greater awareness, research, and resources are needed. Patients benefit from unhurried consultations, continuity, early genetic testing, and an empathic approach aided by diagnostic tools, management algorithms, multidisciplinary teams, and availability of specialist clinics.
- When diagnosis is elusive or symptoms persist, GPs' support, coordination, and whole-person approach are key.

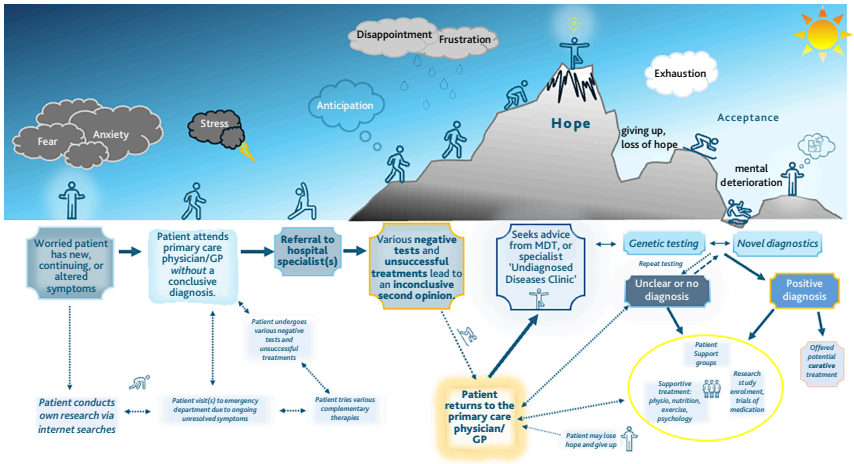

Figure 1. An emotional and clinical journey representative of a person with persistent physical symptoms. MDT = multidisciplinary team.

Pathophysiological links to PPS include low-grade inflammation, 'imbalance' of the autonomic nervous system and microbiome, genetic, and epigenetic changes, and altered interoception.[10] Interrelationships between psychological, social, and physical states are often complex.

The challenge of terminology and coding

Diagnosis and management are complicated by issues of terminology. Medically unexplained symptoms (MUS) and PPS are both widely employed as terms or codes. Because MUS lacks insight into the cause, duration, severity, or significance of symptoms, PPS is now preferred.[11] Many HCPs regard it to be synonymous with persistent somatic symptoms, but 'somatic' can suggest their symptoms are 'all in the mind'. Members of the Witte Raven, a Dutch group of interested physicians, propose the term 'unbearable unexplained symptoms'. This describes a sense of unease and helplessness on behalf of the physician faced with a patient who repeatedly presents with serious complaints, but for whom no cause can be found.[1] Specialty-specific diagnoses may also be considered to come under the PPS umbrella, for example, irritable bowel syndrome. For patients whose response to their symptoms is characterised by excessive and/or abnormal thoughts, feelings, and behaviours, the term 'somatic symptom disorder' is commonly used. Mental health comorbidity is common in those experiencing PPS, with around 50% suffering from associated anxiety or depression.[8]

A further issue is reimbursement. There is no universally agreed code for 'I have no idea what is wrong with this patient'. The closest may be the unspecified World Health Organization ICD-10 code R69 for 'Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified'. Similarly, in 2022, the Orphanet classification of rare diseases introduced the code ORPHA:616874, 'Rare disorder without a determined diagnosis after full investigation', increasing the visibility of undiagnosed patients.[12]

Physicians often do not like to admit that they do not know the diagnosis and in insurance-based systems, unless they code a patient with chest pain as having a cardiac disease, they might not be paid. Not registering 'diagnostic doubt' prevents accurate data collection and may exclude patients from participating in research initiatives. The absence of financial or structural incentives for the systematic documentation and analysis of patients with PPS contributes to the lack of accurate epidemiological data. Introducing the SNOMED code 'Uncertain diagnosis' (Concept ID: 282292002) within primary care records may quantify prevalence and impact.[13]

Effects of not having a diagnosis

It is estimated that around 25% of primary care consultations and up to 50% of hospital attendances do not result in a clear explanation of the individual's problems.[14] NHS data suggest that the problem is increasing.[4] Diagnosis may be delayed if the disease is unfamiliar to the doctor, cuts across specialties, or when the physician incorrectly presumes a functional or psychogenic cause while missing an underlying pathology.[15] Understandably, junior and non-specialist doctors often feel unprepared to manage such complex problems.[16] Where diagnostic labels remain elusive, Health Education England prioritises a generalist attitude, encouraging GPs to practise a 'whole-person' approach to treatment. This may help patients to better manage their symptoms while acknowledging various biopsychosocial elements affecting their day-to-day lives.

However, the escalating demands on HCPs, coupled with diminished consultation durations, impede the effective management of individuals with PPS. Research indicates that patients experiencing greater continuity of care report higher satisfaction and better health outcomes. Conversely, fragmentation, characterised by diffuse interactions across multiple physicians, without central coordination, signifies a breakdown in the therapeutic relationship and undermines patient safety and quality of care.[17]

Available treatments cannot be reliably targeted without knowing the disease aetiology, and this can take years. Limited available data suggest that PPS are associated with a cycle of frequent medical attendances, visits to the emergency department when symptoms overwhelm, inconclusive tests, and unsuccessful, potentially harmful, interventions (Figure 1).[18] Those affected risk mental health problems after being repeatedly told that their pain is solely 'caused by past trauma or stress', or that it is 'all in their head'.[19] Once a patient is labelled as suffering from PPS, 'gaslighting' and equity of access to further potentially valuable tests and treatments become an issue.

