Developing e-health applications to promote a patient-centered approach to medically unexplained symptoms

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CHAPTER 3

3

Self-help for medically unexplained symptoms: a systematic review and meta-analysis.

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ABSTRACT

Background: Medically unexplained symptoms (MUS), which are highly prevalent in all fields of medicine, are considered difficult to treat. The primary objective of this systematic review and meta-analysis was to assess the efficacy of self-help for adults with MUS.

Methods: Four electronic databases were searched for relevant studies. Randomized controlled trials comparing self-help to usual care or waiting list in adults with MUS were selected. Studies were critically appraised using the Cochrane 'risk of bias assessment tool'. Standardized mean differences (Hedges' g) were pooled using a random-effects model. Outcomes were symptom severity and quality of life (QoL) directly post-treatment and at follow-up.

Results: Out of 582 studies identified, 18 studies met all inclusion criteria. Studies were heterogeneous with regard to patient populations, intervention characteristics, and outcome measures. Compared to usual care or waiting list, self-help was associated with lower symptom severity (17 studies, n = 1894, g = 0.58, 95% CI 0.32 – 0.84, p < .001) and higher QoL (16 studies, n = 1504, g = 0.66, 95% CI 0.34 – 0.99, p < .001) directly post-treatment. Similar effect sizes were found at follow-up. A high risk of bias was established in the majority of included studies. However, sensitivity analyses suggested that this did not significantly influence study results. Funnel plot asymmetry indicated potential publication bias.

Conclusions: Self-help is associated with a significant reduction in symptom severity and improvement of QoL. Due to the suboptimal methodological quality of included studies, further research is needed to confirm the findings of this study.

INTRODUCTION

Medically unexplained symptoms (MUS) are physical symptoms, which cannot be adequately explained by organic disease. MUS are highly prevalent and range from single, self-limiting complaints to constellations of chronic and disabling symptoms like irritable bowel syndrome (IBS), fibromyalgia, and chronic fatigue syndrome (CFS) (1). Apart from the suffering and impairments these conditions impose on patients, they are also very costly for society due to the associated productivity losses and burden on health care (2-4). Patients with MUS visit their general practitioner, medical specialist, and emergency department approximately twice as often as other patients (2), ranking their medical costs among the highest of all patient groups (4).

Physicians consider patients with chronic MUS among the most difficult patients (5), probably because treatment possibilities within somatic healthcare are limited (6). Psychological treatments, like cognitive behavioral therapy (CBT), have shown modest effects on symptom severity and quality of life (QoL) in patients with chronic MUS (7, 8). However, psychological treatments are costly, time consuming, and often not easily available due to a shortage of qualified therapists. Furthermore, many patients with MUS are unwilling to visit a mental health professional, because of the associated stigma (9). As a consequence, only a selected subgroup of patients with MUS benefits from psychological treatment. Self-help interventions, which are designed to be conducted largely independently of health care professionals, might overcome these problems and form a valuable addition to current treatment options. Self-help has shown to be effective for a number of conditions like depression, anxiety, and alcohol abuse (10-12). Apart from three systematic reviews on specific forms of self-help for IBS (13-15), no overview has been published on the efficacy of self-help interventions for MUS in general.

Following the PRISMA statement (16), we report on a systematic review and meta-analysis of randomized controlled trials with the primary aim of assessing efficacy of self-help in adults with MUS with regard to symptom severity and QoL. Because we included a variety of MUS, investigating whether treatment efficacy varied according to the type of symptoms was a secondary aim. Studies in patients with depression and anxiety have indicated that guided self-help is associated with better outcomes than unguided self-help (17, 18). Therefore, another secondary aim was to study the influence of therapist contact on treatment efficacy.

METHODS

Search Strategy

Relevant studies were identified by searching electronic databases and scanning reference lists of included articles and related reviews (13-15, 19-21). The following electronic databases were searched from their inception up to May 2014: PubMed, Embase, PsycINFO, and CINAHL. A combination of two sets of text words and indexing (MeSH) terms was used. The first set consisted of the terms MUS, IBS, fibromyalgia, CFS, somatoform disorder, somatization, conversion, and synonyms. In accordance with current recommendations, medical as well as psychiatric diagnostic concepts were incorporated in the search (22). The second set consisted of the terms self-help, self-management, self-care, self-administered, bibliotherapy, and synonyms. Where possible, a filter for randomized controlled trials was applied. In order to reduce risk of bias, searches were conducted without restrictions on language or publication date.

Study Selection

Two researchers (JMG and AG) independently selected studies based on pre-specified eligibility criteria. After removal of duplicates, articles that were identified through the literature search were screened for relevance on the basis of their title and abstract. Subsequently, full text articles of potentially relevant studies were obtained and examined. During both stages, differences in study selection were resolved through consensus.

Inclusion criteria: Studies were considered eligible if they were (1) randomized controlled trials (RCTs) comparing the effects of (2) a self-help intervention (3) to a waiting list or usual care control condition (4) in adults (5) with MUS (6) on symptom severity and QoL.
Self-help was defined as a therapeutic intervention, administered through text (printed or online), audio, or video, and conducted (largely) independently of a health care professional. Guided self-help interventions with minimal therapist contact of facilitative or supportive nature were also considered. MUS were defined as physical symptoms which, after appropriate medical assessment, could not be (fully) explained by a medical disease. The nature of these symptoms may vary considerably. However, research has shown that substantial overlap exists between syndromes such as IBS, fibromyalgia, and CFS (23). Assuming that similarities between patients with MUS outweigh their differences, we decided to include a broad array of medically unexplained symptoms and syndromes into our review.

