

What is the Evidence for the Efficacy of Treatments for Somatoform Disorders? A Critical Review of Previous Intervention Studies

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Objective: To review published literature for the highest level of evidence on the efficacy of treatment for patients with medically unexplained symptoms. **Methods:** A comprehensive literature search was carried out in Cochrane library, Medline (1971–2007), PsychINFO (1974–2006), and EMBASE (1980–2007) to identify pharmacological, nonpharmacological, psychological, and other interventions, using the search terms “medically unexplained symptoms,” “somatisation,” “somatization,” “somatoform disorders,” “psychological therapies,” “cognitive behavior therapy,” “pharmacological therapies,” “management,” “therapy,” “drug therapy,” and “anti-depressants” with Boolean operators AND and OR on the entire text. Searches were confined to literature in English. **Results:** Studies were carried out in primary, secondary, and tertiary care settings. The therapists ranged from medical specialists, psychiatrists, and psychologists to primary care physicians. Three types of interventions (antidepressant medication, cognitive behavioral therapy (CBT), and other nonspecific interventions) were supported by evidence on the efficacy of treatment for patients with medically unexplained symptoms. There is more level I evidence for CBT compared with the amount for other approaches. There was only one study reported from the developing world. **Conclusions:** CBT is efficacious for either symptom syndromes or for the broader category of medically unexplained symptoms, reducing physical symptoms, psychological distress, and disability. A relatively small number of studies were carried out in primary care, but the trend has been changing over the last decade. No studies have compared pharmacological and psychological treatments. Most trials assessed only short-term outcomes. Use of divergent selection procedures, interventions, outcome measures, and instruments, and other methodological differences observed in these studies hamper the ability to compare treatment effects across studies. **Key words:** medically unexplained symptoms, somatization, somatoform disorders, interventions, CBT.

CBT = cognitive behavioral therapy; **MUS** = medically unexplained symptoms; **RCT** = randomized controlled trial; **CFS** = chronic fatigue syndrome; **GP** = general practitioner; **PPC** = psychosocial primary care; **NCCP** = noncardiac chest pain.

INTRODUCTION

At least one-third of physical symptoms in medical care are medically unexplained (1). These symptoms are common all over the world and their health consequences are not a peculiarity to just one culture (2–5). Patients with these symptoms place a heavy burden on the health system because of disproportionate consumption of health resources (3,4,6,7). Therefore, the need for more research on the best management of medically unexplained symptoms (MUS) has been stressed for decades (8,9). The importance of developing simple and feasible but effective interventions, and demonstrating their effectiveness when applied in primary health care by a person without specialized psychiatric skills has also been reiterated (3).

It is therefore important to review from time to time the gaps in the evidence of best management of this challenging group of patients. It is also important to review interventions in primary care and examine the evidence from the developed and developing world, as the available resources may be different in these settings.

The symptoms unexplained by physical diagnosis are a heterogeneous group (2), and occur with depression, anxiety, hypochondriasis, and the other somatoform disorders (2,3,10–

13). But only half of the patients with MUS meet criteria for mood and anxiety diagnosis (14,15). Only a minority meet current *Diagnostic and Statistical Manual* (DSM) criteria for somatization disorder and less than 30% for somatoform disorder (15). Many symptom syndromes (approximately 13), such as irritable bowel syndrome and chronic fatigue syndrome are made up of combinations of MUS that cannot be assumed to be independent of one another. Overlap among these conditions is substantial (16–18). There are also patients with MUS who have neither physical disease nor severe mental illness (19).

Lack of clear operational criteria for the entire category of somatoform disorders leaves a substantial proportion of patients who present with MUS without a clear indication for medication or psychotherapy (20). But individuals who fall below diagnostic criteria can have significant social, emotional, and behavioral problems (21) that may respond to intervention. The difficulties in conceptualizing those presentations can affect the management of this group of patients.

Hence, the term MUS and patients presenting with MUS, were chosen to include all functional problems rather than the sub-groups who met the operational criteria for somatization disorder, conversion disorder, or symptoms syndromes. In formulating the review question and searching for interventions, the aim was to look at the issues with the perspective of public health relevance because patients do present with symptoms rather than with specific diagnostic categories.

Aim

This review attempted to answer the question, what is the highest level of evidence available for the efficacy of pharmaceutical and nonpharmaceutical interventions for patients with MUS and where have these studies been carried out?

The strength of evidence of the effectiveness of any intervention was assessed from a hierarchy based on study design. Search for evidence was confined to level I (systematic re-

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view) and level II (randomized controlled trial (RCT)) evidence. Adapting a hierarchical approach by examining the highest level of evidence was the aim. If evidence was present at level I, the review did not proceed further to obtain level II evidence. The aim was to identify the gaps and then to report any recent advances made since the last systematic review. Therefore, level II evidence (individual RCTs, published since last available systematic review) were also examined.

