

CHAPTER 6

How should we manage adults with persistent unexplained physical symptoms?

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INTRODUCTION

Persistent unexplained physical symptoms, i.e. physical symptoms that exist longer than three months and cannot be (sufficiently) explained by an underlying medical condition after adequate examination, are highly prevalent in all health care settings (1-2). These persistent unexplained physical symptoms may lead to functional impairment, high levels of psychological distress, a troubled doctor-patient relationship and increased health care costs (3-5).

In some cases these symptoms fit criteria of specific functional somatic syndromes such as fibromyalgia, irritable bowel syndrome or chronic fatigue syndrome. But often no specific functional somatic syndrome can be diagnosed.

Many studies have been performed on persistent unexplained physical symptoms, but it remains uncertain how clinicians should manage patients with these symptoms. Therefore, in this paper we will describe which interventions are effective, which are not and how to adequately manage these patients in daily clinical practice. We will not include the specific functional somatic syndromes. For management of these syndromes, we refer to specific guidelines covering this.

WHAT IS THE EVIDENCE OF UNCERTAINTY?

In September 2015, 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) to identify published and ongoing randomised controlled trials (RCTs) examining all interventions as offered in regular health care for patients with persistent unexplained physical symptoms.

To date, four Cochrane reviews have been published on the subject (6-9). To the best of our knowledge, no relevant new studies have been published since.

A Cochrane review examined the efficacy of different types of antidepressants, antipsychotics, the combination of an antidepressant and antipsychotic and natural products (e.g. St. John's wort) (26 RCTs, 2159 participants) (6). This review found a significant positive effect for new generation antidepressants and natural products compared to placebo and for the combination of an antidepressant and an antipsychotic compared to an antidepressant alone for severity of unexplained physical symptoms, the primary outcome. The effect size (standardized mean difference - SMD) was in the range of 0.70-0.90, which is considered clinically relevant.

There was no significant effect for tricyclic antidepressants compared to placebo, nor for tricyclic antidepressants compared to new generation antidepressants, nor for the different new generation antidepressants.

The quality of the studies was low due to a high risk of bias in many domains across the studies, strong heterogeneity and small sample sizes. Also, conclusions could only be drawn for the short-term, as follow-up was often only 6 weeks and never longer than 12 weeks. The small beneficial effects should be weighed against often occurring side effects that frequently cause discontinuation. No significant difference in acceptability (drop-out rate) was found between the intervention and comparison groups.

Another Cochrane review examined the efficacy of different forms of non-pharmacological interventions (21 RCTs, 2658 participants) (7). This review found that all non-pharmacological therapies taken together and cognitive behavioural therapy alone (CBT: therapy based on the cognitive behavioural model which proposes that unexplained physical symptoms are caused by self-perpetuating multifactorial cycles based on the interaction in several domains) had a significant beneficial effect compared to usual care (i.e. no active intervention initiated by the researchers/investigators), or compared to waiting list controls for the primary outcome, severity of unexplained physical symptoms. The effect size was small to moderate (SMD 0.34-0.37). Psychological therapies had a higher proportion of dropouts during treatment compared to usual care. No significant difference was found between psychological therapy and “enhanced care” (consisting of reattribution, where symptoms are reframed by making the link between physical symptoms and presumed underlying psychological problems, or of CBT delivered by a general practitioner (GP)), but enhanced care seemed somewhat more acceptable. No major harms or side effects were reported. No studies could be included that addressed physical therapy. The overall quality of the studies was rated low to moderate, due to a high risk of bias for several items, such as lack of blinding of the participants, therapists and outcome assessors.

A third Cochrane review examined the efficacy of enhanced care (as explained above) and CBT compared to usual care (6 RCTs, 1787 participants) (8). This review found no significant effect of enhanced care on patient outcomes, such as physical symptoms and quality of life. However, the authors did not calculate a pooled effect due to the small sample of studies that also had high risk of bias and strong heterogeneity.