Data Extraction

Data were extracted independently by two researchers (IJB and AG) using standardized forms that were developed a priori. Disagreements were resolved by discussion.

The following data were extracted from each article: study details (first author, publication year, and country), design, sample size (numbers randomized and analyzed), sample characteristics (in- and exclusion criteria, recruitment setting, mean age, percentage of women, symptom duration and severity, and comorbidity), type of intervention (form, theoretical basis, duration, amount of therapist contact) and comparison group (waiting list or care as usual), timing of follow-up assessments, drop-out and compliance, outcome measures, adverse events, and effects (mean and standard deviation of symptom severity and QoL for intervention and control group directly post-treatment and – if available – at follow-up). Some studies did not report all of these outcome data. We contacted seven authors in order to obtain missing outcome data. All of them responded and five were able to provide all of the requested data.

Risk of Bias Assessment

Eligible studies were critically appraised using the Cochrane 'risk of bias assessment tool' (24). This tool determines possible sources of bias in the reporting of RCTs in six domains: (1) allocation sequence generation; (2) allocation concealment; (3) blinding of participants, personnel, and outcome assessors; (4) management of incomplete outcome data; (5) selective outcome reporting, and (6) other sources of bias, like extreme baseline imbalances. Each of these criteria was separately rated as "met", "unmet", or "unclear" by two independent researchers (IJB and AG), corresponding with a low, high or unclear risk of bias in that domain. Disagreements were resolved through consensus.

Data Analysis

Effect Size Calculation. Outcomes of interest were symptom severity and QoL. Most of the included studies reported both of these outcomes with continuous measures. However, different measurement instruments were used. Also, few studies reported effect sizes, and those that did used different methods to calculate effect estimates. Therefore, standardized mean differences were calculated for each study (Cohen's d = difference in post-treatment means between intervention and control group divided by the pooled standard deviation) (25). Because Cohen's d has a slight bias that overestimates the effect size in small samples, d was multiplied by a correction factor J, resulting in the unbiased estimate referred to as Hedges' g (25). For each outcome, we distinguished between post-treatment and follow-up assessments. This led to a maximum of four effect estimates per study: symptom severity post-treatment, symptom severity at follow-up, QoL post-treatment, and QoL at follow-up. Summary statistics used to calculate these estimates (means, standard deviations, and number of participants for treatment and control groups) can be obtained from the corresponding author on request. The sign of some scores was reversed to ensure all scales were aligned (e.g. for QoL high values representing good health on all scales). For two studies, standard deviations were calculated from the reported 95%-confidence interval (26,

27). For one study (28), continuous outcome data on symptom severity were not available, but the numbers of patients with persistent symptoms at several follow-up moments were. We used these data to calculate odds ratios and converted these, via Cohen's *d*, to Hedges' *g* (25). For another study, post-treatment QoL data were not available, but follow-up data were (29). We replaced the missing post-treatment effect estimate by the follow-up effect estimate of that study.

