CHAPTER 5

Non-pharmacological interventions for somatoform disorders and medically unexplained physical symptoms (MUPS) in adults

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NB: This chapter is a concise version of the full Cochrane review

ABSTRACT

Background

Medically unexplained physical symptoms (MUPS) are physical symptoms for which no adequate medical explanation can be found after proper examination. The presence of MUPS is the key feature of conditions known as 'somatoform disorders'. Various psychological and physical therapies have been developed to treat somatoform disorders and MUPS. Although there are several reviews on non-pharmacological interventions for somatoform disorders and MUPS, a complete overview of the whole spectrum is missing.

Objectives

To assess the effects of non-pharmacological interventions for somatoform disorders (specifically somatisation disorder, undifferentiated somatoform disorder, somatoform disorders unspecified, somatoform autonomic dysfunction, pain disorder, and alternative somatoform diagnoses proposed in the literature) and MUPS in adults, in comparison with treatment as usual, waiting list controls, attention placebo, psychological placebo, enhanced or structured care, and other psychological or physical therapies.

Search methods

We searched the Cochrane Depression, Anxiety and Neurosis Review Group's Specialised Register (CCDANCTR) to November 2013. This register includes relevant randomised controlled trials (RCTs) from *The Cochrane Library*, EMBASE, MEDLINE, and PsycINFO. We ran an additional search on the Cochrane Central Register of Controlled Trials and a cited reference search on the Web of Science. We also searched grey literature, conference proceedings, international trial registers, and relevant systematic reviews.

Selection criteria

We included RCTs and cluster randomised controlled trials which involved adults primarily diagnosed with a somatoform disorder or an alternative diagnostic concept of MUPS, who were assigned to a non-pharmacological intervention compared with usual care, waiting list controls, attention or psychological placebo, enhanced care, or another psychological or physical therapy intervention, alone or in combination.

Data collection and analysis

Four review authors, working in pairs, conducted data extraction and assessment of risk of bias. We resolved disagreements through discussion or consultation with another review author. We pooled data from studies addressing the same comparison using standardised mean differences (SMD) or risk ratios (RR) and a random-effects model. Primary outcomes were severity of somatic symptoms and acceptability of treatment.

Main results

We included 21 studies with 2658 randomised participants. All studies assessed the effectiveness of some form of psychological therapy. We found no studies that included physical therapy. Fourteen studies evaluated forms of cognitive behavioural therapy (CBT); the remainder evaluated behaviour therapies, third-wave CBT (mindfulness), psychodynamic therapies, and integrative therapy. Fifteen included studies compared the studied psychological therapy with usual care or a waiting list. Five studies compared the intervention to enhanced or structured care. Only one study compared cognitive behavioural therapy with behaviour therapy.

Across the 21 studies, the mean number of sessions ranged from one to 13, over a period of one day to nine months. Duration of follow-up varied between two weeks and 24 months. Participants were recruited from various healthcare settings and the open population. Duration of symptoms, reported by nine studies, was at least several years, suggesting most participants had chronic symptoms at baseline.

Due to the nature of the intervention, lack of blinding of participants, therapists, and outcome assessors resulted in a high risk of bias on these items for most studies. Eleven studies (52% of studies) reported a loss to follow-up of more than 20%. For other items, most studies were at low risk of bias. Adverse events were seldom reported.

For all studies comparing some form of psychological therapy with usual care or a waiting list that could be included in the meta-analysis, the psychological therapy resulted in less severe symptoms at end of treatment (SMD -0.34; 95% confidence interval (CI) -0.53 to -0.16; 10 studies, 1081 analysed participants). This effect was considered small to medium; heterogeneity was moderate and overall quality of the evidence was low. Compared with usual care, psychological therapies resulted in a 7% higher proportion of drop-outs during treatment (RR acceptability 0.93; 95% CI 0.88 to 0.99; 14 studies, 1644 participants; moderate-quality evidence). Removing one outlier study reduced the difference to 5%. Results for the subgroup of studies comparing CBT with usual care were similar to those in the whole group.

Five studies (624 analysed participants) assessed symptom severity comparing some psychological therapy with enhanced care, and found no clear evidence of a difference at end of treatment (pooled SMD -0.19; 95% CI -0.43 to 0.04; considerable heterogeneity; low-quality evidence). Five studies (679 participants) showed that psychological therapies were somewhat less acceptable in terms of drop-outs than enhanced care (RR 0.93; 95% CI 0.87 to 1.00; moderate-quality evidence).

Conclusions

When all psychological therapies included this review were combined they were superior to usual care or waiting list in terms of reduction of symptom severity, but effect sizes were small. As a single treatment, only CBT has been adequately studied to allow tentative conclusions for practice to be

drawn. Compared with usual care or waiting list conditions, CBT reduced somatic symptoms, with a small effect and substantial differences in effects between CBT studies. The effects were durable within and after one year of follow-up. Compared with enhanced or structured care, psychological therapies generally were not more effective for most of the outcomes. Compared with enhanced care, CBT was not more effective. The overall quality of evidence contributing to this review was rated low to moderate.

The intervention groups reported no major harms. As most studies did not describe adverse events as an explicit outcome measure, this result has to be interpreted with caution.

An important issue was that all studies in this review included participants who were willing to receive psychological treatment. In daily practice, there is also a substantial proportion of participants not willing to accept psychological treatments for somatoform disorders or MUPS. It is unclear how large this group is and how this influences the relevance of CBT in clinical practice.

The number of studies investigating various treatment modalities (other than CBT) needs to be increased; this is especially relevant for studies concerning physical therapies. Future studies should include participants from a variety of age groups; they should also make efforts to blind outcome assessors and to conduct follow-up assessments until at least one year after the end of treatment.

BACKGROUND

Description of the intervention

In previous decades, many pharmacological and non-pharmacological interventions for somatoform disorders and MUPS were developed. The use of antidepressants, in particular, as pharmacological agents for syndromes of MUPS (1,2) or chronic pain (3) was tested. The most relevant groups of antidepressants are the tricyclic antidepressants, selective serotonin reuptake inhibitors, and selective serotonin and noradrenaline (norepinephrine) reuptake inhibitors. In addition to antidepressants, antiepileptic drugs are also commonly used for somatoform disorders (4,5), although they are not advised in guidelines. Pharmacological interventions will be described in a separate forthcoming Cochrane review (6) and this review only focuses on non-pharmacological interventions.

Most non-pharmacological interventions for MUPS focus on addressing cognitions, behaviour, coping styles, and functional consequences of symptoms. These interventions include psychological therapies as well as physical therapies. In the paragraph below, we described examples of several frequently studied forms of psychological and physical therapies.

How the intervention might work

Psychological therapies - cognitive behavioural therapy

The first and most commonly used and investigated psychological therapy for MUPS is CBT, which is based on the cognitive behavioural model (7). This model proposes that MUPS are caused by a self perpetuating multi-factorial cycle, based on the interaction of different factors in several domains, including somatic (physical) aspects, cognitions (thoughts), behaviour, emotions, and environment (8).

Reattribution is a specific form of CBT (9). This method aims to encourage people to reattribute their MUPS to physiological or psychosocial causes rather than to somatic causes. Reattribution consists of three stages: 1. Making the person feel understood; 2. Changing the agenda of the person, and the doctor, and their mutual agenda during the consultations; and 3. Making the link between physical symptoms and psychosocial problems.

Problem-solving treatment is another form of CBT that has been used for people with MUPS and somatoform disorders. The aim is to reduce complaints associated with unresolved problems in daily life by enhancing a person's problem-solving capacities in a step-by-step manner. This therapy has a positive effect on mental and physical health problems in general (10)

Psychological therapies - behavioural therapy

Behavioural therapy, the second group, aims to constructively change a person's behaviour towards their symptoms using operant conditioning - also known as instrumental conditioning - in which a response in a certain context is followed by a reinforcing stimulus or consequence, thereby increasing the likelihood that the same response will follow in future. Biofeedback therapy is an important behavioural intervention relevant to this review. Other forms of behavioural therapy include relaxation therapy (11), and psycho-education (12).

Other psychological therapies

A third group of psychological therapies, more aimed at increasing insight, such as:

1. Third-wave cognitive behavioural therapy (i.e. the development of a new attitude towards symptoms, based on self-regulation of attention and acceptance) (13);
2. Psychodynamic therapies, a form of depth psychology, which focuses on revealing the unconscious content of a person's psyche in order to alleviate psychological of physical tension (14).
3. Humanistic therapies, focusing on self-development, growth, and responsibilities. Treatment aims to help individuals recognise their strengths, creativity, and choices in the 'here and now'.
4. Integrative therapies, which integrate components from several theoretical schools, which aims to work with the person to identify procedural sequences, chains of events, thoughts and emotions that explain how a target problem is established and maintained

Enhanced care

Another group of therapies offered to people with MUPS is enhanced care. Within these therapies people receive care as usual (mostly by their general practitioners (GP)), enhanced with, for example, participant education or structured counselling moments (15). Within these therapies, there is no specific treatment agenda or structure; the aim is to offer the person some tools to assist in the recovery process, stimulating self-management.

Physical therapies - physical activity training

Several studies have indicated that mental health, including mood, pain thresholds, and sleep, can be improved by low- or moderate-intensity activity (16). Graded activity training is an operant-conditioning behavioural approach in which physical activity is expanded step by step, based on a predetermined time schedule.

Other physical therapies

Other examples of physical therapies for somatoform disorders and MUPS include activation therapy, where physical and behavioural activation is increased in a step-wise fashion, and running therapy, where running is used therapeutically, mainly to influence the level of stress.

