

Persistent (unexplained) physical symptoms: evidence-based highlights

Medically unexplained symptoms account for up to 50% of specialist referrals in the NHS, but because they tend to be seen in specialist clinics, health-care staff may not be aware of the variety of presentations and commonalities between different medically unexplained symptoms. This article gives an overview of this field.

A 1-day meeting was held in October 2012 at the Freeman Hospital, Newcastle upon Tyne, UK, to review key research outputs on the approach to what have been variously termed medically unexplained symptoms, functional somatic symptoms and persistent physical symptoms. While the term 'functional somatic symptoms' is increasingly popular, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) version 5 proposes 'somatic symptom disorders' and other researchers propose 'bodily distress disorder' (Fink and Schroder, 2010). Both suggestions endorse the commonalities between syndromes often regarded as clinically distinct. As we do now understand some of the processes and mechanisms involved, and given the commonalities between medically unexplained symptoms and better understood long-term conditions, the authors believe that persistent physical symptoms is the most ideologically neutral and accurate term and as such is the term used in this article.

Prevalence

Two surveys suggest that in the German and the UK general population, approximately a fifth of adults have at least one symptom with severe impairment (Creed et al, 2012) and in secondary care between 30–50% of cases are medically unexplained. In primary care, prevalence estimates vary according to how persistent physical symptoms are defined. Two pragmatic thresholds – in that patients who meet them have impaired quality of life and fail to improve – are:

- Repeated GP consultation with more than one probably 'unexplained' physical symptom in a year, or
- Two or more referrals resulting in a 'no physical cause' or functional syndrome diagnosis (e.g. irritable bowel syndrome) over 5 years.

These two thresholds both pick up around 2% of adults. Definition is difficult in primary care, especially because

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there are no clear cut-off points between 'explained' and 'unexplained' symptoms. Screening questionnaires may also have some value (Korber et al, 2011). Since 1990, a number of studies have looked at the prevalence, aetiology, management and prognosis in children. Kozłowska et al (2007) provide the best data on population incidence. A nationwide study in Australia showed an incidence of 2.0–2.6 cases per 100 000 children, using strict criteria for conversion disorder. In some states the incidence was double, while other areas probably under-reported the problem. Of the paediatric presentations, 64% were motor disorder, 24% sensory disorder, 23% non-epileptic attacks and 14% respiratory symptoms. Several had multiple presentations, and pain and fatigue were common comorbidities. Several cohort studies have shown that children who present with persistent physical symptoms tend to continue to show higher levels of psychiatric disorder (anxiety, depression, psychopathy, substance misuse, obsessive compulsive disorder, dysthymia, dissociative symptoms) than the general population in later life.

The following sections review the evidence for the presentation and treatment of persistent physical symptoms in different specialisms.

Persistent respiratory symptoms

The true incidence of medically unexplained respiratory symptoms is unknown; the commonest presentations are chronic cough and breathlessness or dyspnoea. Medically unexplained dyspnoea, where there is no obvious cause, or symptoms are disproportionate to the physiological impairment, is also termed 'dysfunctional breathing' or 'hyperventilation' (Courtney et al, 2011) and the incidence in the community may approach 8%. Patients with medically unexplained dyspnoea have a heightened perception of dyspnoea. Extant theories suggest that medically unexplained dyspnoea results from a combination of physiological and psychological abnormalities. Patients may exhibit hyperventilation: an erratic, upper thoracic or non-diaphragmatic pattern of breathing and frequent sighing. Only half of patients have a formal psychiatric diagnosis.

Chronic idiopathic, or treatment refractory, cough is diagnosed after exclusion of an underlying organic cause and failed trials of empirical therapy. It predominantly affects middle-aged females. Hypersensitivity of the cough reflex may be observed in these patients but the

mechanisms underlying this are unclear (Chung, 2011). For both these respiratory conditions there are few treatment studies. Breathing retraining therapy can be effective for medically unexplained dyspnoea, but the effects may be non-specific. For cough, antitussive therapy is usually unhelpful. Novel approaches that show promise include the use of behaviour modification training by cough suppression therapy (Chamberlain et al, 2013).

Persistent symptoms in otorhinolaryngology

The commonest presentations are globus pharyngeus, functional dysphonia, tinnitus and dizziness.

Globus pharyngeus was found to have been experienced persistently in the previous 3 months in 6% of a sample of middle-aged women (Deary et al, 1995). There are no high quality treatment studies, and the roles of speech therapy, psychosocial interventions and proton-pump inhibitors require further study.

In a database of almost 55 million individuals, functional dysphonia had a point prevalence rate of 0.98%, higher among females than males (1.2% *vs* 0.7%) and among those >70 years of age (2.5%)(Davids et al, 2012). A Cochrane review found improved patient reported outcomes with a combination of direct and indirect speech therapy, but identified no improvement in psychological and general health wellbeing (Ruotsalainen et al, 2007).