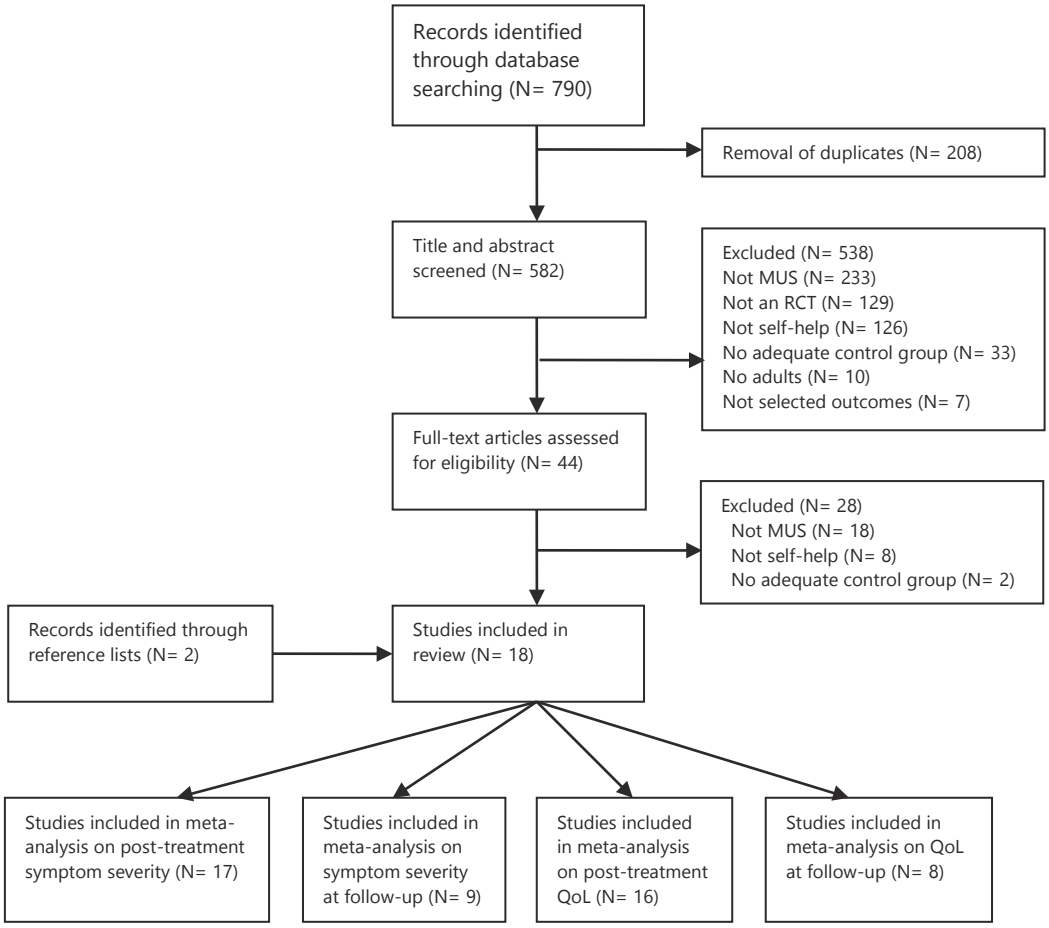
Meta-analysis. The pre-calculated effect estimates were pooled using STATA 13.1. Because of the heterogeneous nature of study populations and interventions, the DerSimonian and Laird random-effects method was chosen. The I^2 statistic was used as a measure of heterogeneity. This is the percentage of between-study heterogeneity that is attributable to variability in the true treatment effect, rather than sampling variation (30). Roughly, an I^2 >75% represents considerable heterogeneity (24). For the interpretation of effect sizes, we followed the rule of thumb as proposed by Cohen: 0.20-0.49 is considered small, 0.50-0.79 medium, and >0.80 large (31). In order to assess the influence of the risk of bias of individual studies on treatment effects, sensitivity analyses were performed using three meta-regression analyses with different sources of bias (low or unclear versus high risk) as covariates. To explore the possibility of publication bias, the symmetry of funnel plots was assessed visually as well as formally with Egger's test. To investigate whether treatment efficacy would differ depending on symptom type, meta-regression was used. Symptoms were divided into four categories: chronic pain (including fibromyalgia, whiplash associated disorder (WAD), or back pain), IBS, CFS, and functional neurological symptoms. Dummies for these four symptom types were used in separate analyses to test whether one of these showed larger treatment effects compared to the other symptom types. Finally, we also used meta-regression to study the influence of therapist involvement (none versus some form of therapist contact) on treatment efficacy. For all meta-regression analyses, post-treatment outcomes were used.

RESULTS

Study Selection

The process of study selection is presented in Figure 1. Searching four electronic databases provided 582 unique citations. Of these, 538 studies were discarded because, after reviewing their title and/or abstract, they did not meet our criteria. Full-text articles of the remaining 44 citations were examined. During this stage, another 28 articles were excluded, leaving 16 eligible studies. Two more studies were identified through reference lists, resulting in a total of 18 studies meeting all eligibility criteria.

Figure 1. Flow diagram of study selection.



Note. MUS = medically unexplained symptoms; RCT = randomized controlled trial; QoL = quality of life.

Characteristics of Included Studies

An overview of study characteristics can be found in table 1. All 18 included studies were RCTs published in English during the last decade. Most studies were performed in the U.S.A. (8/18), followed by the U.K. (3/18) and the Netherlands (3/18).

Participants: Most studies focused on patients with IBS (7/18) or chronic pain (fibromyalgia, WAD, or back pain; 7/18). Three studies involved patients with CFS and one study focused on patients with functional neurological symptoms. Sample size ranged from 28 to 405 participants. Participants were predominantly female (58-100%) and middle-aged (mean age 36-52 years). Mean duration of symptoms was reported in about half of the studies and ranged from 4.5 to 16.5 years, suggesting that most participants suffered from chronic MUS. Co-morbidity, somatic as well as psychiatric, was rarely reported.

Interventions: Nearly all interventions contained educational elements. For some interventions, these were their main ingredient (5/18); for others these formed the base for self-administered CBT (12/18). The study by Robinson et al. is an example of a purely educational intervention. In this study, IBS patients were provided with a guidebook containing information about lifestyle, diet, pharmacological, and alternative therapies (32). In two other studies (28, 33), patients presenting to an emergency department with a whiplash injury were shown a short educational video. The video provided information about expected duration of symptoms and advice on posture, return to regular activities, exercise, and pain-relief methods. This is somewhat similar to an online intervention (34), in which office workers with low back pain received daily e-mail reminders linked to information and videos on posture and physical exercise. Most studies however, also included elements of CBT: relaxation exercises, stress management, problem solving, identifying and challenging unhelpful thoughts (catastrophizing), and graded exposure. Most interventions included homework assignments. One study investigated a specific component of CBT called 'guided imagery'. Using audiotapes, participants were taught to "imagine and experience an internal reality in the absence of external stimuli" (35). Finally, Brattberg examined the self-administration of 'emotional freedom techniques' in patients with fibromyalgia. This intervention combines elements of cognitive therapy, acupuncture, and eye movement desensitization and reprocessing (EMDR). It involves focusing on a disturbing memory, emotion, or sensation, while simultaneously tapping meridians, ending with a series of eye movements (36). Apart from the two studies in which treatment consisted of watching a single video (with a duration of 12-20 minutes), duration of treatment varied from 4 weeks to 9 months. Seven studies did not involve any therapist contact. In the remaining studies, various forms and quantities of therapist contact were incorporated.

