Review Article

Cognitive Behavior Therapy for Medically Unexplained Symptoms: A Systematic Review and Meta-analysis of Published Controlled Trials

Vikas Menon, Tess Maria Rajan, Pooja Patnaik Kuppili, Siddharth Sarkar[1]

ABSTRACT

Medically unexplained symptoms (MUS) commonly present across the board in medical specialties and are often challenging to treat. Our objective was to assess the efficacy for cognitive-behavior therapy (CBT) in MUS. Electronic search of databases was carried out for published controlled trials in English language peer-reviewed journals from inception till August 2016. Effect sizes for the trials were computed using standardized mean difference, and I^2 test was used to assess sample heterogeneity. Pooled mean effect sizes were derived using a random-effects model. Critical appraisal of studies was done using the Cochrane risk of bias assessment tool. A total of 11 trials involving 1235 subjects were included in the study. Ten trials used standard CBT techniques while one studied the efficacy of mindfulness-based CBT technique. The control arms were treatment as usual in five trials, augmented care in four and waitlisted controls in two trials. The pooled mean effect size for CBT was 0.388 (range 0.055–0.806, 95% confidence intervals 0.316–0.461). The I^2 value was 0 using a random effects model indicating low heterogeneity among studies. Risk of bias was noted in many included studies. Egger plot intercept indicated potential publication bias. CBT was superior to the waiting list, treatment as usual or enhanced usual care with moderate effect sizes in the treatment of MUS. These findings are impacted by the limited number of studies in this area and questionable methodological rigor of included studies.

Key words: *Cognitive-behavior therapy, medically unexplained symptoms, randomized controlled trials, somatization, somatoform disorders*

INTRODUCTION

Medically unexplained symptoms (MUS), or somatic symptoms without adequate medical explanation constitute a significant percentage of consults in both primary and specialist care settings.[1-3] These cases are often, among the most challenging to manage and have high rates of disability, social and health-care

Department of Psychiatry, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, [1]Department of Psychiatry, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence: Dr. Vikas Menon
Department of Psychiatry, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry - 605 006, India.
E-mail: drvmenon@gmail.com

costs, patient dissatisfaction, and noncompleted referrals to specialist mental health-care services.[4-8] Notwithstanding, an increasing awareness about the steadily growing evidence for cognitive-behavioral therapy (CBT) based interventions in MUS, the fact remains that these interventions are rarely implemented.[9-12] This may stem from a lack of evidence base regarding the efficacy of such therapies which in turn may lead clinicians to feel skeptical about putting them into practice.

Prior evidence-based reviews on CBT in MUS have focused either on functional somatic syndromes (FSSs) such as irritable bowel syndrome or fibromyalgia or specific Diagnostic and Statistical Manual of Mental Disorders DSM-IV categories such as somatization disorder.[13-16] However, as pointed out by Kroenke,[15] results from FSS may not necessarily extrapolate to the spectrum of somatoform disorders. Further, data from several studies show that total somatic symptom score is predictive of clinical outcomes.[6,17,18] A recent Cochrane review focused on a variety of nonpharmacological interventions and provided pooled results for both somatoform disorders and MUS in adults.[19] Kleinstäuber *et al*.[20] have also carried out a review of several short-term psychological treatments for MUS but the authors studied diverse psychotherapies including hypnotherapy. CBT has many attributes that make it a conceptually attractive therapeutic option for MUS. These disorders are characterized by both cognitive distortions (e.g., catastrophizing and convictions about the physical nature of problems) as well as maladaptive behaviors (e.g., repeated consultations, heightened body attention and checking) and hence lend themselves to therapies such as CBT focused on the here and now.[16,21]

Several CBT-based trials for MUS have been published in the past few years, and therefore, there is a need to periodically synthesize the evidence in this regard with the objective of resolving discrepant findings from individual trials and guide practicing clinicians. The objective of this systematic review and meta-analysis was to ascertain the strength of CBT-based interventions for MUS in published controlled trials to optimize clinical practice as well as identify limitations of current evidence to inform further research.