METHODS

Search Strategy

A comprehensive literature search was carried out using electronic databases: Cochrane library databases (up to 2007), Medline (1966–2007), PsychINFO (1974–2006), and EMBASE (1980–2007). Searches were confined to literature in English. In Cochrane library databases (1971–2007), the search terms “medically unexplained symptoms,” “somatisation,” “somatization,” and “somatoform disorders” were used first for a simple search, for each search term separately, followed by an advanced search combining all search fields with the Boolean operator OR in abstract, key words, or title. These search terms were then used again with the Boolean operator AND with the search fields individually and in combinations; psychological therapies, cognitive behavior therapy, pharmacological therapies, management, therapy, drug therapy, and antidepressants.

Results for Cochrane systematic reviews, other systematic reviews, and RCTs were scrutinized for suitable papers for this review (Table 1). Searches were repeated for Medline (1966–2007) and PsychINFO (1974–2006), as well as EMBASE (1980–2007, week 26), using the OVID database. However, the search terms were modified to suit the search strategies for these databases. To ensure a comprehensive review, search for literature was supplemented by examining the reference lists of the papers generated from the original searches.

Selection of Studies

The author with another colleague jointly scanned the abstracts identified by the electronic searches to select the potentially suitable papers. Abstracts eligible for inclusion were systematic reviews or randomized trials of a psychological (Table 2), pharmacological, or any other type of intervention involving an adult, with patients defined as medically unexplained symptoms, unexplained symptoms, somatoform disorders, somatisation, somatization, functional somatic symptoms, and the abstract was written in the English language.

Data Extraction

Initially, all abstracts that appeared relevant were selected as potentially suitable. The same two assessors then scrutinized them more carefully for definitive inclusion. All abstracts selected were checked for duplications, which, if found were excluded. Systematic reviews or RCTs exclusively on symptom syndromes, such as irritable bowel syndrome, chronic fatigue syndrome (CFS), and fibromyalgia, were excluded. Systematic reviews of MUS incorporating symptom syndromes, however, were included. Papers focusing on children and adolescents were also excluded.

RESULTS

Cochrane searches aggregated to 13 abstracts on systematic reviews and 421 RCTs during simple search. The combined search of all search words yielded 13 abstracts of systematic reviews and 355 of RCTs. The cases were performed in primary, secondary, or tertiary care. The therapists ranged from medical specialists, psychiatrists, and psychologists to primary care physicians. Search results from Medline, PsychINFO, and EMBASE did not yield any suitable systematic reviews. However, there were RCTs; 12, 6, and 8 from these respective databases.

Full-text papers of six potentially relevant systematic reviews were studied in detail. One paper on antidepressants and two on psychological interventions were excluded as they were not strictly systematic reviews even though they were otherwise valuable reviews. One systematic review from a thesis (26) and two other systematic reviews (27,28) were known to the author through previous work. Six systematic reviews were finally included in the review. The last systematic review was published in 2002 and reviewed studies up to 2000.

Two assessors identified 108 abstracts of RCTs that were retrieved for further scrutiny. Seventeen duplicate publications were identified and excluded. Fourteen trials published since 2000 were selected for this review.

TABLE 1. Search Results From Cochrane Library

Search field(s)	Cochrane Reviews	Other Reviews	RCT
Medically unexplained symptom/s	One relevant protocol on consultation letter (22)	One on CBT for MUS (23)	20 total but 12 were potentially suitable
Somatization	One review on psychosocial intervention by GP not relevant	Nil	20 total but 3 were potentially suitable
Somatization	Nil	One—CBT for somatization and symptom syndromes (24)	188 total but 29 were potentially suitable
Somatoform disorder/s	Two—one on psychodynamic psychotherapies for CMD, one on psychosocial intervention by GP. Both not relevant	10 in total but only 3 were relevant: CBT for MUS (23), CBT for somatization and symptom syndromes, CBT for somatization and symptom syndromes (24), and psychosocial interventions for MUS (25)	193 total but 78 were potentially suitable
Combination of MUS, somatisation, somatization, somatoform disorders,	3 identified but only 1 relevant protocol on consultation letters for MUS (22)	10 identified, only 3 suitable (23–25)	355 but 311 potentially suitable

TABLE 2. Summary of the Findings of Systematic Reviews on Psychological Interventions