Control: Six studies used a waiting list control group (36, 38-40, 42, 44). In eleven studies, the control group received 'care as usual' (27-29, 32-35, 37, 41, 43, 45). Very few articles provided information on the nature or content of 'care as usual'. Two studies described that patients in both groups received a fact sheet containing information on their diagnosis and/or advice on managing their symptoms (29, 33). Finally, one study had a slightly different control group (26). In this study, participants with IBS were randomized into nine groups. Groups were based on a combination of self help (no website, website, or website + e-mail support) and medication (bulk-forming laxative, antispasmodic, or placebo). Since these medications are commonly prescribed for IBS, we chose to consider these as 'usual care' and divided the groups as follows: intervention (website and website + e-mail support) versus control (no website), regardless of the medication groups.

Outcomes: Although most studies included one or more follow-up assessments, seven studies only assessed outcomes directly post-treatment. Duration of follow-up ranged from two weeks to one year. All studies evaluated symptom severity as an outcome, but since different types of MUS were studied, different measurement instruments were used. Three out of seven studies on IBS used the IBS symptom severity scale (IBS-SSS). The checklist individual strength (CIS) was used to assess fatigue in two out of three studies on CFS. Many different instruments were used to assess pain. Seventeen studies evaluated QoL as an outcome, using a variety of instruments. Most instruments, for example the IBS quality of life questionnaire (IBS-QOL) which is used in 6 studies, evaluated several aspects of physical, mental, and/or social functioning. The SF-36 physical functioning scale was also a commonly used instrument (5 studies). This is a subscale of the SF-36, which specifically focuses on physical impairments due to health problems. None of the studies explicitly defined adverse events as an outcome. Occasionally, it was reported that no adverse events occurred in the intervention group (34, 40, 43).

Risk of Bias within Studies

Since blinding of participants with regard to self-help interventions is impossible and nearly all studies used self-report measures, a high risk of bias in this domain ('blinding of participants, personnel, and outcome assessors') was inevitable. Regarding the other five domains, a high risk of bias was established in eleven studies (Figure 2). All of these eleven studies showed an imbalance in dropout rates across groups or did not adequately address missing outcome data. Additionally, allocation sequence was not adequately generated and concealed in two studies. Two other studies had a high risk of bias due to selective outcome reporting: based on published protocols, we concluded that not all of their pre-specified outcomes were reported.

Table 1. General characteristics of RCTs on self-help for MUS.

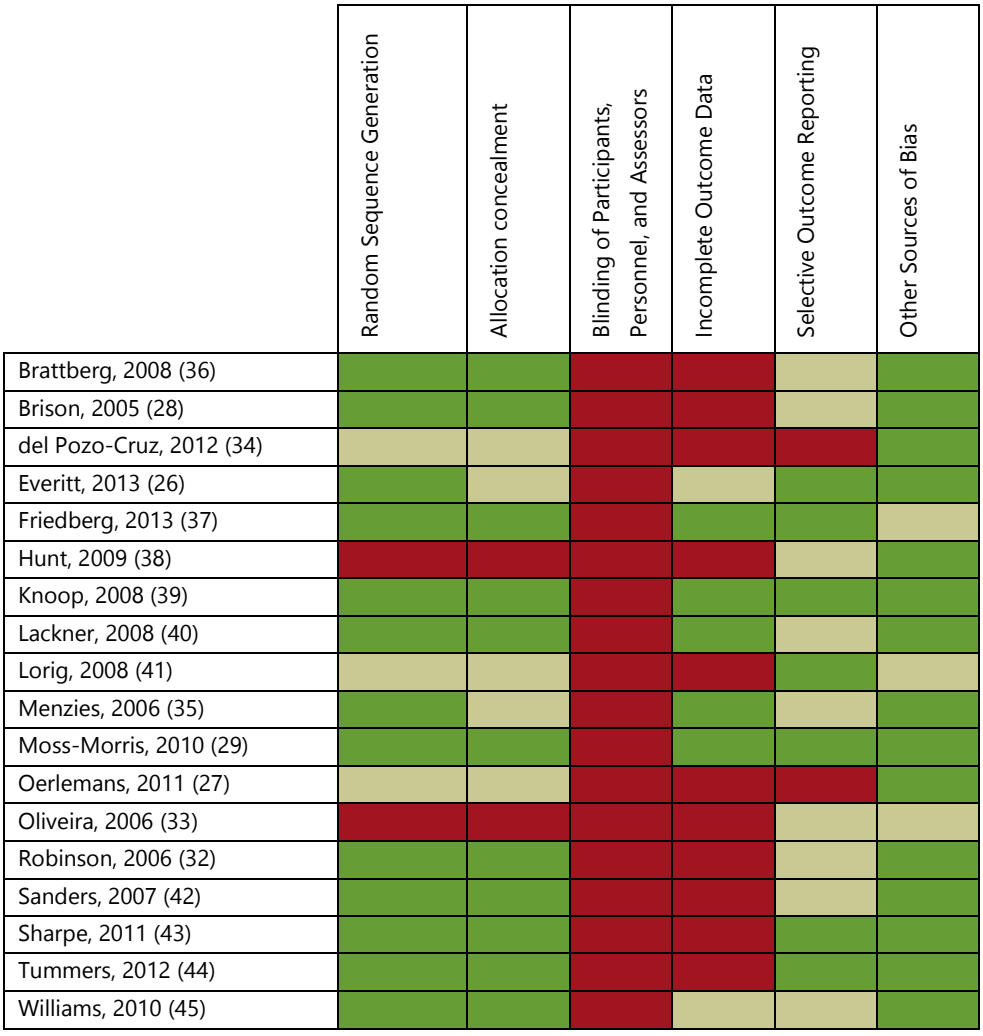
First author, year	N randomized	Type of MUS	Recruitment Setting	Treatment Form	Theoretical Framework	Therapist Contact	Treatment Duration	Follow-up
Brattberg, 2008 (36)	86	Fibromyalgia	Advertisements in newspaper and online discussion forums	Website	EFT	E-mail contact 1x/week	8 weeks	Post-treatment
Brison, 2005 (28)	405	WAD	Tertiary care (emergency departments)	Video	Educational	None	20 minutes	2, 6, 12, 24, and 52 weeks
del Pozo-Cruz, 2012 (34)	100	Back pain	Advertisements	Website, video	Educational	None	9 months	Post-treatment
Everitt, 2013 (26)	135	IBS	Primary care	Website	CBT	30 minutes telephone contact + email support on request or technical email support on request	6 weeks	Post-treatment and 12 weeks
Friedberg, 2013 (37)	73*	CFS	Primary care	Booklet	CBT	Max. 2x 1 hour face-to-face contact	3 months	Post-treatment and 12 months
Hunt, 2009 (38)	54	IBS	Online advertisements	Website	CBT	E-mail contact 1x/week	5 weeks	Post-treatment
Knoop, 2008 (39)	171	CFS	Tertiary care	Booklet	CBT	E-mail contact 1x/2 weeks	≥16 weeks	Post-treatment
Lackner, 2008 (40)	52†	IBS	Secondary care (gastroenterology) and advertisements	Booklet	CBT	4x 1 hour face-to-face + 2x 10 minutes telephone contact	10 weeks	12 weeks
Lorig, 2008 (41)	NR‡	Fibromyalgia	Advertisements websites, newsletters, and online forums	Website	Educational, CBT elements	E-mail reminders	6 weeks	6 and 12 months

