CHAPTER 9

How should we manage adults with persistent unexplained physical symptoms?

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How should we manage

**Background**

Persistent physical symptoms are common and include those symptoms that last at least three months and are insufficiently explained by a medical condition after adequate examination and investigation (Burton 2003; Aamland 2014). Examples include unexplained abdominal pain, musculoskeletal pains, fatigue, headache and dizziness. These symptoms are often associated with functional impairment and psychological distress among patients, and increase healthcare costs (Aamland 2014; Jackson 2005; Smith 1986; Dirkzwager 2007). Observational studies in primary care report that women, especially those aged 35-45 years, more commonly present with these symptoms (Aamland 2014; Dirkzwager 2007).

Defining and categorising an unexplained symptom is tricky and disputed (see box 1, Creed 2010; NHS 2008). Sometimes symptoms fit criteria for somatoform or psychiatric disorders set out in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV, American Psychiatric Association 2000) or functional somatic syndromes such as irritable bowel syndrome. In other cases there is no label to offer the patient. Several pharmacological and psychological interventions have been studied for somatoform disorders, but evidence on their effectiveness is limited and of poor quality.

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**Box 1. Terminology used in this article**

**Persistent unexplained physical symptoms**

Physical symptoms existing for ≥3 months not sufficiently explained by an underlying medical condition after adequate examination and investigation (Aamland 2014).

**Somatoform disorders**

Psychiatric disorders (DSM-IV, ICD-10) with persistent unexplained physical symptoms as key factor (American Psychiatric Association 2000).

**Undifferentiated somatoform disorder**

One or more physical symptoms without medical explanation with clinically significant suffering or functional impairment, existing for ≥6 months (American Psychiatric Association.2000)

**Functional somatic syndrome**

A combination of unexplained physical symptoms occurring together (such as irritable bowel syndrome or chronic fatigue syndrome, Wessely 1999).

**Somatic symptoms disorder**

Recently introduced term (DSM 5): somatic symptoms that are either very distressing or result in considerable disruption of functioning, as well as excessive and disproportionate thoughts, feelings and behaviours regarding those symptoms. To be diagnosed, the individual should have persistent symptoms (typically for ≥6 months). The diagnosis does not require that the somatic symptoms are medically unexplained (American Psychiatric Association 2013).
What is the evidence of uncertainty?

**Search strategy**

We searched the Cochrane Library (including the Cochrane Central Database of Controlled Trials), PubMed, and clinical trial registers (clinicaltrials.gov, controlled-trials.com, who.int/trialsearch) until September 2015 using the following free-text terms:

(somatization or somatisation or somatoform or hysteri* or briquet or polysymptom* or multisomatoform or somatizer* or (somatic NEAR symptom*) or (MUPS or “medical* unexplained” or “unexplained medical*” or (unexplained NEAR (symptom* or syndrom*)) or “frequent attend*” or (multiple NEAR (“physical symptom*” or “symptom diagnos*”)) OR neurastheni*)

We found Cochrane systematic reviews examining efficacy of drugs, psychological interventions, enhanced care, and specialist consultation letters in patients with somatoform disorders or persistent unexplained physical symptoms (Kleinstäuber 2014; van Dessel 2014; Rosendal 2013; Hoedeman 2010). We found no new randomised controlled trials since publication of the reviews. Studies restricted to specific functional syndromes (such as irritable bowel syndrome) were excluded.

There is a lack of evidence to conclude whether pharmacological, psychological, or physical therapy, or enhanced general practitioner care was effective. Table 1 summarises the evidence we found in Cochrane systematic reviews, excluding those related to specific functional syndromes such as irritable bowel syndrome. Studies included patients with a diagnosis of somatoform disorders as well as persistent unexplained physical symptoms. Many studies were of poor quality, included few patients, and followed them for just a few weeks (typically 2-12 weeks).