The fourth Cochrane review examined the effectiveness of consultation letters written by psychiatrists to provide GPs with a diagnosis and treatment advice for patients with unexplained physical symptoms (6 RCTs, 449 participants)(9). This review found that the evidence that a

consultation letter is effective in reducing the symptoms is limited, as they found that only six small studies of moderate quality were performed, all of them in the United States.

IS ONGOING RESEARCH LIKELY TO PROVIDE RELEVANT EVIDENCE?

In September 2015, we searched the clinical trial registers (clinicaltrials.gov, controlled-trials.com, who.int/trialsearch) and identified ten ongoing RCTs evaluating non-pharmacological interventions (including one on the effect of walking training for patients with somatoform disorders (i.e. psychiatric diagnosis where persistent unexplained physical symptoms are central; Schröder 2014; unpublished data only), two evaluating pharmacological treatments, one evaluating enhanced care and none for consultation letters.

Box 1: Recommendation for future research

Large well conducted RCTs 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 and b) clearly defined levels of severity (i.e. 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 CBT delivered by the GP). Treatment characteristics (e.g. duration, intensity, dosage, health care provider) need to be specified, e.g. by using a standardized 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. Particularly for pharmacological interventions, a long follow-up duration (minimum of six months) is needed.

WHAT SHOULD WE DO IN THE LIGHT OF UNCERTAINTY?

In consultations where the GP considers unexplained symptoms, we advise the following steps to work out. First, explore all symptom dimensions (somatic, cognitive, emotional, behavioral, social). Next, perform a thorough but focused physical examination (depending on the nature of the symptoms) and if necessary, refer for additional diagnostics. If reason arises during the consultation, evaluate if the patient has a mental disorder. When a medical condition can be excluded, determine the severity of the unexplained physical symptoms (e.g. high number of symptoms, impact on daily life) and determine if the duration of the symptom is longer than 3 months.

For patients fitting in the category of persistent unexplained physical symptoms, openly share all findings, explain that there is no underlying medical condition and provide a tangible and constructive 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). Discuss the functional impairments and if possible give advice how to cope with these.

We recommend that GPs discuss several non-pharmacological treatment alternatives with the patient. The GP should explain that only CBT has proven to have a beneficial effect, albeit small. Together the patient and the GP can decide which treatment optimally supports the patient. We do not advise pharmacological therapy given the rate of side-effects, non-compliance and low quality of studies. When a specific syndrome exists, such as chronic pain, we advise clinicians to follow specific guidelines for these syndromes.

Box 2: What patients need to know

- Unexplained physical symptoms are common and can be invalidating when persistent
- Sometimes the symptoms fit criteria of specific syndromes such as fibromyalgia or chronic fatigue syndrome, but often this is not the case
- Before establishing the unexplained nature of the symptoms, GPs will explore all symptom aspects and perform necessary examinations
- In case of unexplained physical symptoms, GPs will discuss negatively influencing factors and will give advice how to cope with the symptoms
- There are many treatment options, but not much research has been performed on their effectiveness. Only cognitive behavioural therapy has a proven beneficial effect
- Pharmacological treatment is not recommended

Box 3: How patients were involved in the creation of this article

Two patients with MUPS were asked if this article covers issues that matter to them and what information might help doctors to better manage them. They suggested to provide explanations of some definitions (such as CBT) and to stimulate doctors to talk openly with their patient about all phases of exploration and treatment of unexplained symptoms. These suggestions were adopted in the paper.

Box 4: What you need to know

- If you consider symptoms to be unexplained: explore all symptom dimensions (somatic, cognitive, emotional, behavioural, social) and perform a thorough but focussed physical examination
- In case of unexplained symptoms: be open about your findings and provide a tangible and constructive explanation for the (persistence of) symptoms (for example by using the vicious circle theory)
- Discuss several treatment options with the patient
- Discuss referral for CBT for patients with persistent unexplained physical symptoms
- Discourage pharmacological treatment
- In case of a specific functional syndrome, follow the specific guideline

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