Table 1 (continued). General characteristics of RCTs on self-help for MUS.

Menzies, 2006 (35)	48	Fibromyalgia	Secondary care	Audio	CBT: Guided Imagery	None	6 weeks	Post-treatment and 10 weeks
Moss-Morris, 2010 (29)	64	IBS	Primary care	Booklet	CBT	1 hour face-to-face + 2x 1 hour telephone contact	7 weeks	Post-treatment, 5 and 8 months
Oerlemans, 2011 (27)	76	IBS	Advertisements IBS patient association	PDA	CBT	Feedback through text messages during 3 weeks	4 weeks	Post-treatment and 3 months
Oliveira, 2006 (33)	126	WAD	Secondary care (emergency departments)	Video	Educational	None	12 minutes	1, 3, 6 months
Robinson, 2006 (32)	281§	IBS	Primary care	Booklet	Educational	None	N.R.	12 months
Sanders, 2007 (42)	28	IBS	Secondary care (gastroenterology) and advertisements	Booklet	CBT	None	≥10 weeks	Post-treatment
Sharpe, 2011 (43)	127	Neurological	Secondary care (neurology)	Booklet	CBT	Max. 4x 30 minutes face-to-face/ telephone contact	3 months	Post-treatment and 6 months
Tummers, 2012 (44)	123	CFS	Secondary care (psychiatry)	Booklet	CBT	E-mail contact 1x/2 weeks	≥20 weeks	Post-treatment
Williams, 2010 (45)	118	Fibromyalgia	Primary and secondary care	Website	CBT	None	6 months	Post-treatment

Note. MUS = medically unexplained symptoms; NR = not reported; WAD = whiplash associated disorder; IBS = irritable bowel syndrome; CFS = chronic fatigue syndrome; EFT = emotional freedom techniques; CBT = cognitive behavioral therapy; *111 participants were randomized into three groups. For our analyses, we only included two groups (self-management and usual care). †75 participants were randomized into three groups. For our analyses, we only included two groups (minimal contact CBT and waiting list). ‡855 participants were randomized, but these are patients with different types of chronic pain, including rheumatoid arthritis and osteoarthritis. For the meta-analysis, we only included participants with fibromyalgia (no other rheumatologic conditions). §420 participants were randomized into three groups. For our analyses, we only included two groups (guidebook and control group)

Figure 2. Risk of bias assessment.



Meta-regression showed that the risk of bias of included studies (low or unclear versus high) did not significantly influence our main results (Table 2). This applies to all relevant sources of bias: randomization, management of incomplete outcome data, and selective outcome reporting.

Table 2. Results sensitivity analysis showing effects of different sources of bias.