For pharmacological treatments there was no clear evidence of efficacy of tricyclic antidepressants. There was very low quality evidence for new generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs) being effective in treating symptoms compared with placebo (standardised mean difference −0.91 (95% confidence interval −1.36 to −0.46); 3 studies, 243 participants; I²=63%) with no clear difference in efficacy between different drug classes. A combination of SSRIs and antipsychotics is more effective than SSRIs alone, though evidence is of low quality (standardised mean difference 0.77 (0.32 to 1.22); 2 studies, 107 participants; I²=23%) (Kleinstäuber 2014). The review found low quality evidence favouring natural products such as St John’s wort compared with placebo (standardised mean difference −0.74 (−0.97 to −0.51); 2 studies, 322 participants; I²=0%).

The quality of studies was rated low because of a high risk of bias in many domains, strong heterogeneity in symptoms and study design, small sample sizes, and short follow-up (2-12 weeks).
The small beneficial effect of drugs should be weighed against side effects (such as dry mouth, nausea) that were reported in these studies. However, discontinuation rates were similar between the intervention and comparison groups.

A Cochrane review examined different forms of psychological therapy (21 randomised controlled trials (RCTs), 2658 participants) including cognitive behavioural therapy, behaviour therapies, third-wave cognitive behavioural therapy (mindfulness), psychodynamic therapy, and integrative therapy in patients with somatoform disorders or persistent physical symptoms (van Dessel 2014). Taken altogether, psychological therapies were effective in reducing symptom severity compared with usual care or waiting list, but effect sizes were small and psychological therapies had higher dropout rates than usual care. No harms or side effects were reported. The overall quality of evidence is low due to a high risk of bias with lack of blinding of the participants, therapists, and outcome assessors. No studies addressed physical therapy.

Enhanced care by general practitioners comprises reattribution—where symptoms are reframed, making the link to presumed underlying psychological problems—and cognitive behavioural therapy. A Cochrane review on enhanced care (6 RCTs, 1787 participants) found no significant effect on quality of life in terms of physical and mental health and severity of physical symptoms (Rosendal 2013). A Cochrane review on effectiveness of consultation letters from psychiatrists to provide general practitioners with a diagnosis and treatment advice for patients (6 RCTs, 449 participants) was also inconclusive (Hoedeman 2010).

Overall, the quality of evidence is poor with significant heterogeneity, variations in diagnostic criteria, delivery of interventions, and outcome measures, and a short follow-up.

**Is ongoing research likely to provide relevant evidence?**

We searched clinical trial registers (clinicaltrials.gov, controlled-trials.com, who.int/trialsearch, September 2015) for studies in patients with unexplained physical symptoms or somatoform disorders. We identified 10 ongoing randomised controlled trials evaluating non-pharmacological interventions including psychotherapy, a multidisciplinary intervention (by a neurologist, a psychologist and a physical therapist), and walking. There is one ongoing trial evaluating treatments with dalumin, a herb extract. A trial is planned to evaluate integrated care in general practice for these patients; more details on the intervention are not available. We did not find any ongoing trials on antidepressants in this patient group.
Box 2. Recommendation for future research
Large, well conducted, randomised controlled trials with the following features:

Population
Adult patients with persistent unexplained physical symptoms for whom the nature and severity of symptoms are described by (a) use of a validated and commonly used measurement instrument (such as the Patient Health Questionnaire-15 (Kroenke 2002) and (b) clearly defined levels of severity (that is, duration and number of symptoms). New studies also need to include patients with a low number of symptoms or a recent symptom onset.

Intervention
Different pharmacological and non-pharmacological interventions, including physical therapies (such as walking, running, or yoga therapy) and enhanced care (retribution or cognitive behavioural therapy delivered by the GP). Treatment characteristics (such as duration, intensity, dose, healthcare provider) need to be specified using a standardised treatment protocol.

Comparison
Usual care, waiting list controls, and head-to-head comparisons of different interventions (including pharmacological and non-pharmacological interventions).

Outcome
Severity of symptoms, functional impairment, mental health (including depressive and anxiety symptoms or disorders), treatment acceptability, and side effects. Outcomes should be measured using validated and commonly used measurement instruments. A long follow-up duration (minimum of six months) is needed.

What should we do in the light of the uncertainty?
Research
We recommend that future research focuses on different populations, interventions, and outcomes (see box 2).