Review Author(s)	Patient Group	Intervention	Conclusions by Authors
O'Malley	MUS including symptoms syndromes	Antidepressants	Effective in improving outcome, including symptoms and disability
Kroenke and Swindle (24)	Somatization, somatoform disorders, or persistent symptoms	Individual or group CBT	CBT effective for patients with somatization or symptom syndromes; reduction of physical complaints could occur whether or not psychological distress
Blankenstein (26)	Somatization	Individual or group CBT	CBT effective for somatization and symptom syndromes but the evidence for the effectiveness of CBT for somatization was limited
Nezu et al. (23)	MUS, somatization, somatoform disorders, or symptom syndromes	Individual or group CBT	CBT effective for all 4 categories of patients; improvement on physical symptoms and associated mood disturbances, and overall physical and social functioning for patients with MUS and CFS
Allen (25)	Somatization, somatoform, psychogenic, functional somatic syndrome	Psychosocial interventions	Effect sizes are modest at best. Although beneficial, have not shown a lasting influence on the physical complaints of polysymptomatic somatizers
Looper and Kirmayer (28)	Different diagnostic categories or symptom syndromes	CBT	Most studies used multiple treatment strategies but studies support the efficacy of individual CBT for symptom syndromes and MUS

Level I Evidence (Systematic Reviews)

Pharmacological Therapy

Only one systematic review on antidepressant medication including a meta-analysis qualified.

Antidepressant Medication

O'Malley et al. (27) identified papers by searching Medline (1966–1998), PsychLIT (1974–1998), EMBASE/Excerpta Medica (1974–1998), the Cochrane Library, the Federal Research in Progress database, and bibliographies of relevant articles. The emphasis was on adults with MUS but mainly those with at least one of six symptom syndromes: headache, fibromyalgia, functional gastrointestinal syndromes, idiopathic pain, tinnitus, and chronic fatigue. Ninety-four RCTs compared antidepressant medications; tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI) with placebo, and nonantidepressant medications. The majority of participants were women. Sixty-four (69%) studies demonstrated improvement of one or more of the following outcomes: global assessment (patient or physician), summary symptom index score, or pain severity score.

A meta-analysis showed benefits from antidepressant medication; the standard mean difference was 0.87 (95% confidence interval (CI) 0.59–1.14), or dichotomized outcomes of improvements, odds ratio of 3.4 (95% CI 2.6–4.5). The absolute percentage difference in improvement was 32% and the number needed to treat for the benefit of one additional patient was four.

O'Malley et al. (27) concluded that antidepressant medication could be effective in improving outcome, including symptoms and disability. However, high withdrawal rates were

seen in 63% of the studies. Side effects were reported only in 37% of the studies.

Psychological therapy

Cognitive Behavioral Therapy

Five systematic reviews have shed light on the use of CBT showing varying success in the management of patients with MUS. Kroenke and Swindle (24) searched for studies published between 1966 and 1999. The studies were either RCTs or nonrandomized trials of CBT or cognitive therapy (CT) for somatization, somatoform disorders, or persistent symptoms or symptom syndromes. All these trials (randomized or not) included a control group not receiving CBT or CT interventions.

Of 31 trials reviewed, 29 were randomized. Eleven were performed in the United States, seven in the United Kingdom, five in Netherlands, four in Australia, three in Sweden, and one in Germany. Twenty-five studies targeted specific symptom syndromes; irritable bowel, back pain, chronic fatigue syndrome, chest pain, tinnitus, or fibromyalgia. Only six focused on general somatization, three of those were on patients with MUS and three on those with hypochondriasis. Most studies ($n = 29$) included patients referred to secondary or tertiary care. Only two trials were carried out in primary care: those reported by Speckens et al. (29) and Van Dulmen et al. (30).

Of 1689 patients, the majority were women and 803 received CBT. Primary outcomes were physical symptoms, psychological distress studies, or functional status but some had more than one primary outcome. Physical symptoms appeared

to be the most responsive. CBT patients improved more than control subjects did in 71% of the studies. Group therapy, as brief as five sessions, was reported to be efficacious and its benefits were sustained for up to 12 months.

Kroenke and Swindle (24) concluded that CBT, both individual and group therapy, could be an effective treatment for patients with somatization or symptom syndromes. Benefits in reduction of physical complaints could occur whether or not psychological distress was ameliorated.

Kroenke and Swindle (24) recommended further evaluations on optimal sequencing of CBT in treating primary care patients and identification of those most likely to accept and respond to therapy. Other issues identified were the need for flexible interventions having varying degrees of emphasis on cognitive and behavioral components, different numbers of sessions provided, therapists in most studies were mental health professionals, and mostly short-term follow-up on referred populations.

Blankenstein (26) carried out a systematic review of all randomized trials of treatment for somatization, which were either performed in or applicable to general practice. Only 10 trials were identified as appropriate for the review. Three studies reported using CBT, one of which was group CBT; all were identified as carried out in primary care (29,31,32).

Blankenstein (26) concluded that CBT could be an effective treatment for somatization and symptom syndromes. However, he also noted that the number of trials was small and methodological quality was mediocre; thus, the evidence for the effectiveness of CBT for somatization was limited.