MATERIALS AND METHODS

Search strategy and study selection
Electronic searches of databases such as PubMed, ScienceDirect, and Google Scholar were carried out from inception till August 2016 by two investigators (Tess Maria Rajan and Pooja Patnaik Kuppili). Articles

were generated using the following search terms individually as well as in combination: "Medically unexplained physical symptoms," "MUS," "unexplained medical symptoms," "somatoform symptoms," "cognitive therapy," "CBT" or "behavioral therapy." The search was limited to peer-reviewed articles published in English language. The titles and abstracts of the studies generated were examined by two of the authors (Vikas Menon and Tess Maria Rajan) who removed the duplicates and made a final list. The same reviewers independently scrutinized the full texts of potentially relevant articles to select those that met the inclusion criteria for the present meta-analysis. Any disagreements were sorted out through mutual discussion until consensus. In addition, reference lists of included studies were manually examined to check for potential articles by one of the authors (Vikas Menon). Conference proceedings were not included in the present review due to concerns about incomplete reporting of data and uncertainty about the study quality.

Studies were included if they met the following criteria: dealing with presentations of single or multiple MUS, involving the use of any kind of CBT techniques (including third wave CBT such as mindfulness-based CBT [MBCT]) and having a comparison group. Pre-post studies (where outcomes were studied in a single group of patients before and after the intervention) were excluded. The flowchart for literature search is shown in Figure 1. After following the inclusion and exclusion criteria, 11 trials were included for the present meta-analysis.

Data extraction and selection of outcome measure
Data were abstracted from articles meeting the inclusion criteria on the following items: Author and year of study, country of work, type of trial (randomized versus nonrandomized), total sample size as well as sample size in each group, methodological characteristics such as number of CBT sessions administered, nature of and care received by comparator arm, total duration of study and their primary and secondary outcome measures. To reduce the "apples and oranges" threat to the validity of a meta-analysis by aggregating varied outcome measures,[22] we uniformly used physical symptoms as the outcome measure for calculating effect sizes in case of multiple primary outcomes. If physical symptoms were not among the primary outcomes, then measures describing physical symptoms were selected from secondary outcome measures for the purpose of effect size calculation. Data extraction was done by two of the authors (Vikas Menon and Tess Maria Rajan). The study relied only on published information, and we did not contact the authors for additional data.
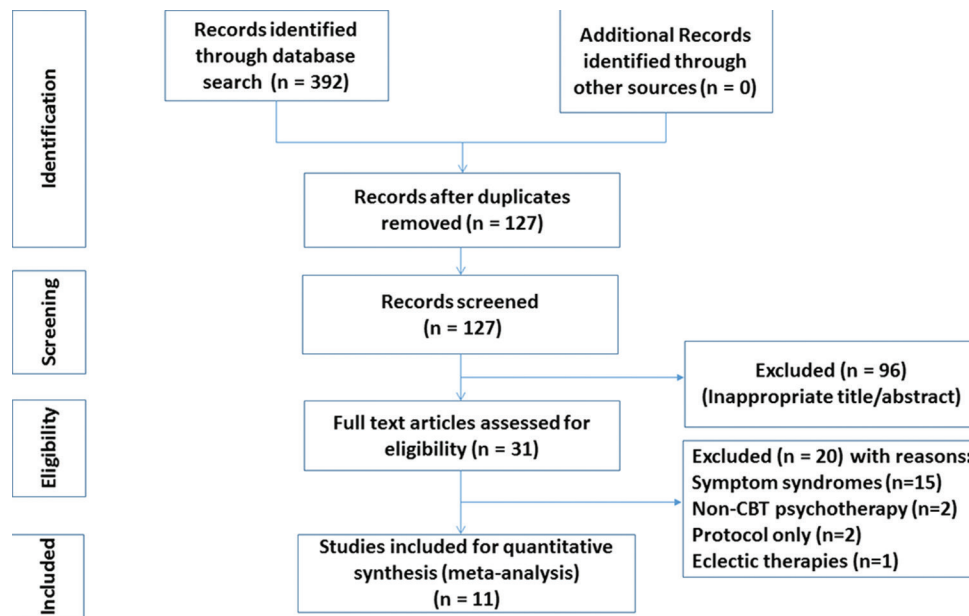
Figure 1: Flowchart for literature search