Tinnitus affects up to 21% of the adult population to varying degrees (Cima et al, 2012). A number of Cochrane reviews have been undertaken. Cognitive behavioural therapy *vs* no treatment did not improve subjective severity, but did improve depression and tinnitus-related quality of life. Tinnitus retraining therapy may offer improved benefit compared to tinnitus masking. Cima et al (2012) have shown a benefit, as documented through a number of self report tinnitus questionnaires, of a specialized stepped approach based on cognitive behavioural therapy and tinnitus retraining therapy, compared to usual care.

Dizziness affects up to 25% of adults (Yardley et al, 2012). A single trial demonstrated cost effectiveness in a booklet-based approach to providing vestibular rehabilitation in the community (Yardley et al, 2012).

Non-cardiac chest pain

Around 20–25% of people report an episode of chest pain in any year and a third of people in population surveys reported having chest pain at some time in their lives. More than 40% of patients presenting with chest pain to accident and emergency departments receive a non-cardiac diagnosis. Non-cardiac chest pain is associated with a good prognosis in terms of cardiac events and mortality, but poorer outcome in terms of continuing chest pain, worry about symptoms, impaired quality of life and use of medical resources (Eslick et al, 2002). There is evidence of a modest to moderate impact of psychological treatment (mainly based on a cognitive behavioural framework) on chest pain (Kisely et al, 2012). Findings suggest the need

for a stepped approach following diagnosis ranging from simple explanations of non-cardiac chest pain or one session approaches to cardiac anxiety, to referral for more intensive psychological treatment for people presenting with more enduring problems.

Persistent symptoms of the upper gastrointestinal tract

During a 6-month period 41% of UK adults complain of dyspeptic symptoms and it is estimated that £450 million is spent on dyspepsia drugs in the UK each year (Moayyedi et al, 2006). Patients with upper gastrointestinal symptoms frequently also report irritable bowel symptoms (Agreus et al, 1995) and suffer from anxiety. Although reporting of upper gastrointestinal symptoms is not associated with higher mortality rates, prevalence of gastrointestinal symptoms is often chronic, with 75% having persisting upper or lower gastrointestinal symptoms at 10 years. Clinical studies confirm a high placebo response rate in patients treated with acid suppressants, and the phenomenon of rebound acid hypersecretion associated with proton pump inhibitors can mean that patients can be locked into taking a medication which is essentially inducing the symptoms it is designed to treat (Reimer et al, 2009). In the many patients with epigastric symptoms, the number needed to treat with *Helicobacter pylori* eradication is 15 and with proton pump inhibitors is 10 (Moayyedi et al, 2006). Other regularly used drugs (prokinetics and antidepressants) have little evidence for effectiveness.

Persistent symptoms of the lower gastrointestinal tract

Irritable bowel syndrome affects 5–20% of the population. There has been relatively more high quality intervention research on irritable bowel syndrome than on other persistent physical symptoms. Current National Institute for Health and Care Excellence (2008) guidelines suggest self-help in the form of dietary, physical activity and relaxation advice, and/or pharmacological treatments such as antispasmodics, laxatives, loperamide, low dose tricyclic antidepressants and selective serotonin-reuptake inhibitors. If first- or second-line treatments are unsuccessful after 12 months then psychological therapy is suggested. Reviewing the evidence since these guidelines were written suggests that while antispasmodics are efficacious, there are greater effects for peppermint oil and otilinium bromide. There is limited efficacy for laxatives and anti-diarrhoeals beyond targeting a single symptom. Evidence is growing for therapies targeting opioid receptors, benzodiazepine receptors and chloride channels. Antibiotics are more effective than placebo but regimens are not yet finalized (Shah et al, 2012). Psyllium fibre shows some efficacy in patients where constipation predominates. Probiotics may play a role – evidence is mixed and favours *Bifidobacterium* (Moayyedi et al, 2010). There is some evidence for both cognitive behavioural therapy and hypnotherapy improving quality of

life and symptoms, but most psychological treatments have low grade evidence (Ford and Vandvik, 2012).

Persistent pain

Diagnostic criteria for pain related to somatization disorder include pain at four or more bodily parts or organ systems, plus two gastrointestinal and one genitourinary non-pain symptoms, plus pseudo-neurology, for example vision change, paralysis or weakness. Other features include fatigue, sleep disturbance, depression, anxiety, memory loss, headache, migraine, diffuse abdominal pain and urinary frequency.