Looper and Kirmayer (28) reviewed studies from 1970 to February 2001 having possible overlap with Kroenke and Swindle (24). The difference of this review is that the analysis was carried out separately for the different diagnostic categories and symptom syndromes. Evidence for the effectiveness was found by the following:

1. Four RCTs using relatively brief individual CBT were effective for hypochondriasis (33–36);
2. Four RCTs for body dysmorphic disorders (37–40);
3. Four RCTs on “undifferentiated somatoform disorder”: chronic fatigue syndrome (41–44);
4. Four RCTs on “undifferentiated somatoform disorder”: noncardiac chest pain (45–48);
5. Four RCTs on “undifferentiated somatoform disorders”; MUS. All four studies were categorized as primary care based (29,49,31,32).

Looper and Kirmayer (28) concluded that there has been considerable progress in establishing the efficacy of CBT for the treatment of somatoform disorders and that the evidence supports the efficacy of individual CBT for the treatment of hypochondriasis, body dysmorphic syndrome (BDD), chronic fatigue, noncardiac chest pain, and MUS. The efficacy of group therapy was also demonstrated in BDD and somatization disorder. Effects were of moderate to large magnitude and the authors recommend CBT as the first line of treatment.

However, they noted that the optimal and minimum duration of treatment and value of maintenance therapy need to be

established. They identified many important methodological considerations. Nonavailability of standardized treatment manuals, not making a blind-rating outcome, and use of intention to treat analysis were the other issues highlighted.

Nezu et al. (23) reviewed 37 studies but only 19 were randomized trials. Nine had targeted MUS, 7 on chronic fatigue syndrome, 16 on fibromyalgia, and 5 on noncardiac chest pain. Significantly, a larger number of studies used group therapy. Five of the nine studies on MUS were performed in the United Kingdom and Sweden.

Nezu et al. (23) also analyzed studies separately for the different diagnostic categories and symptom syndromes. Of nine studies on MUS, only six were RCTs (29,49,31,50–52). The authors concluded that CBT seems effective for reduction of a wide range of physical symptoms, and physical and social functioning. Of seven studies on chronic fatigue syndrome, five were RCTs (41,42,44,53,54). CBT improved CFS symptoms, activity, function, and distress. Of the above highly mixed group of 16 studies, 3 were group interventions, 4 were individual RCTs, and 1 was inpatient care; even the treatment methods were highly variable. Nonetheless, the authors concluded that CBT was beneficial in decreasing psychological and physical symptoms distress and increase quality of life. Five studies were identified on undifferentiated somatoform disorder: noncardiac chest pain (45,47,48,55,56); one included group therapy. CBT was beneficial in reducing chest pain and distress.

The overall duration of sessions ranged from six 40-minute sessions to eight 3-hour group sessions for MUS; 30- to 60-minute outpatient interventions to 10 weeks of inpatient treatment for CFS; nine sessions over 3 weeks to 14 weeks of triweekly intervention for studies of FMS; and 4 to 12 weeks for studies of noncardiac chest pain (NCCP).

The review concluded that, overall, CBT appeared to be effective for all four categories of patients with improvement on a wide range of physical symptoms and associated mood disturbances, and overall physical and social functioning for patients with MUS and CFS. There was a significant decrease in certain psychological and physical symptoms, including improved quality of life, pain, tender points, physical condition, emotional distress, and self-efficacy beliefs in patients with fibromyalgia, and decreased chest pain, activity limitation, and emotional distress in patients with noncardiac chest pain.

Allen et al. (25) searched the literature from 1966 through January 2001. Studies were selected if they compared any psychosocial intervention with a control intervention in the treatment of multiple unexplained physical symptoms. Interestingly, the authors used the term “polysymptomatic somatizers” and included only multiple medically unexplained symptoms, an extreme group, and selected 34 RCTs for their review. These studies included 2 on somatization disorder, 15 on irritable bowel, 5 on CFS, and 12 on FMS. Allen et al. used the term “psychosocial interventions” instead of psychological.

Outcome measures were intensity and frequency of physical symptoms, physical distress, psychological distress, and

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functional impairment. They observed methodological shortcomings and lack of evidence on long-term outcome in over 75% of studies. Their conclusion was that “although seemingly beneficial, psychosocial treatments have not yet been shown to have a lasting and clinically meaningful influence on the physical complaints of polysymptomatic somatizers” (25).

Psychodynamic Psychotherapy

There were no systematic reviews on psychodynamic psychotherapy.

Family Therapy

There were no systematic reviews on family therapy.

Other Interventions**Consultation Letter**

There was no systematic review on consultation letters but a Cochrane protocol was available proposing to assess the effectiveness of consultation letters to assist general practitioners or occupational health physicians in the treatment of patients with multiple MUS in primary care. There were no other systematic reviews.

Level II Evidence: Individual RCT**Psychodynamic Psychotherapy**

Guthrie (57) identified three studies using psychodynamic psychotherapy for patients with “somatisation disorders” (58–60) and concluded that the small number of studies makes it difficult to generalize the results to other somatic conditions.