Objectives

To assess the effects of non-pharmacological interventions for somatoform disorders (specifically somatisation disorder, undifferentiated somatoform disorder, somatoform disorder unspecified, somatoform autonomic dysfunction, pain disorder, and alternative somatoform diagnoses proposed in the literature) and MUPS in adults in comparison with treatment as usual, waiting list controls, attention placebo, psychological placebo, enhanced or structured care, and other psychological or physical therapies.

METHODS

Types of studies

We included randomised controlled trials (RCTs) and cluster randomised controlled trials (CRCTs). We also planned to include data from the first phase of crossover trials, but we identified no such trials that met our inclusion criteria. We excluded quasi-randomised trials (e.g. allocation to the study group by day of the week).

Types of participants

Participant characteristics

Participants had to be at least 18 years old. We applied no maximum age, as the condition can be present at any age. We placed no restriction on gender or culture.

Diagnosis

1. Participants had to meet the criteria for a somatoform disorder or the criteria for one of the alternative somatoform diagnoses proposed in the literature. The primary diagnosis (a somatoform disorder) had to be made on the basis of a structured clinical interview or diagnostic checklists
2. Participants were characterised with MUPS as their primary problem, on the basis of a validated scale for the assessment of MUPS

As the subdivision of these two diagnostic concepts (somatoform disorders and MUPS) is based on differences in selection methods used in different research settings rather than on differences between individual people, it is possible that the nature and severity of symptoms may show a certain overlap between the two groups. We disregarded the DSM-5 criteria for somatoform disorders for this version of the review.

Co-morbidities
As we aimed to summarise interventions for multiple symptoms, we excluded studies and reviews that examined participants diagnosed with only one specific functional syndrome or symptom.

Subsets of participants
Some studies could include 'eligible' participants as well as 'ineligible' participants for this review, for example when an age cut-off was used that was different to the cut-off of this review. When no detailed information was available about these subsets of participants, we requested the data from the trial authors.

Types of interventions

Experimental interventions
Eligible studies included one or more of the following experimental interventions.

1. *Psychological therapies:* CBT, behavioural therapy, third-wave CBT, psychodynamic therapies, humanistic therapies, integrative therapies
2. *Physical therapies:* physical activity training, other physical therapies

We excluded interventions based on complementary medicine from this review. In addition, pharmacological interventions and consultation letter interventions were beyond the scope of this review; they were evaluated in other Cochrane reviews (17, 6). In several of the studies, in both study arms a consultation letter was sent to the primary care physician after baseline assessment, in addition to the planned psychological therapy or comparison condition. Post-hoc, we decided that this was not a reason for exclusion, and we categorised these studies according to the main comparison.

Comparator interventions

1. Normal/usual treatment or waiting list procedures.
2. Attention or psychological placebo
3. Enhanced or structured care
4. Other psychological therapies
5. Other physical therapies

Types of outcome measures

We included studies that met the inclusion criteria described above regardless of whether they reported on the following outcomes.

Primary outcomes

1. Severity/intensity of somatic symptoms
2. Acceptability

Secondary outcomes

1. Depression and anxiety
2. Dysfunctional cognitions, emotions, or behaviours (participant-rated)
3. Adverse events
4. Treatment response (responder versus non-responder)
5. Functional disability and quality of life
6. Health care use

Hierarchy of outcome measures

If there were multiple instruments measuring the same outcome, we preferred whichever instrument was most commonly used from those listed above.

Timing of outcome assessment

We analysed primary and secondary outcomes at the following time points, if available: immediately post treatment; within 12 months after treatment ending; and more than 12 months after treatment ended.

Search methods for identification of studies

Detailed information from the search methods are described in the full review. In summary, we performed electronic searches in the Cochrane Depression, Anxiety and Neurosis Review Group's Specialized register (CCDANCTR), conducted complementary searches in Cochrane Central Register of Controlled Trials (CENTRAL) and searched for ongoing clinical trials.

Also we searched the following other resources: grey literature, hand searching for conference proceedings reference lists and correspondence to authors.

Data collection and analysis

Selection of studies

In the first step, two review authors (NvD, MdB) independently screened the titles and abstracts of reports identified from the literature search. We discarded studies that obviously did not fulfil the inclusion criteria at this stage of the screening process. Two review authors (NvD, MdB) retrieved eligible or potentially eligible articles for full-text assessment. We identified and excluded duplicate records and we collated multiple reports that related to the same study so that each study - rather than each report - was the unit of interest in the review. After full-text assessment, the review authors identified studies for inclusion and exclusion. We recorded reasons for exclusion of studies, and resolved disagreements by consensus - if necessary with the involvement of a third review author (JvdW). We listed studies for which additional information was required in order to determine their suitability for inclusion in the review as 'Studies awaiting assessment'.

Data extraction and management

We used a data collection form, piloted on one study in the review, to extract study characteristics and outcome data. Independently, four review authors (NvD, MdB, HvdW, HvM) extracted study characteristics and outcome data from included studies. If necessary, we contacted the authors of trial reports for clarification or for additional information. We organised data using the most recent version of Review Manager 5 software (RevMan 2012). We negotiated disagreements with another review author. We extracted data on the following study characteristics.

1. Trial characteristics
2. Details of methodology
3. Participants' characteristics
4. Intervention characteristics
5. Outcome measures

6. Notes

Two review author (NvD, HvdW) entered data into Review Manager 5 for analysis (RevMan 2012). We double-checked that data had been entered correctly by comparing the data presented in the systematic review with the data in the study reports. A third review author (MdB) spot-checked study characteristics for accuracy against the trial reports.

Main comparisons

Based on the available data, we present the following comparisons:

1. Psychological therapy versus usual care (or waiting list procedures)
2. Psychological therapy versus enhanced (or structured) care
3. Psychological therapy versus another psychological therapy

Assessment of risk of bias in included studies

Independently, two review authors (NvD, MdB) assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (18). We resolved any disagreements by discussion or by involving another review author (HvM, HvdW). We assessed the risk of bias for the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding
4. Incomplete outcome data
5. Selective outcome reporting
6. Other sources of bias
7. Treatment fidelity
8. Researcher allegiance

We judged each potential source of bias as to be of high, low, or unclear risk. Then we summarised the risk of bias judgements across different studies for each of the domains

Measures of treatment effect

Dichotomous data

For dichotomous outcomes, we used risk ratio (RR) as the summary statistic, together with 95% confidence intervals (CI).

Continuous data

As different measures were used to assess the same outcome, we pooled data using the standardised mean difference (SMD); we calculated 95% CI. Specific attention was paid to the secondary outcome 'functional disability and quality of life', as the direction of scales for these outcomes can differ.

Assessment of heterogeneity

We assessed the groups for clinical similarities including elements such as age, gender, and setting. First, we assessed statistical heterogeneity visually by inspecting forest plots of standardised mean effect sizes and of relative risks. We used the I^2 statistic as a second test: I^2 describes the percentage of variability in effect estimates that is due to heterogeneity rather than chance.
We used conventions of interpretation defined by Higgins (18). In the case of substantial levels (i.e. where I^2 = 50% to 90%) and considerable levels (I^2 = 75% to 100%) of heterogeneity, we explored data further by means of subgroup and sensitivity analyses (see below). These were not clear-cut criteria, as the importance of the observed I^2 also depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (19; 20); for example: if the I^2 value fell slightly below 50% (e.g. 45%) and the direction and magnitude of treatment effects suggested important heterogeneity, we investigated the data further.

Assessment of reporting biases

We created funnel plots (treatment effect versus standard error of the effect size), if we included at least 10 trials in a meta-analysis, according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (18, 21). When analysing and interpreting a funnel plot, we considered all potential reasons for asymmetry, not just publication bias (e.g. differences in methodological quality, true heterogeneity in intervention effects).

Data synthesis

If we found two or more included studies in a comparison category (see Data extraction and management) that used the same outcome construct, we performed a meta-analysis of the results. Two authors (NvD, JvdW) entered data into Review Manager 5 software (RevMan 2012). We expected to find high heterogeneity in non-pharmacological therapy approaches and in symptom severity, duration of symptoms and co-morbidities among the various study populations. Therefore,
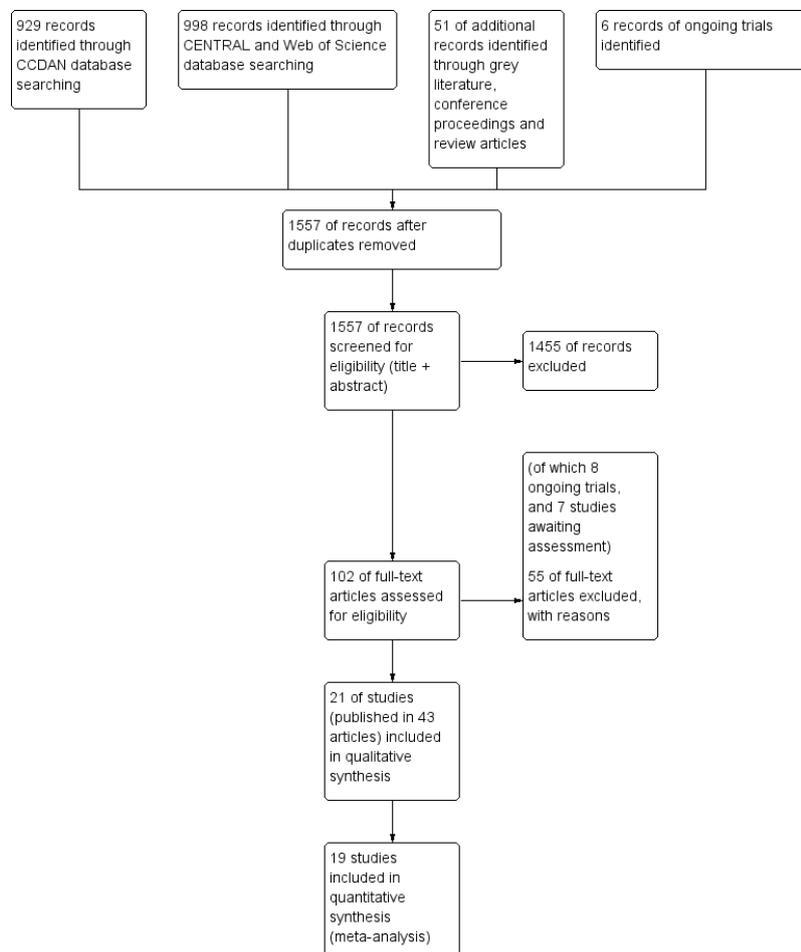
we analysed dichotomous and continuous treatment effects using a random-effects model. For studies of which data could not be combined, we summarised the results narratively.