Practice
Several countries have developed guidelines for the management of patients with persistent unexplained symptoms (Hausteiner-Wiehle 2012; Stuurgroep 2011; Dutch College of GPs 2013). Based on Dutch guidelines (Stuurgroep 2011; Dutch College of GPs 2013), we encourage clinicians to explore all symptom dimensions (somatic, cognitive, emotional, behavioural, and social). For example, if a patient presents with unexplained muscular pain, explore

- The characteristics of the pain, such as location, severity, duration, and associated symptoms.
- The patient’s thoughts and expectations about the pain.
- How it affects the patient emotionally.
- Behavioural consequences, such as avoiding exercise, absenteeism.
- Impact on social life (relationships, work, and social activities).
Perform a thorough but focused physical examination and if necessary refer for relevant investigations. Screen for an undiagnosed mental health problem such as depression or anxiety and if screening is positive consider referral to a psychiatrist.

Share your findings based on the examination and investigations with the patient and explain that no underlying medical condition has been identified and is unlikely to be found. Where possible, provide an explanation for the persistence of symptoms—for example, by using the vicious circle theory, where pain can lead to less exercise and less exercise can lead to more pain. Treatment for symptomatic relief such as for pain may be offered for a limited time if the patient requests, but explain the pros and cons of treatment.

We consider cognitive behavioural therapy worth offering but do not advise pharmacological therapy. If the patient has a preference for medication, share uncertainty in evidence of any benefit and potential side effects. If a specific functional somatic syndrome is identified—such as chronic pain, fibromyalgia, or irritable bowel syndrome—follow guidelines for management of these syndromes. Not being able to identify an underlying condition does not completely exclude there being one. Ask the patient to report changing or worsening of symptoms, or new symptoms which may require reassessment.

What patients need to know

- Some persistent physical symptoms fit criteria of specific syndromes (such as fibromyalgia or chronic fatigue syndrome) or of psychiatric disorders, in which case management is more defined. But often no medical cause for the symptom(s) is identified.
- Before concluding that the symptoms cannot be explained, your doctor will explore all symptoms and perform the necessary examination.
- In case of unexplained physical symptoms, your doctor will discuss factors that may influence your symptoms negatively—for example, personal coping styles such as pain avoidance.
- Doctors may advise medication, psychological therapies, or strategies to cope with the symptoms. Evidence of benefit for any of these options is limited.
- Patients differ in their acceptance of certain treatments. Discuss the options with your doctor and choose a treatment strategy that is acceptable to you.
- Not being able to identify an underlying condition does not completely exclude there being one. Report changing or worsening of symptoms or new symptoms to your doctor, as these may require reassessment.
<table>
<thead>
<tr>
<th>Population (all adults)</th>
<th>Primary outcomes (measured by questionnaires)</th>
<th>Intervention</th>
<th>Comparator</th>
<th>RCTs (N), participants (N)</th>
<th>Evidence</th>
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<td>Tricyclic antidepressants</td>
<td>Placebo</td>
<td>2 RCTs, 239 patients</td>
<td>No clear evidence of efficacy</td>
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<td>Somatoform disorder</td>
<td>Severity of symptoms</td>
<td>New generation antidepressants (including SSRIs)</td>
<td>Placebo</td>
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<tr>
<td></td>
<td></td>
<td>Tricyclic antidepressants</td>
<td>New generation antidepressants</td>
<td>3 RCTs, 177 patients</td>
<td>Low quality evidence: no clear difference</td>
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<tr>
<td>Somatoform disorder or unexplained physical symptoms</td>
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<td>Quality of life including physical functioning and mental health</td>
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<td>Usual care</td>
<td>4 RCTs, 313 patients</td>
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<td></td>
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<td>Joint consultation by psychiatrist and GP followed by letter with advice for GP</td>
<td>Usual care</td>
<td>2 RCTs, 314 patients</td>
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</tbody>
</table>

*RCT=randomised controlled trial. SSRIs=selective serotonin reuptake inhibitor. GP=general practitioner.*

*Table 1. Summary of evidence from Cochrane systematic reviews for different treatments of persistent unexplained symptoms.*