Bassett and Pilowsky (58) reported an RCT that compared 12 sessions of psychodynamic psychotherapy with six sessions of supportive therapy for patients in a pain clinic. A small difference in pain reduction was shown between the treatment and control groups. Svedlund (59) compared the effectiveness of routine medical treatment with dynamic therapy for patients with irritable bowel syndrome from an outpatient clinic. Patients who received 12 sessions of psychotherapy showed a significantly greater reduction in gastrointestinal symptoms. Guthrie et al. (60) reported a placebo-controlled trial involving 100 patients with chronic unresponsive symptoms of irritable bowel syndrome. The treatment of seven sessions of exploratory psychotherapy was compared to the control of seven sessions of supportive listening. They reported significantly greater improvement in the treatment group in reduction of symptoms.

Family Therapy

Empirical studies using family therapy for MUS or symptom syndromes are almost nonexistent. Real et al. (61) reported a study that used brief family therapy for 18 patients who suffered from somatoform disorder for at least 1 year. A general practitioner trained in short family therapy, applied therapy under the supervision of a trained psychologist. Only the abstract is available and it reports 61.1% “therapeutic success” (61).

Reattribution

The reattribution model consists of an interview with an assessment and a management part. There are three phases in the session with the patient a) feeling understood, b) changing the agenda, and c) making the link (62). Evaluation of the teaching package on the reattribution model revealed that the skills can be effectively learned (63). Training family practitioners in reattribution to manage patients with MUS is feasible and acceptable, and its effectiveness is measurable in routine primary care (64).

Larisch et al. (65) in a two-level cluster randomized trial compared psychosocial interventions based on the modified reattribution model for somatizing patients in general practice (GP) with those of nonspecific psychosocial primary care alone. Forty-two GPs were randomized; 23 to intervention and 19 to the control arm. In total, 127 patients were included. Primary outcome measures were somatoform symptoms and quality of life. These revealed a reduction of physical symptoms ($p = .007$), an improvement in physical functioning ($p = .0172$), and a reduction of depression ($p = .0211$) and anxiety ($p = .0388$) in the intervention group compared with in the control group at the 3-month follow-up. Results no longer remained significant after controlling for baseline and covariate variables for most of these variables, although physical symptoms were still reduced at 6-month follow-up ($p = .029$). Compared with nonspecific psychosocial primary care, the effects of reattribution techniques were small and limited to physical symptoms.

Problem-Solving Approach

Wilkinson and Mynors-Wallis (66) reported a pilot study of problem-solving therapy for the treatment of MUS in 11 primary care patients. Ten of the 11 patients completed between 7 and 10 treatment sessions. The mean Symptom Checklist (SCL)-90 score was 90 before the treatment and fell to 50 after the treatment ($t = 5.4, p < .001$); the mean Whitley Index score was 8.9 before treatment and dropped to 5.1 ($t = 3.1, p < .005$), and the mean number of visits to general practitioner reduced from 4.9 to 2.1.

Therapeutic Benefits Arising From an Assessment/Consultation

Patients with MUS who were randomized to receive “positive” suggestion (told that they had a definite diagnosis and they would be better soon) compared with “negative” suggestion (that their diagnosis and outcome were uncertain), did significantly better in terms of both satisfaction and subjective improvement (64% versus 39%; $p = .001$) than the negative group did (67).

Smith et al. (8) in a crossover RCT tested the efficacy of a psychiatric consultation in reducing the medical costs of patients with somatization. Thirty-eight patients in intervention or control arms were followed up for 18 months. The intervention consisted of a psychiatric consultation leading to suggestions on the management for the primary care physicians. After the psychiatric consultation, the quarterly health care

charges for the first treatment group declined by 53% ($p < .05$). The quarterly charges in the control group were significantly higher than those in the treatment group ($p < .05$). After the control group crossed over, their quarterly charges declined by 49% ($p < .05$). The reductions in expenditures in both groups were due largely to decreases in hospitalization. They conclude that psychiatric consultation reduced subsequent health care expenditures of patients with somatization disorder without affecting changes in health status or the patients' satisfaction with their health care.

Consultation Letter

Smith et al. (68) conducted another RCT with 51 physicians treating 56 somatizing patients who had a history of seeking help for 6 to 12 unexplained physical symptoms. At the start of the experiment, physicians randomized to the treatment condition received a psychiatrist's consultation letter recommending a specific management approach. Physicians randomized to the control then crossed over to receive this letter after 12 months. Data on health outcomes and charges were collected every 4 months for up to 2 years. Patients in the intervention arm reported significantly increased physical functioning and remained stable during the year after the intervention. The intervention reduced annual medical care charges by \$289 (95% CI \$40–\$464) in 1990, which equates to a 32.9% reduction in the annual median cost of their medical care. Somatizing patients with a lifetime history of 6 to 12 medically unexplained symptoms benefited by the treatment based on the recommendations after a psychiatric consultation. The consultation is cost-effective and reduces subsequent charges for medical care, and improves health outcomes in a chronically impaired population.