RESULTS

Description of studies

Searches were conducted up to November 2013 (CCDAN registers) and April 2014 (cited reference searches). Figure 1 shows the flow diagram of study selection.

1. Flow diagram of study selection

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┌─────────────────┐  ┌──────────────────────┐  ┌──────────────────┐  ┌──────────────────────┐
│ 929 records     │  │ 998 records identified│  │ 51 of additional │  │ 6 records of ongoing │
│ identified      │  │ through CENTRAL and   │  │ records identified│  │ trials identified    │
│ through CCDAN   │  │ Web of Science        │  │ through grey     │  └──────────────────────┘
│ database        │  │ database searching    │  │ literature,      │
│ searching       │  └──────────────────────┘  │ conference       │
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                                          │ (of which 8      │
                                          │ ongoing trials,  │
                                          │ and 7 studies    │
                                          │ awaiting         │
                                          │ assessment)      │
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        ┌──────────────────────┐         │ 55 of full-text  │
        │ 102 of full-text     │────────▶│ articles excluded,│
        │ articles assessed    │         │ with reasons     │
        │ for eligibility      │         └──────────────────┘
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        ┌──────────────────────┐
        │ 21 of studies        │
        │ (published in 43     │
        │ articles) included   │
        │ in qualitative       │
        │ synthesis            │
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        ┌──────────────────────┐
        │ 19 studies           │
        │ included in          │
        │ quantitative         │
        │ synthesis            │
        │ (meta-analysis)      │
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Literature database searches

In the search of the CDANCTR-Studies and CCDANCTR-Reference Register (from now on referred to as CCDAN database), we found 929 abstracts after de-duplication. We excluded 842 records, based

on the title and abstract, leaving 82 references (65 studies) selected for full-text retrieval. After reading the full-text, we judged 27 studies (49 articles) eligible for inclusion in this review. We excluded 35 studies (38 articles) and six articles are still awaiting assessment, for example, due to unavailability of a full-text article or difficulties in contacting authors.

The search of CENTRAL database found 995 records. After removing duplicates from the CCDAN search, there were 568 new references. After title and abstract screening, we excluded 560 references, and selected eight articles for full-text reading. After full-text reading, we excluded five articles, and judged three articles eligible for inclusion; however, all three articles described studies already included in the review (e.g. long-term follow-up results) (22, 23, 24). As the Schröder article reported a more detailed trial methodology and higher number of participants, we decided to use this article as the main reference of this study (23) instead of Zaby 2008 (25), which was retrieved from the CCDAN search.

We performed a cited reference search on the Web of Science, for citations to primary reports of all studies expected to be included in this review. When hand searching the retrieved articles, we identified three additional relevant references. After full-text reading, we included one new study (26), and excluded one article due to randomisation method (27). One article (28) described an already included study (29).

Grey literature

We performed searches for grey literature but found no new articles. We screened the conference proceedings and found no new articles.

Systematic reviews

We found 14 reviews about (specific) non-pharmacological interventions for somatoform disorders or MUPS. After title screening in the reference lists of the reviews, we selected seven additional articles for screening of abstract. After abstract reading, we excluded four articles, and selected three articles for full-text reading. None of these three articles were eligible due to lack of randomisation or inappropriate selection method (30, 31, 32).

Trial registers

We performed ongoing trial searches in the databases of www.clinicaltrials.gov, www.controlled-trials.com, and www.who.int/trialsearch. We found six potentially eligible ongoing trials. As full

details of the design and study results were not available, we could not include these studies in the review.

Contacting authors

We tried to contact 10 trial authors for missing information regarding the eligibility of studies; four responded and provided the desired information (33, 34, 35, 36). We contacted authors of 20 of the included studies for additional information regarding study design and outcomes, of which 10 provided requested data.

Included studies

We included 21 studies, reported in 43 publications, in this review. All included studies concerned psychological interventions.

Design
Twenty of the included 21 studies had a parallel-group, individually randomised design (RCT). One study had a cluster-randomised design (37). We found not trials with a crossover design.

Sample size
The total number of randomised participants was 2658, a mean number of 127 per study (range 32 to 328). Two studies included fewer than 25 participants per arm (26, 38). Most studies reported 25 to 75 participants per arm. Three studies included 75 to 100 participants per arm (39, 40, 41), and two studies included more than 100 participants per arm (29, 37). The largest study was Schaefert 2013 (37), with 328 randomised participants.

Setting

Eight studies recruited participants in primary care only (26, 39, 42, 37, 40, 43, 41; 13). Only two studies recruited in secondary care (e.g. outpatient clinics) (28, 44) and one study recruited inpatients in hospitals (45). Seven studies recruited via medical settings as well as the open population (e.g. through advertisements) (46, 47, 38, 48, 49, 23, 24). Three studies recruited via primary care as well as secondary care (50, 33, 51).
In one study, treatment was performed in group sessions by GPs in primary care who were trained in the specific psychological technique, combined with a psychosomatic specialist (37). In six other studies, treatment took place at a department of psychiatry or psychology (46, 39, 50, 38, 48, 13).

Another six studies treated participants in other outpatient clinics (47, 33, 51, 43, 41, 24). Five studies treated participants in specific outpatient symptom clinics or outpatient clinics for psychosomatics (26, 49, 28, 23, 44). One study treated participants as inpatients (45). One study treated participants at home (40). Finally, in one study the treatment setting was unknown (42).

Participants

Most studies recruited women than men, as found in epidemiological studies (52, 53). Only one study reported more men (56%) in the intervention group (44). The proportion of women among all participants in all treatment groups ranged between 66% (26) and 89% (46).

The mean age was 43 years in all included studies, ranging from 35 years (48) to 49 years (49). Diagnostic criteria and inclusion criteria varied widely between studies. Fourteen studies used standardised diagnostic interviews to establish the diagnosis, the other seven studies used standardised questionnaires. In nine studies, symptoms were referred to as medically unexplained symptoms or unexplained physical symptoms. Three studies used the diagnoses of somatisation disorder and somatoform disorder to describe the symptoms and two studies used only the term somatisation. One study spoke of abridged somatisation disorder and two other studies spoke of multiple somatoform symptoms.

Exclusion criteria varied between studies, but often included dementia, severe psychopathology such as psychosis, active suicidal thoughts, alcohol dependence, pregnancy, and current psychological therapy.

Eleven studies reported severity of symptoms at baseline in terms of number of symptoms. This number varied widely, ranging from a lifetime number of seven symptoms (49), to a current number of 32 symptoms (51).

Interventions

As described in the Types of interventions section, we aimed to select studies investigating psychological therapies, as well as studies on physical therapies. We found no studies on physical therapies that were eligible for inclusion. All 21 included studies evaluated a form of psychological therapy. We classified psychological therapies into six subcategories, as pre-defined by the Cochrane Depression, Anxiety and Neurosis Review Group: CBT, behaviour therapy, or other therapies such as third-wave CBT, psychodynamic therapy, humanistic therapy, or integrative therapies. Fourteen studies described certain forms of CBT. Two studies evaluated behaviour therapies (38, 40). Two studies described third-wave CBT (mindfulness) (50, 13), and two studies described psychodynamic therapies (29, 37). In the study of Kolk et al., participants received CBT, client-centred or eclectic

therapy, depending on the therapist the participant was assigned to (48); we classified this as integrative therapy. None of the included studies described humanistic therapies.

In eight studies, the participants received group therapy, and in 11 studies they received individual therapy. In one study, participants received both (51), and in one study there were two intervention groups of which one group received group CBT, and one group received personal CBT (42).

The duration of treatment ranged from one day (one single session) (49) to nine months (37), most often between one and three months.

The mean number of sessions varied among studies and ranged from one session (49) to 13 sessions (24). Thirteen studies used five to 10 sessions. Four studies used one to five sessions (26, 49, 40, 45). Four studies used more than 10 sessions (29, 37, 44, 24).

All studies performed follow-up assessment, but one did not report the outcomes of all follow-ups (40). Reported duration of follow-up varied between two weeks (45) and 24 months (40).

Comparisons

As described in the Types of interventions section, we aimed to select the following comparator interventions: usual treatment or waiting list, attention or psychological placebo, and other psychological/physical therapies. Fifteen studies compared an intervention to usual treatment or a waiting list. One of these studies had two intervention groups (receiving psychological therapy) and one control group (receiving usual care) (42). None of the included studies described a placebo comparator intervention, but five included studies compared an intervention with enhanced or structured care (i.e. more than just usual care or a waiting list condition) (50, 29, 51, 44, 43). We had not foreseen this comparator at the protocol stage, so we added this later as an additional comparison. Examples of the enhanced care control condition were a basic training for GPs in the detection and management of psychiatric disorders (44).