Study quality assessment

The quality of the individual trials was assessed using the Cochrane collaboration tool for risk of bias.[23] This includes six parameters used to assess study quality: information about random sequence generation (selection bias), details about allocation concealment (also selection bias), blinding of study personnel and participants (performance bias), blinding of outcome raters (detection bias), handling incomplete outcome data (attrition bias), and selectively reporting originally mentioned outcomes (reporting bias). Incomplete outcome data were coded negative (indicating a high risk of attrition bias) if dropout rate ≥20%. Two of our authors examined the full texts of the included articles to categorize every trial on these six parameters which were reported as present, absent or unclear. Inter-rater reliability for study quality assessment, using kappa statistics, was fair for most domains (κ = 0.26–0.40) except for performance bias and detection bias (κ = 0.84 and 0.75, respectively).

Statistical analysis

For each trial that compared the efficacy of CBT with either care as usual, enhanced usual care or waitlisted controls, effect sizes were computed as standardized mean difference yielding Cohen's d statistic with 95% confidence intervals (CIs).[24] Wherever proportions of people improving in the experimental and control group were reported, binary proportions (logit method) was used to compute the effect size (d) and CIs.

Pooled mean effect sizes for CBT interventions were calculated using both the fixed and random effects model for the studies as a whole. Random effects model was, however, deemed to be more appropriate for the present meta-analysis given the heterogeneity of comparison groups and components of CBT used in the individual studies. The I^2 statistic was used to assess heterogeneity among the studies. Its value may range from 0 to 100 with higher values suggesting greater heterogeneity.[25,26]

The assessment of publication bias was done using the Egger's plot.[27,28] This is essentially a regression test of the standard normal deviate (SND) (computed as effect size/standard error) against precision (reciprocal of standard error) for individual studies. In the presence of a systematic error or bias in effect sizes, the regression line will cut the Y-axis at a higher point other than 0.

RESULTS

Characteristics of selected studies

A total of 11 trials met the inclusion criteria and were included in the present meta-analysis.[29-39] The characteristics of the included studies are shown in Table 1. The sample size of individual trials ranged from 32[29] to 206[39] and the pooled sample size was 1235. While all the other trials incorporated standard CBT techniques in their intervention, one study evaluated the efficacy of third wave CBT, namely, MBCT intervention in MUS.[38] The comparator arms were care as usual in five trials,[29,30,32,36,39] enhanced or augmented usual care in four trials[33,35,37,38] and waitlisted controls in two of them.[31,34] The number of mandatory CBT sessions varied from 1[32] to 16[35] (median of eight sessions). The duration of follow-up in the individual

Table 1: Characteristics of included studies (*n*=11)