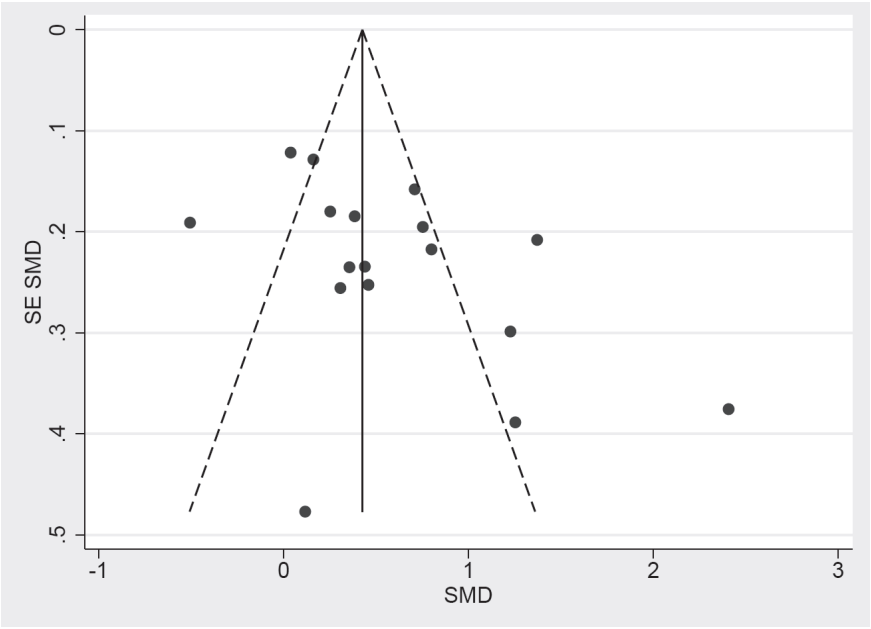
	Symptom severity			Quality of life		
Possible source of bias	**Estimate**	**95% CI**	**p**	**Estimate**	**95% CI**	**p**
Random Sequence Generation and Allocation Concealment	.83	-.16 – 1.82	.10	.53	-.81 – 1.87	.41
Incomplete Outcome Data	-.14	-.83 – .55	.67	.02	-.88 – .92	.96
Selective Outcome Reporting	-.01	-1.06 – 1.04	.98	.69	-.61 – 1.98	.28

Note. Results of meta-regression with post-treatment outcomes.

Publication Bias

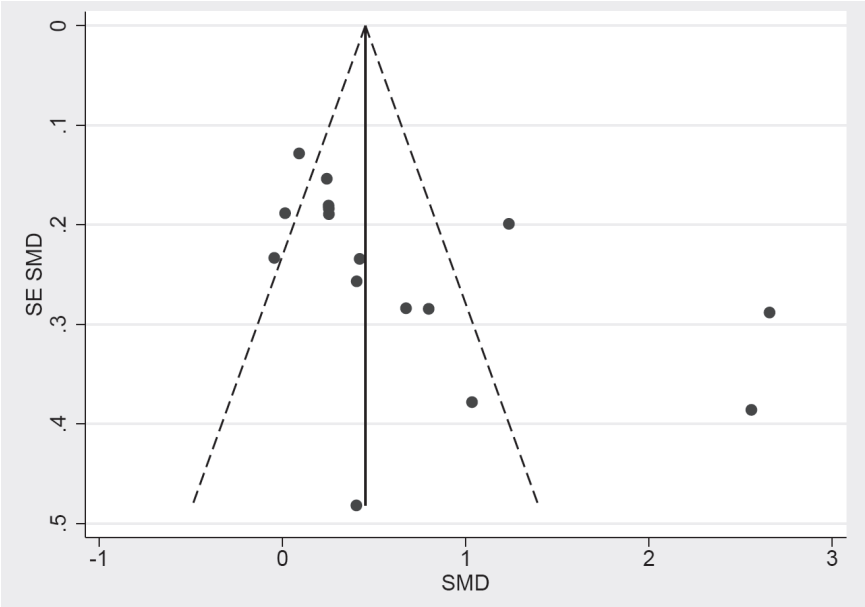
Visual assessment as well as Egger's test showed that the funnel plots for symptom severity (4.00, 95% CI 0.34 – 7.66, p = .03) and QoL (5.22, 95% CI 0.92 – 9.51, p = .02) displayed significant asymmetry (Figures 3 and 4).

Figure 3. Funnel plot (random effects model), for symptom severity.



Note. SMD = standardized mean difference (Hedges' g); SE = standard error.

Figure 4. Funnel plot (random effects model), for quality of life.