One study used compared two psychological therapies (23). This study also included a waiting list group, but we excluded data from this group from our analysis as participants were not randomly assigned to this group. We found no studies that compared psychological interventions with physical therapies.

In one study, GPs in both study arms were trained in diagnosis and management of medically unexplained symptoms (37). In addition, the GPs in the intervention group conducted group sessions for people with MUPS, together with a psychosomatic specialist.

In six studies, in both study arms a consultation letter was sent to the primary care physician after baseline assessment, in addition to the planned psychological therapy (46, 39, 50, 38, 42, 51). This

was not a reason for exclusion, and we categorised these studies according to the main comparison. In sensitivity analyses, we assessed the effect of the interventions excluding these studies.

Risk of bias in included studies

We classified the methodological quality of the 21 studies according to The Cochrane Collaboration's tool for assessing the risk of bias. Figure 2 presents the risk of bias summary figure.

Figure 2. Risk of bias summary: review authors' judgments' about each risk of bias item for each included study.

Allocation (selection bias)

Sequence generation

While all studies specified that participants were randomly allocated to conditions (or GP practices randomised to treatment or control conditions), there were two studied that did not describe how sequence generation was performed (47, 23). Therefore, we rated them as 'uncertain'. We rated the other studies as 'low risk' as they all used random sequence generation methods, whether by computer or non-digital, for example, using random number tables (48, 49), or a sequence of labelled cards in envelopes or bags (50, 40, 45, 43).

Allocation concealment

For five studies, it was unclear who performed allocation, or whether the person allocating participants to the trial groups was independent. Therefore, we rated these studies 'unclear' (46, 39, 47, 38, 23). We rated the remaining 16 studies 'low risk of bias' as there was an adequate description of the person performing allocation or the relation to the researchers and therapists(e.g. "randomisation was carried out independently by a nurse who was not participating in the study") (33).

Blinding (performance bias and detection bias)

Blinding of participants and personnel

In 18 studies, blinding of participants and personnel was not possible, due to the nature of the interventions (e.g. psychological group therapy versus waiting list). As this may have influenced the judgement, we rated almost all studies 'high risk'. We rated two studies 'unclear' because one of the two groups (participants or personnel) was blinded and the other was not (43, 37). One study did not describe blinding of personnel (23), and, therefore, we rated it 'unclear'.

Blinding of outcome assessment

In 19 studies, blinding of outcome assessment was not possible as most outcomes were participant reported. In one study, outcomes were assessed by blinded interviewers, but they did this together with the participants (who were not blinded) (39). We rated this study 'unclear'. One study mainly used clinician-rated instruments (42). The outcome assessor was blinded, but, as there also were a few participant report instruments (and participants were not blinded), we rated this study 'unclear'.

Incomplete outcome data (attrition bias)

All studies reported follow-up rates; nine (43%) studies reported a loss to follow-up of 20% or less. We rated these studies 'low risk'. We rated one study 'unclear', because it had a high loss to follow-up, but corrected for this statistically by multiple imputation (50). The remaining 11 studies reported high loss to follow-up (greater than 20%) and, therefore, we rated them 'high risk'.

Selective reporting (reporting bias)

Seventeen studies reported all intended outcomes and, therefore, we rated them 'low risk'. For one study, a protocol was lacking, therefore it was impossible to evaluate the possibility of selective outcome reporting (50). We rated this study 'unclear'. We rated the remaining three studies 'high risk'. In Kashner 1995, the outcome 'days in bed' was described as assessed, but was not reported in the article (47). In Moreno 2013, healthcare use and CGI were mentioned as outcomes in the protocol, but they were not reported (42). Schilte 2001 performed follow-up measurements at six, 12, and 24 months, but only reported outcomes of the last follow-up moment (40).

Treatment fidelity

Sixteen studies used a treatment manual or protocol for studied treatments. We rated them 'low risk'. Three studies did not apply a structured intervention according to a protocol (26, 48, 40), therefore, we rated them 'high risk'. The two remaining studies did provide information about a form of structure in treatment, but did not mention a protocol or manual for this. We rated them 'unclear'.

Researcher allegiance

In 18 studies, researchers did not report to have a preference for one of the treatment modalities. In the studies of Burton 2012, Lidbeck 1997, and Schaefert 2013, an author was also (one of) the therapist(s), which may have caused some bias. Therefore, we rated these studies 'unclear' (26, 33, 37).

Other potential sources of bias

We included two multiple intervention studies (42, 23). In the first study, data were presented for each groups to which participants were randomised, so no other potential sources of bias were found (rating: 'low risk'). In the second study, participants were randomised for CBT or progressive

muscle relaxation (PMR) using random sequences. When both groups were full, newly included participants were allocated to the waiting list group. In a later stage, these participants were included in both intervention groups. As participants were their own controls due to this method, we decided to exclude data from the waiting list group from analysis. For this reason, we rated this study 'unclear'.

One of the studies was a CRCT (37). GPs were randomised, after which individuals were recruited. We considered the randomisation method and statistical analysis appropriate for the study design. In the studies of Schilte 2001 and Katsamanis 2011, we found considerable baseline imbalances (40, 38). In the study of Schweickhardt 2007, a high percentage (29%) of participants from the control group became involved in psychotherapy (45). This may have influenced the results, although this study provided data for only one outcome (acceptability) and the effects were in the same order of magnitude as in other studies. We rated these three studies 'unclear'.

Effects of interventions

For the description of the results, we stratified the comparisons in the following way (as per the categories of therapies presented in Types of interventions, where data allowed):

1. Psychological therapies versus usual care or waiting list
   a. CBT versus usual care or waiting list
   b. Behavioural therapy versus usual care or waiting list
   c. Third-wave CBT versus usual care or waiting list
   d. Psychodynamic therapy versus usual care or waiting list
   e. Integrative therapies versus usual care or waiting list
2. Psychological therapies versus enhanced or structured care
   a. CBT versus enhanced or structured care
   b. Third-wave CBT versus enhanced or structured care
   c. Psychodynamic therapy versus enhanced or structured care
3. Psychological therapy versus another psychological therapy
   a. CBT versus behavioural therapy

Most studies provided data for some of the outcomes. One study did not provide any data that were suitable for meta-analysis, because the authors only reported change scores (40). Across all comparisons, outcomes, and time points, we created 44 forest plots. Most of these included data from only a limited number of studies: 25 of the forest plots included three or fewer studies, only two included 10 or more studies. Below, we present the results of the meta-analyses. We also give

attention to the subgroups that included a considerable proportion of the studies contributing to the overall comparisons: CBT versus usual care or waiting list and CBT versus enhanced or structured care, because these subgroups were more homogeneous in terms of type of intervention than the overall comparisons. In terms of risk of bias, the studies that provided outcomes for the meta-analyses were representative for the whole group (i.e. covered the broad spectrum of risk of bias assessments across items).

1. Psychological therapy versus usual care or waiting list

Fifteen studies, with 1805 randomised participants, compared some form of psychological therapy with usual care or waiting list controls. They addressed the following psychological therapies:

1. CBT versus usual care or waiting list
    a. Ten studies, 1037 randomised participants (46, 26, 39, 47, 33, 49, 42, 45, 43, 24)
2. Behavioural therapy versus usual care or waiting list
    a. Two studies, 209 randomised participants (38, 40)
3. Third-wave CBT versus usual care or waiting list
    a. One study, 125 randomised participants (13)
4. Psychodynamic therapy versus usual care or waiting list
    a. One study, 328 randomised participants (37)
5. Integrative therapies versus usual care or waiting list
    a. One study, 106 randomised participants (48)

In four of these studies, this was combined with a consultation letter sent to the primary care physician after baseline assessment, in both treatment arms (46, 39, 38, 42). A consultation letter provided recommendations for the primary care physician tailored to the individual person's diagnosis, symptoms, and problems. In one study, the GPs in both treatment groups were trained in diagnosis and management of MUPS (37).

Apart from CBT, for each of the other types of psychological therapy only one study provided outcomes. Hence, for each of these separate treatment types there was insufficient evidence. Below, we described results for the whole group and for the subgroup of studies that compared CBT with usual treatment.