Fibromyalgia affects 2–4% of the population and pain occurs in the absence of inflammation or tissue damage. Fibromyalgia patients are also characterized by multiple comorbidities including neuropathy, circulatory disorders, depression, diabetes and sleep disorders (Berger et al, 2007). Amitriptyline and the serotonin-noradrenaline reuptake inhibitors duloxetine and milnacipran are first-line treatments. A small number of patients experience substantial symptom relief, but many discontinue therapy because of intolerable side effects. There is insufficient evidence to support the use of valproic acid or sodium valproate as a first-line treatment for neuropathic pain (Gill et al, 2011).

Community-deliverable exercise improves pain and physical function in at least some groups of adults with arthritis (Kelley et al, 2011). Gabapentin provides pain relief of a high level in about a third of people with neuropathic pain (Moore et al, 2011). A Cochrane review (Williams et al, 2012) of psychological therapies concludes that there is some limited evidence for cognitive behavioural approaches, including acceptance and commitment therapy, but that effect sizes are modest. Component analysis of these complex interventions may yield more information than further randomized controlled trials.

Psychosocial interventions for 'persistent physical symptoms' in general

The most recent meta-analysis (Kleinstaub et al, 2011) compared 27 treatment studies in 1781 treated patients. Patients were diagnostically mixed (including body dysmorphic disorder and hypochondriasis), while therapy varied by type, modus and outcome measures. Given these caveats, there was an aggregate between-group effect of psychological treatment on physical symptoms of 0.4 ($P < 0.001$) at 1-year follow up. This small to medium effect size is in line with systematic reviews.

A narrative review found few well-conducted trials of primary care treatment (Gask et al, 2011). Mostly these involved some form of reattribution in which the doctor attempts to interpret the symptoms in relation to stress or other mental problem. These interventions appear to have little benefit. A novel approach – tested in a successful pilot trial – is a 'symptoms clinic' where the key approach is to explain the symptoms in terms of bodily dysfunctions without underlying psychological cause (Burton et al, 2012). In children several case controlled

studies have shown a benefit from cognitive behavioural therapy and acceptance and commitment therapy in reducing symptoms in recurrent abdominal pain and other unexplained pain syndromes.

There are no case controlled studies that look at these interventions in those with conversion symptoms of weakness, sensory abnormality and non-epileptic attacks. A small series (Calvert and Jureidini, 2003) reported good outcomes for some neurological presentations using an approach that combined psychological methods aimed at the child and family alongside rehabilitation – a technique similar to graded exercise therapy that has been shown to be successful in for young people with chronic fatigue syndrome or myalgic encephalomyelitis (Husain et al, 2007).

Conclusions

The dilemmas around the nosology of persistent physical symptoms reflect more profound dilemmas as to the ontology of these conditions. A review of explanatory models on persistent physical symptoms highlighted their variety (van Ravenswaaij et al, 2010), and concluded that given the evidence for specific physiological, affective, cognitive and behavioural processes, it likely to be the interaction of these processes that maintain symptoms. Further research needs to be done in each of these domains and one emergent area of interest in the physiology of persistent physical symptoms is the role of autonomic dysfunction (Newton et al, 2007).

Given the variety of disease models, the conditions have also attracted an unusually wide range of therapeutic interventions, each based on different aetiological or pathological theories. Even within specialisms, general conclusions are hard to draw, let alone across specialisms. However, these conditions share significant commonalities, most especially in the presence of other markers of somatopsychic distress such as anxiety and depression, and physical symptoms such as fatigue and pain. Also, all seem to respond to complex psychosocial intervention. Psychological therapies, cognitive behavioural therapy specifically, have a small to medium effect on persistent physical symptoms. However, this is in contrast to cognitive behavioural therapy's effect on anxiety and depressive disorders where larger effect sizes (>0.8) are reported. More importantly, and as highlighted by the Cochrane review in persistent pain, it is unclear how cognitive behavioural therapy is achieving its effect with models ascribing change variously to physical re-conditioning, decreased symptom focus and/or neurophysiological changes. More mediation studies, component analyses and physiological as well as functional outcomes are needed. Moving towards more experimental designs, where particular interventions are focussed on particular physiological and neuropsychological mechanisms and attempts are made to measure change in these with appropriate outcome measures, may allow better treatment and understanding of these very common conditions. **BJHM**

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KEY POINTS

- The nosology and ontology of what are sometimes called medically unexplained symptoms remains in dispute; the term persistent physical symptoms recognizes the commonalities between explained and 'unexplained' symptoms.
- Persistent physical symptoms represent a considerable health-care burden, accounting for up to 50% of referrals in some specialisms.
- The level of evidence for treatment varies quite widely between conditions but a symptom management approach has a small to moderate impact on most symptoms.
- Further research is needed into the biopsychosocial causes of persistent physical symptoms, and into the mechanisms of effect of psychosocial interventions.