Rost et al. (69) performed an RCT in which 59 primary care physicians received a psychiatric consultation letter providing treatment recommendations for 73 patients either at baseline or at the end of the year-long study. Patients of doctors receiving the consultation letter reported greater physical capacity than did patients of control physicians (mean difference = 17.9, 95% CI 1.0–34.9) with a \$466 reduction (95% CI \$132–\$699) in health care charges. In addition to a net 21% reduction in health care charges for the typical somatization disorder patient, the consultation letter improved physical functioning in a group of highly impaired subjects. Psychiatric consultation letters are also associated with reduction of health costs either as part of individual care (70) or with additional group therapy (52).

Progress Made Over the Last Decade

RCTs carried out since the last systematic review in 2002 (RCTs up to 2001) are presented in Table 3. Overall, there were 14 RCTs that qualified for the review; 7 from primary care, 5 from secondary care, and 3 from tertiary care. All were from the developed world and were selected samples of defined study populations introducing some selection bias. Three drug trials were double blind (72,74,79). Understandably, none of the psychotherapy trials could be double blinded, but

the efforts to mask the assessors were described in six trials (65,71,76,77,80,81). Prior power calculations were reported in five studies, (73,74,76,80,83), effect sizes of treatment difference were reported in seven (73,74,76,78,80,82,83), and long-term outcome in three studies (73,82,83).

DISCUSSION

The review reveals that two types of interventions, antidepressant medication and CBT, are supported by level I evidence as benefiting patients with MUS. In addition, there is limited level II evidence for other pharmacological and psychological interventions: assessment or consultation including collaborative care model, consultation letter, reattribution, bioenergetics exercise, St John's wort extract (LI 160), and levosulpiride. However, there were no studies comparing the efficacy between pharmacological and psychological treatments for MUS.

All six systematic reviews reached similar conclusions, that CBT may be efficacious for these disorders whether defined as symptom syndromes or grouped under the broader heading of MUS. The impact of CBT has been shown to range from reduction of physical symptoms to psychological distress and disability. However, all reviews recommended further high-quality studies and noted the low number of studies in primary care.

There has been a positive trend over the last decade toward more studies being performed in primary care but, still, there is a crucial and significant deficit of intervention research for MUS in the developing world. Only one study has been reported to date (32). It could be because of the publication divide (84) or simply a result of limited research capacity in the developing world (85).

Antidepressant Medication

Evidence for the effectiveness of antidepressants is available for different subgroups of somatoform disorders. There isn't much new evidence on other medication.

The O'Malley et al. (27) review did not comprehensively address the issue of side effects. Only 37% of the studies covered had examined the issue of side effects and the high withdrawal rates of 63% in such studies may be an indicator of this problem. The potential for side effects is a serious consideration when using antidepressants, particularly tricyclics, for patients with MUS because the side effects in response to medication may be misinterpreted as worsening of symptoms.

In a commentary on the work of O'Malley et al. (27), Price (86) concluded that for MUS or symptoms syndromes, antidepressant medication could be effective in improving outcome, including symptoms and disability. However, Price noted that for antidepressants there was as yet no information on the optimum dose, duration of treatment, or long-term outcome and there was no firm evidence that antidepressants or any other pharmaceutical agent can be regarded as the best approach for treating MUS.

There were two recent trials on St John's Wort (72,74) reporting efficacy for MUS independent of depressive mood.