Primary outcomes
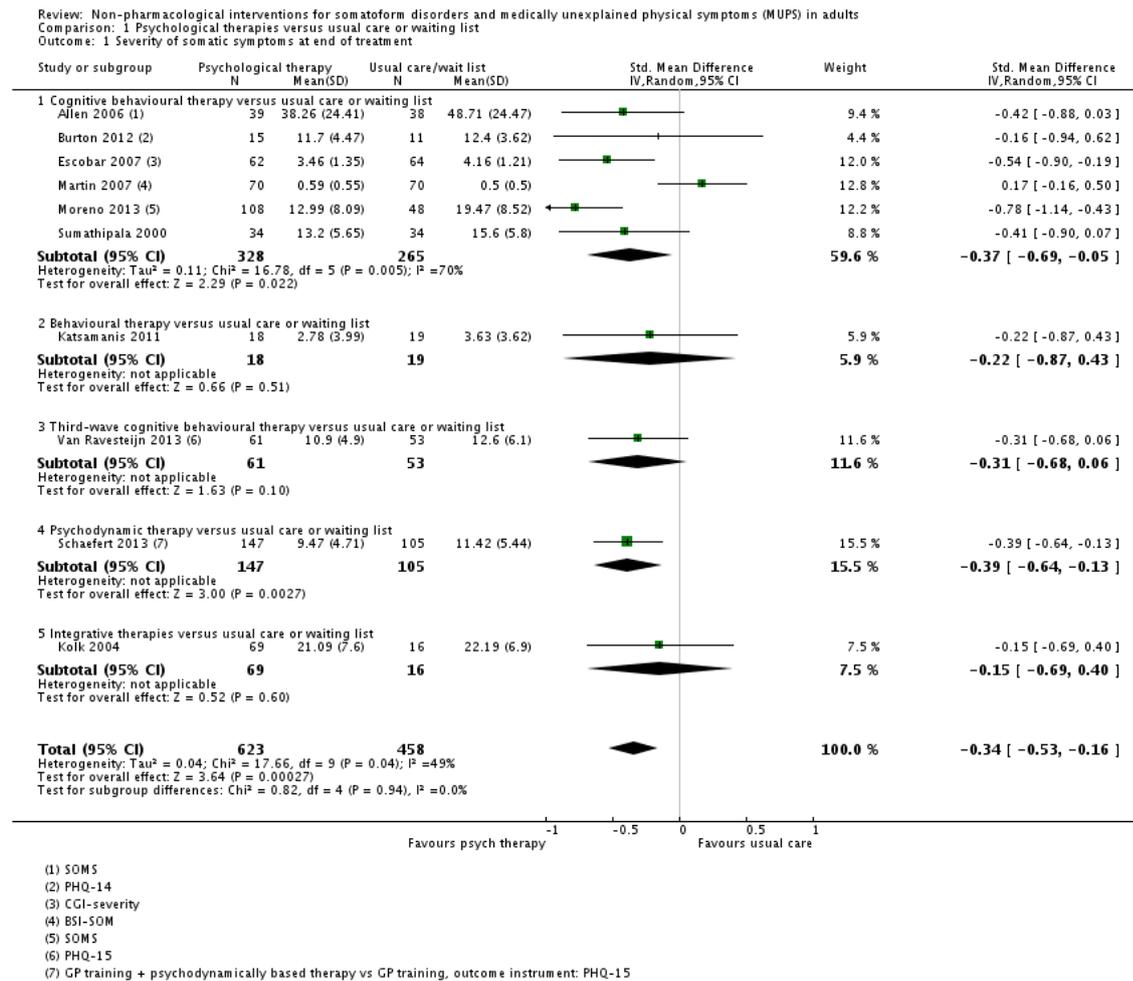
1.1 Severity of somatic symptoms

Combining all studies that compared some psychological therapy with usual care or waiting list, psychological therapies were significantly more effective at end of treatment, though the effect was small (SMD -0.34; 95% CI -0.53 to -0.16; 10 studies, 1081 analysed participants) (figure 1). Heterogeneity was moderate (I^2 = 49%), and the overall quality of the evidence was low. Compared with usual care, the subgroup of studies that used CBT were also significantly more effective in reducing severity of symptoms at end of treatment (SMD -0.37; 95% CI -0.69 to -0.05; 6 studies, 593 participants, random-effects model). Heterogeneity was substantial (I^2 = 70%), and the overall quality of the evidence was low. The point estimates of all but one of the studies favoured the CBT group. The two studies with the smallest effects offered low-intensity CBT (27, 49). A post-hoc analysis without these two studies provided an SMD of -0.58 (a moderate effect size) (95% CI -0.77 to -0.38) and reduced heterogeneity (I^2 = 0%.

At follow-up, measurements within one year of follow-up, the effect of psychological therapies remained significant (SMD -0.24; 95% CI -0.37 to -0.11; 7 studies, 950 participants; I^2 = 0%). The same was the case for the subgroup of CBT studies (SMD -0.29; 95% CI -0.49 to -0.09; 4 studies, 496 participants). Heterogeneity was low (I^2 = 17%).

Only two studies (all of CBT) with 228 participants provided data for this severity of symptoms beyond one year of follow-up (SMD -0.52; 95% CI -0.80 to -0.24). Heterogeneity was low (I^2 = 0%).

Figure 3. Psychological therapies versus usual care or waiting list controls

Review: Non-pharmacological interventions for somatoform disorders and medically unexplained physical symptoms (MUPS) in adults
Comparison: 1 Psychological therapies versus usual care or waiting list
Outcome: 1 Severity of somatic symptoms at end of treatment

Study or subgroup	Psychological therapy N	Mean(SD)	Usual care/wait list N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Cognitive behavioural therapy versus usual care or waiting list							
Allen 2006 (1)	39	38.26 (24.41)	38	48.71 (24.47)		9.4 %	-0.42 [-0.88, 0.03]
Burton 2012 (2)	15	11.7 (4.47)	11	12.4 (3.62)		4.4 %	-0.16 [-0.94, 0.62]
Escobar 2007 (3)	62	3.46 (1.35)	64	4.16 (1.21)		12.0 %	-0.54 [-0.90, -0.19]
Martin 2007 (4)	70	0.59 (0.55)	70	0.5 (0.5)		12.8 %	0.17 [-0.16, 0.50]
Moreno 2013 (5)	108	12.99 (8.09)	48	19.47 (8.52)		12.2 %	-0.78 [-1.14, -0.43]
Sumathipala 2000	34	13.2 (5.65)	34	15.6 (5.8)		8.8 %	-0.41 [-0.90, 0.07]
Subtotal (95% CI)	328		265			59.6 %	-0.37 [-0.69, -0.05]
Heterogeneity: Tau² = 0.11; Chi² = 16.78, df = 5 (P = 0.005); I² =70%							
Test for overall effect: Z = 2.29 (P = 0.022)							
2 Behavioural therapy versus usual care or waiting list							
Katsamanis 2011	18	2.78 (3.99)	19	3.63 (3.62)		5.9 %	-0.22 [-0.87, 0.43]
Subtotal (95% CI)	18		19			5.9 %	-0.22 [-0.87, 0.43]
Heterogeneity: not applicable							
Test for overall effect: Z = 0.66 (P = 0.51)							
3 Third-wave cognitive behavioural therapy versus usual care or waiting list							
Van Ravesteijn 2013 (6)	61	10.9 (4.9)	53	12.6 (6.1)		11.6 %	-0.31 [-0.68, 0.06]
Subtotal (95% CI)	61		53			11.6 %	-0.31 [-0.68, 0.06]
Heterogeneity: not applicable							
Test for overall effect: Z = 1.63 (P = 0.10)							
4 Psychodynamic therapy versus usual care or waiting list							
Schaefert 2013 (7)	147	9.47 (4.71)	105	11.42 (5.44)		15.5 %	-0.39 [-0.64, -0.13]
Subtotal (95% CI)	147		105			15.5 %	-0.39 [-0.64, -0.13]
Heterogeneity: not applicable							
Test for overall effect: Z = 3.00 (P = 0.0027)							
5 Integrative therapies versus usual care or waiting list							
Kolk 2004	69	21.09 (7.6)	16	22.19 (6.9)		7.5 %	-0.15 [-0.69, 0.40]
Subtotal (95% CI)	69		16			7.5 %	-0.15 [-0.69, 0.40]
Heterogeneity: not applicable							
Test for overall effect: Z = 0.52 (P = 0.60)							
Total (95% CI)	623		458			100.0 %	-0.34 [-0.53, -0.16]
Heterogeneity: Tau² = 0.04; Chi² = 17.66, df = 9 (P = 0.04); I² =49%							
Test for overall effect: Z = 3.64 (P = 0.00027)							
Test for subgroup differences: Chi² = 0.82, df = 4 (P = 0.94), I² =0.0%							

-1 -0.5 0 0.5 1
Favours psych therapy   Favours usual care

(1) SOMS
(2) PHQ-14
(3) CGI-severity
(4) BSI-SOM
(5) SOMS
(6) PHQ-15
(7) GP training + psychodynamically based therapy vs GP training, outcome instrument: PHQ-15

1.2 Acceptability

Compared with usual care, psychological therapies resulted in a higher proportion of drop-outs (RR acceptability 0.93; 95% CI 0.88 to 0.99 favouring usual care; 14 studies, 1644 participants). Heterogeneity was moderate (I^2 = 70%). For the studies comparing CBT with usual care, results were of the same magnitude but no longer statistically significant (RR acceptability 0.93; 95% CI 0.85 to 1.01 favouring usual care; 10 studies, 1037 participants). Heterogeneity was considerable (I^2 = 78%). The overall quality of the evidence for this outcome was moderate.

Secondary outcomes

1.3 Severity of anxiety or depressive symptoms (or both)

For participant-rated anxiety symptoms, there was no significant difference at end of treatment (SMD 0.06; 95% CI -0.20 to 0.32, 4 studies, 270 participants). For the studies comparing CBT with usual care, results were similar (SMD 0.07; 95% CI -0.22 to 0.37; 3 studies, 185 participants). Within one year of follow-up only two studies were available (SMD 0.18; 95% CI -0.22 to 0.58; 134 participants).

For clinician-rated anxiety symptoms at end of treatment, there was a statistically significant difference at end of treatment in favour psychological therapies (SMD -0.40; 95% CI -0.63 to -0.17; 3 studies, 320 participants). Within and beyond one year of follow-up, differences remained statistically significant (within one year: SMD -0.66; 95% CI -1.15 to -0.18, 2 studies both CBT, 251 participants; beyond one year: SMD -0.91; 95% CI -1.26 to -0.55; 1 study, 156 participants).

For participant-rated depressive symptoms, there was no significant difference at end of treatment (SMD -0.03; 95% CI -0.22 to 0.16; 6 studies, 661 participants). Similar results were found for the studies that compared CBT with usual care (SMD 0.09; 95% CI -0.13 to 0.31; 4 studies, 325 participants), and for outcomes after not more than one year of follow-up (SMD 0.04; 95% CI -0.34 to 0.42; four studies, 535 participants).