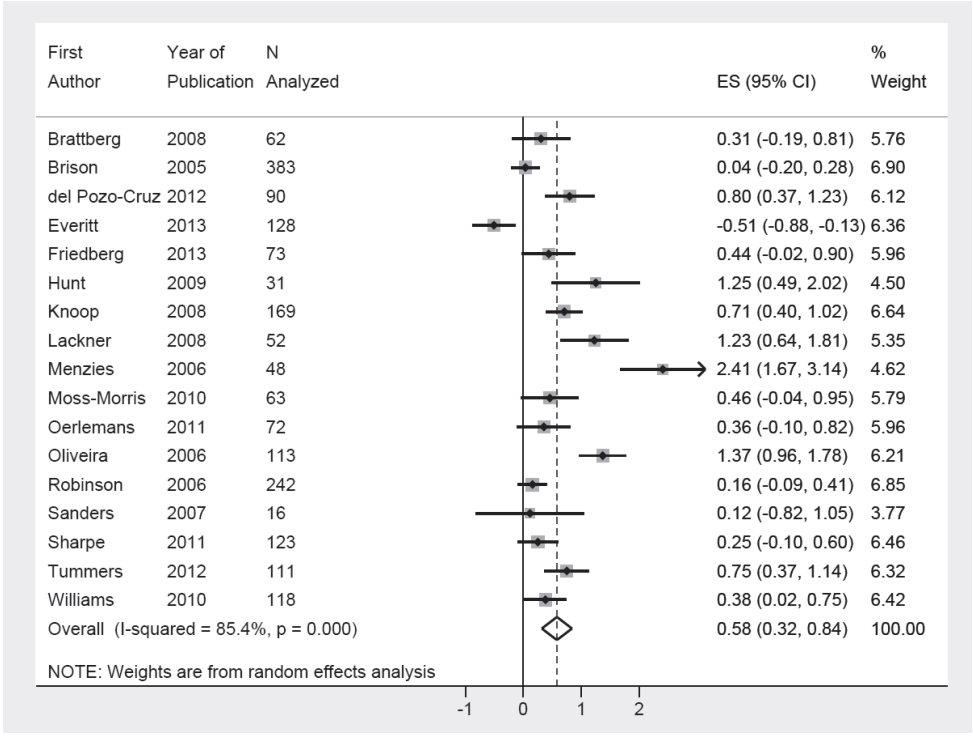
Note. SMD = standardized mean difference (Hedges' g); SE = standard error.

Effect of Self-Help on Symptom severity and Quality of Life

Post-treatment outcome data on symptom severity were available for 17 studies with a total of 2067 participants randomized and 1894 analyzed. Compared to control, self-help was associated with lower symptom severity (g = 0.58, 95% CI 0.32 – 0.84, p < .001) directly post-treatment (Figure 5). Strong evidence of heterogeneity was observed (I^2 =85%, 95% CI 78 – 90%, p < .001). At follow-up, self-help was still associated with lower symptom severity compared to control (9 studies, n = 922, g = 0.52, 95% CI 0.18 – 0.86, p = .002).

For QoL, post-treatment data from 16 studies were used with a total of 1662 participants randomized and 1504 analyzed. Compared to control, self-help was associated with a higher QoL (g = 0.66, 95% CI 0.34 – 0.99, p < .001), directly post-treatment (Figure 6). Strong evidence of heterogeneity was observed (I^2 =89%, 95% CI 83 – 92%, p < .001). At follow-up, self-help was still associated with a higher QoL compared to control (8 studies, n = 581, g = 0.73, 95% CI 0.25 – 1.21, p = .003).

Figure 5. Forest plot showing effects of self-help on symptom severity (N = 1894).



Note. Markers represent point estimates of standardized mean differences; marker size represents study weight in random-effects meta-analysis. Horizontal bars indicate 95% confidence intervals.

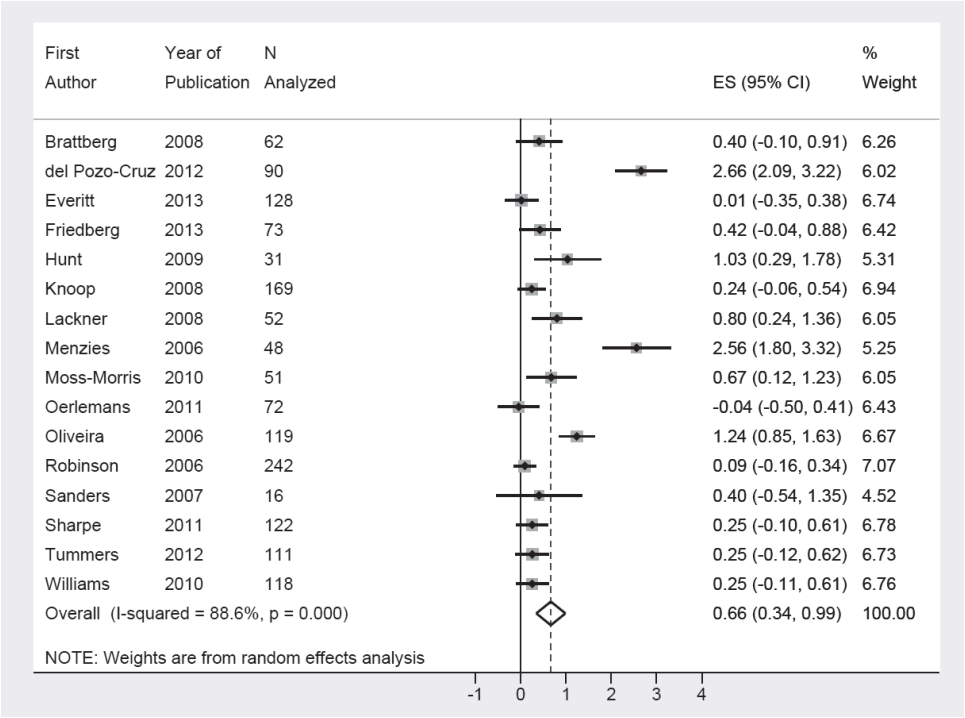
Type of Symptoms

Meta-regression showed that the effect of self-help on symptom severity was not significantly influenced by symptom type. The effect of self-help on QoL was significantly larger in patients with chronic pain (fibromyalgia, WAD, and back pain) compared to other symptom types (β = 1.00, 95% CI 0.23 – 1.77, p = .02).