In the case of Maureen, the primary cause for her diverse symptoms was found to be Ehlers–Danlos syndrome, a genetic multisystem connective tissue disease (prevalence 1:500). Unsurprisingly, management of similar individuals comes with a high socioeconomic burden and cost to the health system.[20]

Moving forward

The number of patients involved and the costs associated with delayed diagnosis should be of concern to decision makers and payers. Matters to consider include redundant consultations, unnecessary tests and treatments, and the economic burden of inactivity. While guidelines and individual initiatives do exist, to the authors' knowledge no country has implemented a fully integrated national approach to the management of PPS open to all.[3] Efforts are being made to develop undiagnosed disease programmes in the US (Undiagnosed Disease Network [UDN], https://undiagnosed.hms.harvard.edu), and in several European countries multidisciplinary expert groups discuss individual cases. In Germany, for example, undiagnosed disease clinics are a mandatory service offered by centres for rare diseases, and interested clinicians are now planning to go beyond this to help patients for whom genetic testing has failed. An interesting legislative approach that could be adopted elsewhere is that of Serbia, where Zoja's Law now compels doctors to send samples from symptomatic patients to overseas laboratories for testing after 6 months without a diagnosis (Law on Prevention and Diagnosis of Genetic Diseases, Genetically Conditioned Anomalies and Rare Diseases, https://www.zivotorg.org/en/faq/general-questions). In addition, there are national and international research projects aiming to solve undiagnosed diseases, such as the EU-funded network project Solving the Unsolved Rare Diseases (Solve-RD), which is now continued within the European Rare Diseases Research Alliance (ERDERA, https://erdera.org).

The argument for a proactive approach to PPS: what can be done?

A multifactorial problem requires a multifactorial approach at a local and national level, coupled with acknowledgement of this important issue, additional funding, and a sustained willingness to succeed:

1. *Patients with complex symptoms need protected consultation time, continuity and coordinated care.* For some, diagnostic efforts are abandoned too early when an in-depth symptom review plus appropriate testing could elucidate the problem. Often physicians shut down the sharing of new information. Patients are experts of their own experience, increasingly informed by the internet. Their stories are important and we must let them speak.[21] Doubt and curiosity should be encouraged through education. While some will continue to burden their doctors by frequent attendance and multiple demands, a supportive environment should be fostered for neurodiverse or socioeconomically, intellectually, and linguistically challenged patients, free from diagnostic overshadowing and unconscious bias.
2. *Development of appropriate resources.* HCPs can no longer be expected to know about the full range of diseases that may affect their patients. They could be helped by evidence-based diagnostic tools and management algorithms. Similarly, providing signposting to support patients and families obtain appropriate care would be welcomed by all stakeholders.
3. *Greater availability of specialist centres, advanced genetic testing, and novel diagnostics.* Here we can replicate the example of others, for instance, the Center for Rare Diseases, University Hospital Würzburg (https://www.ukw.de/en/clinical-departments/clinical-profile-centers/center-for-rare-diseases-reference-center-northern-bavaria-zese). Elsewhere, Splinter *et al*, as part of UDN, established a diagnosis in 35% of a selected group of adults and children undergoing complete exome sequencing.[22] The Dutch Witte Raven group claim to facilitate a diagnosis in 10% of complex cases through careful review of patients' notes and literature exploration (personal communication).[1]
4. *Adoption of appropriate coding where diagnostic doubt can be recorded without fear of criticism, or financial loss.* Accurate recording will facilitate management and research.
5. *Make greater use of multidisciplinary teams across primary and secondary care.* By this means, a patient presenting with irritable bowel symptoms, migraines, and joint pain may receive the combined expertise of a gastroenterologist, rheumatologist, psychiatrist, and psychologist.
6. *Promote research to discover why some patients are forgotten, diseases missed, or potentially valuable initiatives are dropped.* Could a re-examination of symptom clusters using artificial intelligence reveal new disease entities, potentially amenable to treatment?

Diagnostic dilemma

It could be argued that there is little point in diagnosing something that cannot be treated effectively. Patients such as Maureen hold different views, and receiving an explanation can be reaffirming while helping those around them to better understand and support their needs. A diagnosis also enables access to financial support, living aids, and specialist care such as clinical psychology and physiotherapy.

Unfortunately, even if the above measures are implemented, many patients will continue to experience PPS and, if central brain mechanisms are responsible, there may not be an underlying disease to diagnose. Some will feel reassured by the efforts of involved HCPs, that their problems are taken seriously, and will continue to be so as knowledge evolves. Treatment options should be offered based on an evolving understanding of interoception, symptom perception, and biophysical integration. Psychological treatments such as cognitive behavioural therapies can help and are increasingly available.[8] Burton *et al* have shown that GP-led clinics seeking to recognise and validate the patient experience can be beneficial.[11]

Conclusion

A goal of most modern health systems is equitable care. This is not happening for many frustrated and lost patients as they struggle with PPS. Money and resources are better placed in support of an integrated system where the patient's symptoms are believed and appropriately responded to. This would likely bring individual and societal benefits, thereby reducing cost and morbidity.

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