For clinician-rated depressive symptoms, there was a statistically significant difference at end of treatment in favour of psychological therapies (SMD -0.25; 95% CI -0.48 to -0.02; 3 studies, 316 participants). Within one year of follow-up, the difference was no longer statistically significant (SMD -0.55; 95% CI -1.17 to 0.07; 2 studies, 251 participants). Only one study reported on this outcome beyond one year after treatment (SMD -0.81; 95% CI -1.16 to -0.46; 156 participants).

1.4 Dysfunctional cognitions, emotions, and behaviours

Three studies, two of which compared CBT with usual care, with 440 participants, reported on dysfunctional cognitions, emotions, and behaviours. At end of treatment, there was no significant difference between the two groups (SMD -0.11; 95% CI -0.37 to 0.16). The quality of the evidence was moderate. At follow-up within one year, differences remained non-significant (SMD -0.16; 95% CI -0.38 to 0.07).

1.5 Adverse events

Only three studies, all comparing CBT with usual care, reported on adverse events during the treatment period. One study could not be included in the meta-analysis, because no adverse events were found in both groups. The pooled result of the other two studies also showed no significant differences between both conditions (RR 1.31; 95% CI 0.47 to 3.66; 445 participants; I^2 = 0%).

1.6 Treatment response (clinician rated)

All four studies addressing clinician-rated treatment response comparing CBT with usual care. At end of treatment, results strongly favoured the treatment group (RR 3.30; 95% CI 2.08 to 5.21; 4 studies, 391 participants; I^2 = 19%). We considered the quality of the evidence to be low for this outcome. Three studies provided data for clinician-rated treatment response within one year after end of treatment, still in favour of the treatment group (RR 2.53; 95% CI 1.25 to 5.10; 332 participants; I^2 = 59%). At longer follow up (greater than one year after treatment) only two studies reported outcomes, highly favouring the treatment group (RR 10.31; 95% CI 2.95 to 36.02; 240 participants).

1.7 Functional disability and quality of life

Seven studies, of which four addressing CBT reported on functional disability and quality of life, using a variety of instruments. At the end of treatment, a statistically significant effect was found favouring the psychological therapies (SMD 0.17; 95% CI 0.03 to 0.32; 7 studies, 730 participants; I^2 = 0%). We judged the evidence to be moderate. At follow-up within one year after treatment, differences were similar but no longer significant (less than one year: SMD 0.16; 95% CI -0.01 to 0.33; 4 studies, 526 participants; I^2 = 0%). After one year, only one study provided data for functional disability and quality of life.

Four studies compared CBT with usual care. At end of treatment, a non-significant difference was found favouring CBT (SMD 0.15; 95% CI -0.06 to 0.37; 4 studies, 341 participants; I^2 = 0%).

1.8 Health care use

Six studies assessed healthcare use, operationalized in different ways, with moderate quality of evidence. During the treatment phase, two studies found a significant difference in the number of participant-initiated doctor visits and medication usage in favour of CBT (SMD -0.68; 95% CI -1.06 to -0.30; 117 participants). In the period less than one year after treatment, perhaps a more relevant timeframe, four studies found no clear evidence of a difference (SMD -0.09; 95% CI -0.31 to 0.12; 532 participants; I^2 = 20%). We judged the quality of the evidence to be moderate. For one of the studies, the effect was in the opposite direction, that is, favouring the control group (48). No study provided data for healthcare use beyond one year after treatment. See footnotes of analyses for details about the way healthcare use was assessed.

2. Psychological therapy versus enhanced or structures care

Five studies with 680 randomised participants compared a certain psychological therapy with enhanced or structured care. They addressed the following treatments:

1) CBT versus enhanced or structured care
   a) Three studies, 349 randomised participants (51, 44, 43)
2) Third-wave CBT versus enhanced or structured care
   a) One study, 120 randomised participants (50)
3) Psychodynamic therapy versus enhanced or structured care
   a) One study, 211 randomised participants (29).

In two of these studies, treatment was combined with a consultation letter sent to the primary care physician after baseline assessment, in both treatment arms (50, 51).

Below we describe the main results, sorted by outcomes. Apart from CBT, only one or two trials provided data for each of the three other types of psychological therapy; hence, for each of these other treatment types there was insufficient evidence.

Primary outcomes

2.1 Severity of somatic symptoms

Five studies (with 624 analysed participants) assessed severity of somatic symptoms comparing some psychological therapy versus enhanced care (pooled SMD -0.19; 95% CI -0.43 to 0.04; I^2 = 53%). We considered the quality of the evidence to be low. Within one year of follow-up, this effect was similar but now statistically significant (SMD -0.21; 95% CI -0.40 to -0.02; 5 studies, 593 participants; I^2 = 25%). Only two studies each comparing a different psychological therapy to enhanced care, assessed severity of somatic symptoms beyond one year after treatment (SMD -0.32; 95% CI -0.73 to 0.10; 172 participants). The subgroup of studies comparing CBT with enhanced care showed similar results. Heterogeneity was substantial at the end of treatment (I^2 = 62%) and moderate within one year after treatment (I^2 = 39%).

2.2 Acceptability

Five studies, with 679 analysed participants, showed that psychological therapies were less acceptable in terms of drop-outs than enhanced care (RR 0.93; 95% CI 0.87 to 1.00). Heterogeneity was moderate (I^2 = 36%), and we judged the quality of the evidence to be moderate. The largest subgroup was CBT. Compared with enhanced care, moderate-quality evidence showed that there was no clear difference between CBT and enhanced or structured care (RR 0.91; 95% CI 0.82 to 1.02; 3 studies, 331 participants). Heterogeneity was moderate to considerable (I^2 = 50%).

Secondary outcomes

2.3 Severity of anxiety or depressive symptoms (or both)

Five studies assessed severity of anxiety or depressive symptoms (or both) at end of treatment (SMD -0.14; 95% CI -0.30 to 0.02; 624 analysed participants; I^2 = 0%), showing no clear difference. Similar results were found within one year after treatment (SMD -0.13; 95% CI -0.29 to 0.03; 5 studies, 593 participants) and beyond one year after treatment (SMD -0.26; 95% CI -0.55 to 0.03; 2 studies, 184 participants).

The studies investigating CBT showed no significant difference in level of anxiety and depressive symptoms between CBT and enhanced care at end of treatment (SMD -0.17; 95% CI -0.40 to 0.05; 3 studies. 307 participants) and within one year after treatment (SMD -0.17; 95% CI -0.40 to 0.06; 3 studies, 289 participants). Heterogeneity was low (I^2 = 0% at end of treatment and within one year after treatment). Only one CBT study reported on severity of anxiety or depressive symptoms (or both) beyond one year after treatment.

2.4 Dysfunctional cognitions, emotions, and behaviours

Four studies, with 499 analysed participants, provided data for dysfunctional cognitions, emotions, and behaviours at end of treatment, showing no clear evidence of a difference between psychological therapy and enhanced care (SMD -0.09; 95% CI -0.29 to 0.10; I^2 = 14%). We judged quality of the evidence to be moderate. At follow-up within one year after treatment, the difference was statistically significant (P value = 0.05), favouring the psychological therapy over enhanced care (SMD -0.24; 95% CI -0.49 to 0.00; 4 studies, 477 participants; I^2 = 42%). Beyond one year of follow-up, only two studies reported on dysfunctional cognitions, emotions, and behaviours and showed no significant difference (SMD -0.58; 95% CI -1.27 to 0.11; 2 studies, 184 participants; I^2 = 82%).

The two studies comparing CBT with enhanced care showed no clear evidence of a difference in dysfunctional cognitions, emotions, and behaviours at end of treatment (SMD -0.28; 95% CI -0.57 to 0.01; 2 studies, 182 participants). Heterogeneity was low (I^2 = 0%). Within one year after treatment, levels of dysfunctional cognitions, emotions, and behaviours were significantly lower for CBT (SMD -0.45; 95% CI -0.83 to -0.07; 2 studies, 173 participants), though more heterogeneous (I^2 = 37%). This effect was even more significant at more than one year after treatment, although this comparison only included one study (SMD -0.94; 95% CI -1.36 to -0.51; 94 participants) (51).

2.5 Adverse events

None of the studies comparing psychological therapy versus enhanced or structures care reported information about adverse events.

2.6 Treatment response

None of the included studies comparing psychological therapy versus enhanced or structures care reported about treatment response using a standardised method as described in Secondary outcomes. One study reported about treatment response, but for this outcome measure the SF-36 was used (51). In this review, we used the outcomes of this questionnaire in the analyses of functional disability. Another study reported about participants' perceived change in symptoms (44). At all measurement moments after baseline, participants were asked if their symptoms were "recovered", "improved", "the same", or "worse" since the previous measurement, using a non-standardised questionnaire. At the end of treatment, 32 (82%) participants in the intervention group declared that symptoms were improved or recovered versus 24 (64%) participants in the control group. Six months after treatment, 27 (73%) participants of intervention group reported recovery or improvement versus 23 (59%) participants of the control group.

2.7 Functional disability and quality of life

At end of treatment, four studies with 497 analysed participants reporting on functional disability and quality of life, found no significant difference (SMD 0.13; 95% CI -0.05 to 0.30; I^2 = 0%). We considered the quality of the evidence to be moderate. Within one year of follow-up, there was a small effect in favour of psychological therapies (SMD 0.20; 95% CI 0.02 to 0.38; 5 studies, 727 participants; I^2 = 0%). Only two studies reported on functional disability and quality of life beyond one year of follow-up and there was no clear evidence of a difference between the interventions (SMD 0.22; 95% CI -0.16 to 0.60; 2 studies, 184 participants).