Therapist Contact

Whether the interventions included some form of therapist contact did not significantly influence effects on symptom severity (β = -0.22, 95% CI -0.90 – 0.47, p = .51) or QoL (β = -0.77, 95% CI -1.59 – 0.04, p = .06).

Figure 6. Forest plot showing effects of self-help on quality of life (N = 1504).



Note. Markers represent point estimates of standardized mean differences; marker size represents study weight in random-effects meta-analysis. Horizontal bars indicate 95% confidence intervals.

DISCUSSION

This is the first study to quantify the effects of self-help interventions for various types of MUS. Meta-analysis showed that self-help significantly reduced symptom severity and improved QoL compared to usual care or waiting list. Overall, we found medium effect sizes. However, these should be interpreted with caution, because statistical heterogeneity between studies was considerable.

This meta-analysis has several methodological strengths. Four databases were searched with broad selection criteria. In order to reduce risk of bias, searches were conducted without restrictions on language or publication date. Study selection, data extraction, and risk of bias assessment were conducted independently by two researchers. After obtaining missing data from the original researchers, we were able to use data from all of the 18 studies that were identified during the systematic literature review. Although we included a substantial number of studies into our meta-analysis, it should be taken into account that heterogeneity

between these studies with regard to patient populations, intervention characteristics, and outcome measures was substantial. Specifically, the variety in QoL outcome measures has to be considered an important limitation. While most studies used instruments that assess several aspects of QoL, others used specific subscales assessing, for example, only physical functioning. Like for most meta-analyses, the results of our study are also limited by possible biases in included studies. First, the inevitable lack of blinding of participants causes a possible bias in all included studies. Furthermore, a high risk of bias in other domains was established in eleven studies (61%). These studies might have overestimated treatment effects because of inappropriate randomization, selective outcome reporting, or because incomplete outcome data were not adequately addressed. However, sensitivity analyses showed that our main results were not significantly influenced by the risk of bias of individual studies. We also assessed potential publication bias. Asymmetrical funnel plots suggested that selective reporting might have led to an overestimation of effect sizes in small trials.

In addition to three systematic reviews demonstrating positive effects of 'minimal contact' psychological treatments for patients with IBS (13-15), we have shown that a broad array of self-help interventions reduces symptom severity and improves QoL in patients with different types of MUS. The effect sizes we found were larger than those found for conventional psychotherapies. A recent Cochrane review on psychological treatments for MUS and somatoform disorder demonstrated small effect sizes for symptom severity (d = 0.34, 95% CI 0.16 – 0.53) and QoL (d = 0.17, 95% CI 0.03 – 0.32) (8). Similar results were found by another recent meta-analysis on psychotherapy for MUS (7). We found medium effect sizes for both outcomes (g = 0.58, 95% CI 0.32 – 0.84, and g = 0.66, 95% CI 0.34 – 0.99). This difference might be explained by the stricter inclusion criteria of those meta-analyses, resulting in patients with more severe symptoms and disabilities. Thus, self-help might be a useful additional treatment option, especially for patient with less severe, chronic, and debilitating symptoms.

Considerable heterogeneity in treatment effects was observed. We investigated two factors that might explain this heterogeneity. First, we explored the role of the type of symptoms. We found that the impact of self-help on symptom severity did not differ according to symptom type. However, the effect of self-help on QoL was larger in patients with chronic pain compared to other symptom types. Secondly, we explored the role of therapist contact. In our study, the level of therapist contact did not influence treatment outcomes. This contradicts the findings of studies on self-help in patients with depression and anxiety, for which guided self-help was found to be superior to unguided interventions (17, 18). This inconsistency might be explained by differences in study populations; patients with depression or anxiety disorders may have lower intrinsic motivation, which increases the

additional value of therapist guidance. Other factors that might explain heterogeneity of treatment effects are differences in study populations, like the duration of complaints, differences in the form, content, duration, and intensity of interventions, differences in the content and amount of care that is received in ('usual care') control conditions, and differences in the duration of follow-up. Unfortunately, due to the relatively small number of included studies, it was not possible to explore the role of these factors using statistical analyses. Further research will have to show which patients benefit most from self-help and which characteristics and elements of self-help interventions are associated with the best outcomes.

CONCLUSIONS

In conclusion, self-help is a promising form of treatment for patients with MUS. Especially when offered online, self-help can be made widely available at relatively low costs. Unguided, internet-based interventions might be implemented in primary care as a first step in a stepped care approach (46). If symptoms persevere, self-administered CBT with minimal therapist contact might offer an alternative to psychotherapy for patients who are unwilling or unable to visit a mental health care facility. Because the quality of research designs and reporting of included studies was far from optimal, further research is needed to confirm the findings of this study. To ensure transparency and consistency in the reporting of trials, the CONSORT statement and checklist should be followed (47). The content of intervention and control conditions should be described in detail. Furthermore, future studies should use uniform and validated measurement instruments. We strongly recommend the use of intention-to-treat analyses instead of completers-only analyses. Also, follow-up assessments are encouraged in order to study long-term effects of self-help interventions. Furthermore, future research should focus on the effectiveness of self-help in various clinical care settings and identification of moderators to optimize treatment effects and overcome potential barriers for implementation.

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