TABLE 3. Randomized Clinical Trials Since 2001

	N	Population	Treatment Condition	Control Condition	Reported Results and Conclusions by Authors
Studies in primary care Schilte et al. 2001 (71) Netherlands	161	Frequent attendees with somatizing symptoms from 10 general practices	Disclose emotionally important events in their life	Normal care from GP	85% completed the trial and doctor's disclosure had no effect on the subjective health, use of medical services, or sick leave
Volz et al. 2002 (72) Germany	151	ICD-10 somatization disorder, undifferentiated somatoform disorder, or somatoform autonomic dysfunctions from 21 general practices	St John's wort hypericum extract LI 160, 600 mg/day	Placebo	Primary outcome; Hamilton Anxiety Scale, subsfactor somatic anxiety (HAMA-SOM) decreased from 15.39 (SD 2.68) to 6.64 (4.32) in hypericum group and from 15.55 (2.94) to 11.97 (5.58) in the placebo group ($p = .001$); somatization disorder efficacy independent of depressive symptomatology
Dickinson et al. 2003 (73) USA	188	Multisomatiform disorder from 3 family practices	A care recommendation (CR) letter intervention on patients immediately after enrollment	A care recommendation (CR) letter intervention on patients 12 months after enrollment	12-month intervention effect on the physical functioning (PCS) scale of the SF-36 was 5.5 points ($p < .001$); CR letter has favorable impact on physical impairment
Muller et al. 2004 (74) Germany	184	ICD-10 somatization disorder, undifferentiated somatoform disorder, and somatoform autonomic dysfunction without major depression	300 mg of St John's wort extract LI 160 twice daily	Placebo	Primary outcome measures including somatic subscores significantly better than for placebo. St John's wort patients, 45.4% were classified as responders compared with 20.9% with placebo ($p = .0006$); effective and safe for somatoform disorders of mild to moderate
Posse 2004 (75) Sweden	10	Alexithymia and high scores on somatization in primary care	Jungian psychotherapy for 6 months	No psychotherapy but contact as before with their GP	Treatment feasible, able to engage patients in a trusting therapeutic relationship. No definite conclusions can be drawn
Larisch et al. 2004 (65) Germany	127	Somatizing patients in general practice	Psychosocial interventions based on the modified reattribution model	Nonspecific psychosocial primary care (PPC) alone	Compared with nonspecific PPC, the effects of reattribution techniques were small and limited to physical symptoms
Van der Feltz-Cornelis et al. 2006 (76)	81 from 36 practices	Persistent medically unexplained symptoms	A collaborative care model of training and psychiatric consultation	Training plus care as usual by the GP	Intervention group, severity of the main MUS decreased by 58%. A collaborative care model combining training with psychiatric consultation in the GP setting is an effective intervention for MUS
Secondary care Peters et al. 2002 (77) UK	228	Symptoms of chronic fatigue and fibromyalgia	Aerobic exercise	Stretching	Aerobic exercise offers no benefits over nonaerobic exercise but primary health care use was reduced

(Continued)

TABLE 3. Continued

	N	Population	Treatment Condition	Control Condition	Reported Results and Conclusions by Authors
Nanke and Rief 2003 (78) Germany	50	Somatization syndrome	Biofeedback treatment	Relaxation group	Biofeedback modified patients' cognitive schemata: patients with somatization syndrome of the biofeedback group showed a greater reduction of catastrophizing of somatic sensations and higher acceptance of psychosocial causal attributions than the control group did
Altamura et al. 2003 (79)	78	Somatiform disorders; somatoform disorders diagnosed according to ICD-10 and DSM-III-R criteria	Evosulpiride 50 mg bd for 4 weeks	Placebo	Levosulpiride significantly reduced the number of SD symptoms compared with those of placebo ($p = .007$) after 4 weeks of treatment
Allen et al. 2006 (80) USA	84	Somatization disorder	Standard medical care augmented by a psychiatric consultation intervention; patients' primary care physicians the psychiatric consultation letter (PCL)	A 10-session, manualized, individual CBT by psychologists added to the psychiatric consultation intervention; PCL	At 15 months from baseline, somatization symptoms significantly reduced in CBT group (0.84 points on the CGI-SD 7-point scale) ($p < .001$). CBT was associated with greater improvements in self-reported functioning, somatic symptoms, and a greater decrease in health costs
Smith et al. 2006 (81) USA	206	Medically unexplained symptoms	A behaviorally defined patient-centered method consisting of CBT, pharmacological, and other treatment by nurse practitioners	Usual care	Relative risk for improvement was 1.47 (CI: 1.05–2.07), and the number needed to treat was 6.4 (95% CI: 0.89–11.890).
Tertiary care Bleichhardt et al. 2004 (82) Germany	191	Somatization syndrome DSM-IV somatoform symptoms	Individual therapy and problem-focused group therapy, assertiveness training and, for other therapy modules focusing on comorbid disorders	34 waiting list controls	Long-term improvements in number of somatoform symptoms, subjective health status, life satisfaction, visits, anxiety, and depression
Nickel et al. 2006 (83) Germany	128	Turkish immigrants with chronic somatoform disorders	Bioenergetics exercises (BE)	Gymnastic exercises	BE appears to improve symptoms of somatization, social insecurity, depression, anxiety, and hostility in the inpatient therapy of subjects with chronic somatoform disorders

Werneke (87) discussed some methodological issues of the Muller study (74); exclusion of placebo responders after the placebo run-in phase, leading to a bias in favor of St John's Wort, and that the trial was conducted over a shorter period of 6 weeks. Therefore, more replication studies were recommended.

Cognitive Behavioral Therapy

There is more level I evidence for CBT compared with for other approaches and the evidence is increasing. CBT seems to be effective in the reduction of a wide range of physical symptoms and associated mood disturbance, as well as in producing improvements in overall physical and social functioning.