For the studies comparing CBT with enhanced care, at end of treatment, moderate-quality evidence showed no significant difference in terms of level of function/quality of life, with a large CI but homogeneous population (SMD 0.21; 95% CI -0.08 to 0.51; 2 studies, 182 participants; I^2 = 0%). There was a small but significant difference in favour of CBT within one year after treatment (SMD 0.30; 95% CI 0.00 to 0.60; 2 studies, 173 participants). At this time point, heterogeneity was low (I^2 = 0%). After one year of follow-up, only one study provided data. In this study, CBT resulted in a significantly higher level of function compared with enhanced care (SMD 0.42; 95% CI 0.01 to 0.83; 94 participants).

2.8 Healthcare use

Only two studies provided usable data for this analysis and quality of the evidence was low (41, 29). There were no significant differences healthcare use between psychological therapies and enhanced care, neither at end of treatment, nor within one year after end of treatment. See footnotes of analyses for details about the way healthcare use was assessed.

3. Psychological therapy versus other psychological therapy

Only one included study addressed psychological therapy versus other psychological therapy (23; 173 randomised participants). The study compared CBT with PMR therapy. The study also included a waiting list group, but we excluded this group from analyses as participants in the waiting list group were not randomly assigned.

Primary outcomes and secondary outcomes

3.1 Severity of somatic symptoms

No significant difference was found for severity of somatic symptoms between CBT and PMR at end of treatment (SMD 0.10; 95% CI -0.33 to 0.53; 84 participants).

3.2 Acceptability

There was no significant difference in drop-out rates between CBT and PMR during treatment (SMD 0.98; 95% CI 0.83 to 1.15; 90 participants).

3.3 Severity of anxiety or depressive symptoms (or both) at end of treatment

There was no significant difference in level of depression and anxiety between CBT and PMR at end of treatment (SMD 0.01; 95% CI -0.42 to 0.44; 84 participants).

3.4 Dysfunctional cognitions, emotions, and behaviours

The study did not report about dysfunctional cognitions, emotions, and behaviours.

3.5 Adverse events

The study comparing CBT with PMR did not report about adverse events.

3.6 Treatment response

The study comparing CBT with PMR did not report about treatment response.

3.7 Functional disability and quality of life

There was no significant difference in level of function between CBT and PMR at end of treatment (SMD 0.28; 95% CI -0.15 to 0.71; 84 participants).

3.8 Healthcare use

The study comparing CBT with PMR did not report about healthcare use.

DISCUSSION

Summary of main results

Psychological therapy versus usual care

Fifteen studies compared some form of psychological therapy with usual care or a waiting list. Combining 10 of these studies, the psychological therapy was significantly more effective on symptom severity at end of treatment, though the effect was small. Heterogeneity was considerable and the overall quality of the evidence was low. Six of the 10 studies compared CBT with usual care; for this subgroup it was also apparent that CBT was more effective in reducing severity of symptoms at the end of treatment. The treatment effect of psychological therapies as a whole was also noted within one year of follow-up (seven studies). After one year, the evidence was limited to two studies (both CBT), but still in favour of the psychological therapy. Results for treatment response, one of our secondary outcomes, supported the findings for symptom severity, with moderate-quality evidence. Regarding the other primary outcome, acceptability, we found a 7% difference in drop-outs, favouring the usual care group. The quality of the evidence was moderate. After we removed an apparent outlier, the result was smaller (5%), but still statistically significant. There was no significant difference in drop-out rates between CBT and usual care.

For participant-rated symptoms of depression and anxiety, there was no significant difference at the end of treatment or at follow-up. In three studies using clinician-rated instruments, the level of anxiety and depression was slightly lower in the psychological therapy groups at the end of treatment. For anxiety, this difference became larger at follow-up. For clinician-rated depressive symptoms, this effect fluctuated during follow-up (no effect within one year (two studies) and a large

effect after one year of follow-up (one study)). Only three studies reported adverse effects and dysfunctional cognitions, emotions, and behaviours. There was no clear evidence of a difference on these outcomes. There was a small difference in functional disability at the end of treatment favouring psychological therapies. This effect was not apparent during follow-up. Two studies (both on CBT) found a small difference in favour of psychological therapies on healthcare use during treatment, four studies found no effect within one year of follow-up. Due to the small number of studies, these results should be considered with caution.

Only two studies compared behavioural therapy with usual care, of which only one provided relevant data (38). In this study, there were no significant differences for any of the outcomes. Only one study compared third-wave CBT (mindfulness therapy) with usual care (13). In this study, mindfulness was more acceptable than usual care, but no evidence of differences was found with respect to other outcomes. One study compared a variety of psychological therapies with usual care (therapy depended on the orientation of the 15 participating therapists) (48). In this study, there was no evidence of differences with respect to any of the outcomes. This comparison had a high external validity as it emulated the way the referral process normally works.

Psychological therapy versus enhanced or structured care

Five studies compared a certain psychological therapy with enhanced or structured care. The quality of the evidence was moderate for most outcomes. At the end of treatment, there was no clear evidence of a difference for symptom severity, but there was a small statistically significant difference within one year after end of treatment. The psychological therapy groups had a 7% higher drop-out rate than the control groups.

There was no clear evidence of a difference between the groups in terms of severity of anxiety or depressive symptoms (or both) at the end of treatment and within one year after treatment. There was no clear evidence of a difference between the groups in terms of dysfunctional cognitions, emotions, and behaviours at end of treatment, but at follow-up within one year of treatment there was a small effect in favour of psychological therapy over enhanced care. None of the studies in this comparison reported information about adverse events or treatment response in a standardised way. For functional disability and quality of life, there was no clear evidence of a difference at the end of treatment, but there was a small significant difference within one year of follow-up. There were no significant differences in healthcare use between psychological therapies and enhanced care.

Three of the studies compared CBT with enhanced or structured care. For symptom severity, CBT showed similar results as the whole group. There were no differences in drop-out rates. In addition,

there were no significant differences in levels of anxiety and depressive symptoms at the end of treatment and within one year after treatment. Only one study reported data after one year. At the end of treatment, CBT did not result in lower levels of dysfunctional cognitions, emotions, and behaviours, compared with enhanced care. Within one year of treatment, these levels were lower for CBT (two studies). Only one study reported beyond one year of treatment. The level of functional disability at the end of treatment was comparable for CBT and enhanced care. Within and after one year of treatment there was a small difference in favour of CBT, although only a few studies were included in these analyses. Only one CBT study reported data about healthcare use and found no evidence of difference.

Psychological therapy versus another psychological therapy

Only one study compared two forms of psychological therapy (CBT versus PMR). There were no differences between the groups for any of the outcomes.

Studies

A thorough literature search in electronic databases and many other resources such as conference proceedings, international trial registers, grey unpublished literature, and reference lists resulted in 21 studies that could be included in this review. In comparison to other existing reviews about non-pharmacological interventions for MUPS or somatoform disorders (e.g. 54, 15), this number of eligible studies is quite high. Hence, a considerable number of studies was available in order to address our questions. Only a few studies contributed to most of the outcomes. In addition, due to the small number of studies, we were unable to consider the effect of study characteristics (setting, severity, chronicity) on the outcomes.

We believe that the included studies cover a broad spectrum of settings, and both RCTs and CRCTs were included. Participants were recruited in various ways and from various healthcare settings, including primary care, secondary care, tertiary care, and the open population. In the included studies, therapists had different backgrounds (e.g. GPs, psychologists, and other physicians) and different levels of experience. A limitation of the included studies was the relatively low number of included participants per study as most studies only included 25 to 75 participants per study arm.

Participants

With only two exceptions (41, 43), studies were performed in developed countries (Western Europe and USA). Most studies randomised more women than men. This is in line with existing reviews, as

MUPS and somatoform disorders are more common among women. Included studies cover a broad age range. However, as the mean age of participants was in the 30s or 40s in most of the studies, it may be possible that younger and older people were relatively underpresented. Severity of MUPS at baseline was mostly analysed based on the number of symptoms or duration (or both) of symptoms. The number of symptoms at baseline varied widely, ranging from a lifetime number of symptoms of seven (49) to a current number of symptoms of 32 (51). Baseline duration, only reported in nine studies, ranged on average from four to 25 years. This suggests that most of the included participants may have had chronic symptoms at baseline. Included studies also reported high psychiatric co-morbidity rates, percentages of participants with a current co-morbid axis 1 disorder varied between 41% (24) and 92% (39). Taking these findings together, we can say that a limitation may be that participants of included studies were people with relatively severe forms of somatoform disorders and MUPS. The milder forms, with lower levels of co-morbidity may have been underrepresented. In contrast, people with milder symptoms may need less intensive therapy.

Interventions

Fourteen of the included studies compared CBT with another intervention. As a result, relatively robust conclusions could be drawn about the effectiveness of CBT. The number of studies describing other psychological therapies (such as behavioural therapies, third-wave CBT, or psychodynamic therapies) was too low to draw conclusions about these forms of therapy. Duration and number of treatment sessions varied widely between the included studies.

It is especially remarkable that we found no studies on physical therapies (such as running therapy). We believe that there is a clear need for this type of research.

Many included studies used forms of enhanced care or other forms of therapy as the control treatment. A limitation of this method may be an underestimation of the treatment effect, due to small inter-group differences. This is illustrated since these studies found fewer and smaller effects than studies comparing a treatment with usual care.

Outcomes

In this review, the outcome of functional impairment introduced a problem, as a certain number of studies used SF-36 subscales as the outcome measure. As a result, we reported physical functioning and mental functioning or even subdomains separately. We decided to pool the two main domains into one outcome, but this led to the limitation that differences in effects for physical and mental functioning, as found in some studies (24), disappeared.