Author, year	Region	Sample characteristics	Intervention	Comparison group	Sample size (intervention vs. control)	Duration of study	Outcome measure for effect size calculation	Effect size (CIs)
Speckens *et al.*, 1995[35]	Netherlands	18-64 years, single or multiple MUS with moderate intensity on analog scale	6-16 session CBT	Optimized medical care	79 (39 vs. 40)	12 months	Proportion of patients recovered/improved on physical symptoms	0.317 (−0.402-1.035)
Lidbeck 1997[31]	Sweden	30-60 years, fulfilling definition of functional somatic symptoms by Kellner[51]	8 session CBT	Waitlisted controls	50 (33 vs. 17)	6 months	Illness behavior questionnaire	0.332 (−0.248-0.912)
Sumathipala *et al.*, 2000[36]	Sri Lanka	16-65 years, ≥5 MUS for at least 6 months identified by trained primary care physicians	6 session CBT	Treatment as usual	68 (34 vs. 34)	3 months	Bradford somatic inventory	0.643 (0.155-1.130)
Smith *et al.*, 2006[39]	USA	18-65 years, primary MUS identified by trained physician chart raters	12 session CBT	Treatment as usual	206 (101 vs. 105)	12 months	Medical outcomes survey short form - 36; physical component summary	0.361 (0.051-0.671)
Escobar *et al.*, 2007[30]	USA	≥18 years fulfilling criteria for abridged somatization by Escobar *et al.*	10 session CBT	Treatment as usual	172 (87 vs. 85)	6 months	Clinical global impression-improvement	0.806 (0.449-1.163)
Martin *et al.*, 2007[32]	Germany	No age criteria, ≥2 MUS in last 6 months identified by physician	One session CBT	Treatment as usual	140 (70 vs. 70)	6 months	Brief symptom inventory-somatization subscale	0.923 (0.525-1.321)
Sumathipala *et al.*, 2008[37]	Sri Lanka	16-65 years, ≥5 MUS for at least 6 months identified by trained primary care physicians	6 session CBT	Structured care	150 (75 vs. 75)	12 months	General health questionnaire	0.113 (−0.226-0.452)
Burton *et al.*, 2012[29]	UK	18-65 years, opined as MUS by treating GP with at least 2 specialist referrals in last 3 years	4 session CBT	Treatment as usual	32 (16 vs. 16)	3 months	Medical outcomes survey short form - 12; physical component summary	0.323 (−0.460-1.106)
Schröder *et al.*, 2012[33]	Denmark	20-45 years; Chronic bodily distress syndrome (≥2 years) of multi-organ type with impairment in daily living	9 session CBT	Enhanced usual care	120 (54 vs. 66)	16 months	Short form health survey-36; physical component summary	0.546 (0.186-0.896)
Schröder *et al.*, 2013[34]	Germany	≥18 years; ≥2 somatoform symptoms; medical explanation ruled out by physician	8 session CBT	Waitlisted controls	93 (49 vs. 44)	6 months	Screening for somatoform symptoms-severity index	0.451 (0.041-0.861)
van Ravesteijn *et al.*, 2013[38]	Netherlands	18-70 years; physical symptoms for at least 6 months not explained by disease with functional impairment	8 session MBCT	Enhanced usual care	125 (64 vs. 61)	9 months	Visual analog scale for general health	0.055 (−0.321-0.430)

CBT – Cognitive behavior therapy; MBCT – Mindfulness based CBT; MUS – Medically unexplained symptoms; GP – General practitioner; CIs – Confidence intervals

studies ranged from a minimum of 3 months in two studies[29,36] to a maximum of 16 months (median duration of 6 months).[33]

Efficacy outcomes

Effect sizes of individual trials ranged from 0.055[38] to 0.806.[30] The effect sizes and CIs for each trial are

depicted in Figure 2 (forest plot). Meta-analysis of the 11 trials using the random effects model yielded a pooled mean effect size of 0.388 (n = 1235, CIs: 0.316–0.461) for CBT intervention in MUS. The I^2 value for heterogeneity of the analyzed studies was 0 using a random effects model. This indicates low levels of heterogeneity[40] which also justified analyzing all the 11 studies together as a group.

Quality of studies

The risk of bias table for the studies included in the meta-analysis is shown in Table 2. Most of them were randomized controlled trials. The method of randomization, however, was unclear in one trial[34] while allocation concealment was unclear in two studies.[30,33] None of the trials involved double blinding, and this was often not possible due to the nature of the intervention. As most studies relied on patient reported outcomes, there was some detection bias in every trial except one.[30] Attrition bias was present in six trials.[29,30,33,34,36,37] Reporting bias was not observed in any of the trials as all outcomes mentioned in study methodology were elaborated on in the respective results.