Antidepressants are moderately effective for MUS and effect sizes are homogenous across functional syndromes but no trials have compared antidepressants with CBT. However, there are other reasons, beyond efficacy and empirical evidence, for the choice of CBT over antidepressants. Fewer than 50% of patients with chronic diseases maintain compliance in the longer term (88,89). Compliance by patients with MUS will be a particular problem as they seek treatment from many different categories of therapists. The cognitive behavioral model accommodates each factor that contributes to the patient's distressed state. Working with this model, the therapist is able to go beyond the medical model that searches for a physical cause and treatment by prescription of medication, which has so far failed to help the patient. Another possible advantage is, in contrast to antidepressant medication, patients do not experience unwanted side effects from CBT.

Lack of clarity on what interventions qualify to be defined as CBT remains a problem. Although Nezu et al.'s (23) review claimed to be on CBT, the interventions reported were diverse and may not strictly fall under the category of CBT. Relaxation training, problem-solving training, assertiveness training, visualization, use of behavioral experiments, graded increases in activity level, coping-skills training, education, biofeedback, exercise, and breathing training were included as variants of CBT. Ismail et al. (90) categorized psychological therapies into four groups: supportive or counseling therapy, CBT, psychoanalytically informed therapies, and family systems therapy, and some of the above techniques were classified as counseling.

On the contrary, Allen et al. (25) used the definition "psychosocial interventions" instead of psychological. However, from the results it seems they have included trials using short-term dynamic psychotherapy, relaxation, cognitive therapy, behavioral therapy, and individual and group CBT. Hence, it may be misleading to categorize them together as psychosocial interventions.

Existing evidence on brief dynamic psychotherapies is very limited for MUS. Dynamic psychotherapy has still not shown convincingly better results than placebo or good clinical care do but harm may also occur from dynamic intervention (91). Although there are elements common to both these therapies, there are differences too. CBT focuses more on practical methods of managing current symptoms whereas dynamic

psychotherapy concentrates on the historical origin of symptoms and on relationships including that of the patient with the therapist.

Other Interventions

Assessment as an Intervention

An assessment itself without formal psychotherapy has therapeutic effects (86). A rounded clinical assessment might modify such cognitive factors as symptom attribution and improve outcome (92).

The trials that include a comprehensive assessment, thus, seem to have a positive impact on the outcome of patients with physical symptoms whether they are medically explained or unexplained. The factor influencing the outcome may be a result of change in cognition.

Limitations of the Intervention Studies Carried Out to Date

Most of the studies have adopted divergent selection procedures, interventions, outcome measures, and instruments and these clinical and methodological differences hamper comparison of treatment effects. Many issues remain unanswered and most trials have assessed short-term outcomes only. Although MUS are common in primary care, most studies up to 2000 were not carried out in primary care. However, it is encouraging to see that over the last few years more studies have been conducted in primary care; but it is striking that evidence from the developing world is very limited.

Many studies have not provided equal time for the controls and for the intervention group. Finally, another limitation of this review is that it is confined to literature in English.

Implications for Classification

The challenges posed by the existing systems on classifying MUS pose similar challenges and limitations in reviewing intervention studies on MUS as well. The variation of the numbers of reviews and RCTs retrieved by using different search words for the same problem is a good example. The limitations imposed by these divergent criteria seriously hamper a comparison of the reported work. Maybe the terms "thick folder patients," "crocks," "hysterics," "the terror of the doctor," "problem patients," "painful woman," "hypochondriac," and "amplifiers" (93) are replaced with the more sophisticated MUS, somatization, somatoform disorders, functional syndromes but the alternatives are still diverse.

Directions for Future Research

Treatment of patients with MUS involves a complex intervention, consisting of different components, which may act both independently and interdependently (94) but the active component may not be easily defined. Therapists' and patients' characteristics, delivery, frequency, timing of trial procedures, recruitment into a trial per se, availability of information leaflets, the consent process, nonspecific effects of structured appointments, and the

regular structured follow-up assessment, all may be part of active components.

Hence, future research should consider using factorial designs; compare the efficacy of CBT with other alternative treatment, antidepressants in particular and combinations (78); group and individual CBT therapy (28); other combined regimes (81); or stepped care (95). Optimum treatment intensity or duration (i.e., dose) and place of booster sessions (28) should be considered. Qualitative work to identify strategic components to develop a culturally sensitive and patient friendly intervention should also be embedded with RCTs (94). As most studies used short-term benefits, it is crucial to monitor longer-term benefits (80).

Even if evidence exists for efficacy, we need more pragmatic controlled trials to have a chance of implementing these therapies in more realistic clinical settings (23,16) and that can be carried out with relevance to accessibility (96).

More studies are warranted in the developing world with more locally sensitive and culturally appropriate interventions. Evidence-based guidelines on treatment will be useful only if the subjective elements of patients' preferences and values are acknowledged and explored (89).

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