Another problem of the current review was that, with one exception, there were not enough studies to assess reporting bias with funnel plots. According to recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions*, there should be at least 10 studies to perform this (21). In future updates of this review, the addition of new studies may enable us to produce funnel plots for more comparisons and outcomes.

Adverse effects were very infrequently reported and various ways of reporting were used. Therefore, it was impossible to extract these in a standardised way in order to include them in our meta-analytical calculations, except for the first comparison (psychological therapy versus usual care or waiting list). We also have to emphasise again that RCTs and CRCTs are not sufficient to gain information about the more rare or longer-term (or both) adverse events.

Quality of the evidence

According to the first quality criterion risk of bias defined by the guidelines by GRADE, Figure 2 and Figure 3 showed that in regard to different types of biases most of our included studies showed a low risk. However, a few specific domains were often rated as being at high risk of bias across the studies. Especially for blinding of the outcome measurement, we identified a high risk of bias in most of the included studies. Most studies could not blind the outcome reporters, mostly the participants, due to the nature of the intervention. A high risk of bias in blinding of participants and personnel was found for the same reason. Nine studies (43% of studies) reported incomplete outcomes, defined as a loss to follow-up of more than 20%. Reasons for loss to follow-up were not systematically described. Another study aspect that affected the quality of the evidence was the generally low number of included participants per study. It has to be taken into account that several of the included studies were performed before the publication and implementation of current quality criteria for conducting and reporting RCTs.

The small number of studies did not allow us to assess the effects in subgroups of participants or interventions. Apart from CBT, all other comparisons between specific therapies and usual care or enhanced care, the number of studies was too small (often only one study). We did not consider indirectness (a GRADE item comparing the interventions and outcomes in which we are interested to what was actually studied in the included studies) and publication bias to be important sources of risk of bias, publication bias because of our thorough search process; the overall completeness of reporting, and the fact that several studies that did not find an effect.

Potential biases in the review process

This review has several methodological strengths. The quality of meta-analyses depends on the robustness of the search methods used. In this review, the electronic search was thorough and large in scale with broad parameters. We evaluated published and unpublished studies. The selection criteria were broad, which led to the selection of a relatively high number of studies. We also included non-English studies. As a result, it seems likely that all or almost all evidence in the searched databases that should have been included was included. However, as we did not search Asian databases, this may have led to a potential bias.

The study was performed according to a pre-published protocol. Different review authors performed evaluation of studies for selection, extract data, and assess risk of bias, with the possibility of consulting another review author to resolve disputes. However, due to the fact that not all choices that had to be made were foreseen, there were also post hoc decisions. Excluding studies that trained GPs to deliver some psychological therapy was one of these decisions. In addition, we performed the allocation of the included studies to the different groups of treatment for analyses post hoc. Another post hoc decision was the addition of enhanced or structured care as a comparator. We made decisions very carefully and included achieving consensus between several review authors with specific knowledge in the field. However, some studies were difficult to categorise, as, for example, treatments included elements of different treatment categories. Therefore, allocation of these studies remained slightly arbitrary. Another post hoc decision was to combine the physical component scale and the mental component scale of the SF-36 into one outcome. Other post hoc decisions were to carry out sensitivity analyses by excluding studies that included consultation letters in both study groups, and by excluding studies with the least intensive interventions.

Although we attempted to obtain missing data from the authors of included studies, it was not possible in every case to obtain these data, and, therefore, the included studies were not represented fully in the meta-analyses. This may also have led to a certain form of bias, although it is difficult to say in what direction this bias would be.

As described in the section Types of outcome measures, we aimed to retrieve data about severity/intensity of MUPS; acceptability; depression and anxiety; dysfunctional cognitions, emotions, or behaviours; adverse events; treatment response; functional disability; and quality of life. However, the number of studies reporting on many of our outcomes was relatively low. Results about depression; anxiety; dysfunctional cognitions, emotions, and behaviours; adverse events; and treatment response were frequently lacking. Therefore, we could not draw robust conclusions about these outcome measures.

Although acceptability was a primary outcome of our study, we restricted this to the period from randomisation to the end of treatment. We did not take into account the acceptability of the interventions in the recruitment phase. Participants for whom the intervention or control condition was unattractive probably did not participate. This affects the external validity of study findings.

In this review, we used point estimates at all follow-up periods to evaluate treatment effect, instead of scores based on change from baseline. We chose this method as these results were retrievable from most of the studies, and combining follow-up outcome data with change from baseline data was considered inappropriate given our choice of SMDs due to the variety of outcome measures that had to be combined. However, pooling the results of follow-up measurements has the disadvantage that baseline values (and possible baseline differences) are not taken into account. As data were pooled in most analyses, we believe that distortions such as these are generally corrected by the other studies in the analyses. Some studies only reported data about change from baseline (without the actual baseline data) (e.g. 26, 50). These data could not be used in this review. We contacted authors in order to be obtain the required data, and were successful in many cases though not all.

Agreements and disagreements with other studies or reviews

Several systematic reviews have addressed non-pharmacological treatments for participants with some form of somatoform disorder or MUPS (e.g. 54, 55, 15). As many of the included studies in our review were published after 2005, we focused this discussion on the systematic reviews that were published after 2005. In general, we can say that the results of this review are in line with results of existing reviews. In most reviews, the majority of included studies concerned CBT in some form, and small effect sizes were found. In other reviews, also limited evidence was found for other forms of psychological therapies. Studies investigating physical therapies for somatoform disorders or MUPS were also hardly reported in other reviews.

Authors' conclusions

Implications for practice

The overall quality of the evidence provided by 21 randomised controlled trials was low to moderate. All psychological therapies combined were superior to usual care or waiting list condition for symptom severity, our first primary outcome, but effect sizes were small. As a single treatment, only cognitive behavioural therapy (CBT) was adequately studied to allow conclusions for practice. Compared with usual care or waiting list conditions, CBT reduced somatic symptoms, with a small effect and substantial differences in effects between CBT studies. The effects were durable within and after one year of follow-up.

Compared with enhanced or structured care, psychological therapies generally were not more effective for most of the outcomes. CBT was also not superior to enhanced care. The question remains how specific CBT is over structured improvements of care. No major adverse events were reported in the intervention groups, although most studies did not describe adverse events as an explicit outcome measure. Apart from CBT, neither psychological nor other non-pharmacological therapies have been adequately studied.

In daily practice, a substantial percentage of people with medically unexplained physical symptoms (MUPS) may not be willing to accept psychologically oriented treatments. Whether such acceptance is associated with the effect of psychological treatments for the total MUPS population was not clear. Due to the small number of studies, we could not draw conclusions about the effect of characteristics such as a profession and experience of the therapist, about treatment intensity and treatment location, on treatment efficacy.

Further optimisation of CBT to target optimal participant profiles and match treatment providers, treatment characteristics, and participants could improve outcomes. Motivating and preparing people for CBT is important for this participant group. As drop-out rates were not much lower than in control groups, this indicates that when a person has accepted involvement in the treatment, the prospects that the treatment will be completed are good.

Implications for research

Based on the findings in this review, we can make several recommendations for future research. The number of studies investigating various treatment modalities other than CBT needs to increase to build a broader and more varied evidence-base for the treatment of somatoform disorders and MUPS. As physical therapies may offer a more acceptable starting point for treatment for these people than psychological approaches, investigating the effectiveness of physical therapies is to be considered. We found no such studies.

Most studies in our review focused on chronic manifestations of physical symptoms, often of considerable severity. It is conceivable that interventions were more effective in people with milder symptoms, or of shorter duration, but this needs further testing. A related conceptual issue is that chronic conditions deserve a World Health Organization chronic care or chain care approach as acute treatments will not suffice. Preventing symptoms from become chronic may be a relevant outcome to be added in future studies.

In future research, more attention should be paid to the impact of interventions on risk factors for recurrence and persistence of symptoms in somatoform disorders and MUPS. These factors include anxiety; depression; and dysfunctional cognitions, emotions, and behaviours. Most included studies in this review did not report on all of these factors. Specific attention to the effect of treatment duration and number of treatment sessions is also needed. In the studies included in this review, duration and number of sessions varied widely, and it is yet unclear which treatment intensities are effective for which participants.

Psychological treatments were not superior to enhanced care. It could be argued that an active comparator such as enhanced care underestimates treatment effects. However, as this comparative treatment is probably cheaper than more intensive psychological interventions, it would deserve further study.

In our view, teaching people how to tolerate uncertainty and deal with their bodily symptoms can be problematic and will probably always involve high levels of clinical skills. One potential intermediate factor is the amount of trust that people have in their therapist or physician, a factor to be taken into account in the design of new studies.

There is a clear need for developing and testing strategies for motivating and preparing people for CBT. CBT is the only evidence-based psychological treatment available at the moment.

A more structural question is, how psychological therapies for participants with somatoform disorders can be better integrated into the healthcare system. Can the healthcare system be restructured in such a way that it facilitates the access of people with somatoform disorders to psychological therapies?

As the cost of treatment can be substantial, but also the cost of the disorder in terms of absenteeism and healthcare use, cost-effectiveness needs to be addressed in future studies.

Future studies should include more participants, preferably use a uniform set of validated outcome measurements, and extend follow-up assessments beyond one year after treatment.

Finally, as newer-generation antidepressants and particularly natural products also reduce somatic symptoms, a preference-led or profile-led approach may be possible. The aim would be to evaluate to what extent an intervention (consisting of a choice between non-pharmacological and pharmacological therapy combined with chain care), would improve symptoms over usual care.

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