Evidence of publication bias

To assess the presence of publication bias, Egger's plot was derived [Figure 3]. The SND was regressed against its precision, and the regression equation for the sample of studies was as follows:

$$SND = 3.091 + 0.374 \times (precision).$$

The Y-intercept (constant) for the equation was 3.091 (CIs: 1.356–4.826, P = 0.003, adjusted R^2 = 0.199) which suggested that there was evidence of publication bias among the selected sample of studies.

DISCUSSION

Our findings suggest that CBT-based interventions are more effective than control conditions for MUS presentations. The pooled mean effect size was 0.388 which suggests a moderate effect size. However, on closer
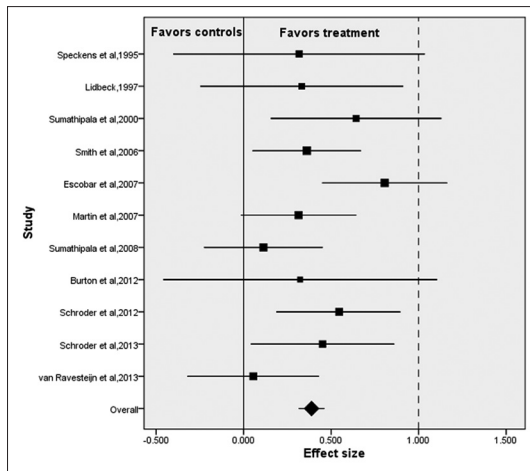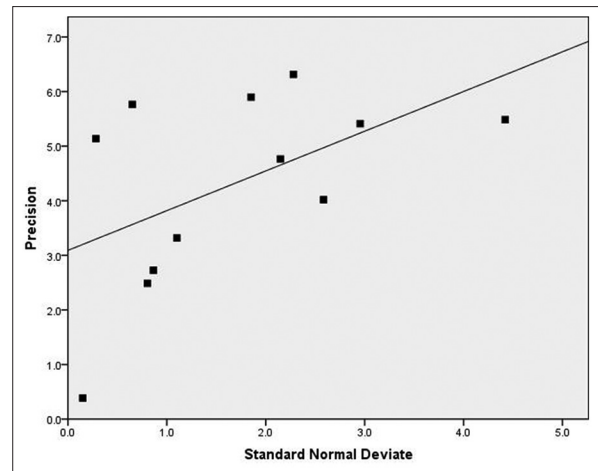

Figure 2: Forest plot for included studies

Figure 3: Publication bias plot

Table 2: Risk of bias assessment for included trials (*n*=11)

Author, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)
Speckens *et al.*, 1995[35]	+	+	-	-	+	+
Lidbeck, 1997[31]	+	+	-	-	+	+
Sumathipala *et al.*, 2000[36]	+	+	-	-	-	+
Smith *et al.*, 2006[39]	+	+	-	-	+	+
Escobar *et al.*, 2007[30]	+	?	-	?	-	+
Martin *et al.*, 2007[32]	+	+	-	-	+	+
Sumathipala *et al.*, 2008[37]	+	+	-	-	-	+
Burton *et al.*, 2012[29]	+	+	-	-	-	+
Schröder *et al.*, 2012[33]	+	?	-	-	-	+
Schröder *et al.*, 2013[34]	?	+	-	-	-	+
van Ravesteijn *et al.*, 2013[38]	+	+	-	-	+	+

+ − Low risk of bias; - − High risk of bias; ? − Unclear risk of bias

analysis, the CIs for effect size spanned zero for 6 of the 11 trials included in the meta-analysis.[29,31,32,35,37,38] The studies whose CIs were noninclusive of the null value (zero) ($n = 5$)[30,33,34,36,39] were all varied in the use of their control group indicating that the comparator arm did not play an important role in determining the effect size of the intervention. This also justifies the lack of a subgroup analysis, based on control subject status, in the present work. Intriguingly, of these five trials whose CIs for effect size did not span 0 (hereafter referred to as significantly effective trials), except the Sumathipala *et al.* study,[36] all the others employed more than 8 CBT sessions in their intervention.[33,34,39,41] This seems to suggest that the intensity and duration of CBT work has a bearing on outcomes and may be kept in mind by health-care providers working with MUS.

Interventions were carried out by primary care physicians for three of the significantly effective trials[30,36,39] while specialists delivered the intervention for the other two trials[33,34] suggesting that CBT delivered by primary care physicians for MUS are as effective as those delivered by specialists. This provides some food for thought for both care providers and policymakers as most MUS patients do not complete referrals to specialist health-care services and prefer to have psychosocial services delivered by their primary care physician.[42-44] CBT techniques should be an integral component of the management of MUS in primary care, and more resources may be allocated to disseminate information about CBT techniques.

To the best of our knowledge, there is no prior meta-analysis focusing exclusively on CBT for broad spectrum MUS presentations. Two prior related reviews found that CBT interventions were efficacious for a wide variety of clinical presentations characterized by the presence of physical symptoms.[15,16] The conclusions of these reviews were not based on a calculation of treatment effects but synthesis of the evidence reported by the authors of respective papers. We have evaluated the efficacy of CBT in MUS through effect size computations. This may help to fill an important knowledge gap.

Although overall we found meaningful benefits with CBT for MUS, a few trials did not show positive efficacy results.[29,31,32,35,37,38] The question that follows is whether it is possible to empirically identify MUS patients who are likely to benefit from CBT work. Preliminary evidence of such a kind is already available in psychological conditions such as depression[45,46] and need to be studied among MUS patients also. Many reasons can be postulated for the mixed effects of CBT observed in the trials. First and foremost, no standardized procedure exists for CBT in MUS,

and this may have led to heterogeneity in treatment. Second, the number of CBT sessions employed was markedly varied between trials. Third, the role of nonspecific factors (such as participation in the trial itself) contributing to treatment outcomes cannot be discounted in MUS. Thus, improvement may have occurred independent of changes in cognition and behavior targeted through CBT, and these factors are difficult to quantify.

Publication bias was observed in the present quantitative synthesis. However, one should keep in mind the low volume of research that is occurring in this area. We found that 8 of the 11 trials selected[29,30,32-34,37-39] were carried out in the last decade, but of this, only 4 were conducted in the last 5 years[29,33,34,38] indicating inadequate growth of research in this field. With such a low sample of studies, perhaps, the power to detect asymmetry through Egger's test was low.[47,48]

Some limitations of present meta-analysis should be kept in mind before drawing conclusions. First, the studies reviewed were markedly heterogeneous in definitions of caseness, components of interventions, nature of comparator arm, outcomes and duration of follow-up. Second, many studies reported several outcomes and did not distinguish between primary and secondary outcome measures. We had to resort to a consensus approach to decide on the selection of outcomes for effect size calculation. This may have potentially inflated the effect sizes in the absence of analysis not being controlled for multiple hypotheses testing in individual trials. Third, several studies had low sample sizes, and therefore group differences had to be of comparatively higher magnitude to achieve statistical significance. Fourth, the lack of allocation concealment and nonblinding of outcome raters were among several potential sources of bias noted in the present review.

CONCLUSION

There is adequate evidence to support the efficacy of CBT in MUS. Our conclusions are, to an extent, impacted by limited number of studies in this area and more research is needed to make firmer conclusions. There is a paucity of trials focusing on other psychotherapeutic techniques which are inherently less heterogeneous than CBT such as interpersonal therapy and problem-solving therapy in MUS. Given wide variations in presenting patterns of MUS,[49] it is likely that eclectic psychotherapies and combination treatments (e.g., hospital-based CBT with pain self-management programs) may work better. Modifications of CBT such as MBCT also appears promising on the basis of positive effects of the single trial reported here.[38] Lack of adequate research in this

area is striking and warrants attention by the practicing community given the significant societal and economic costs associated with MUS.[50,51]

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Conflicts of interest
There are no conflicts of interest.

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