A brief cognitive behavioral intervention is cost-effective for primary care patients with medically unexplained physical symptoms compared to usual care

Article  (Accepted Version)

Van Marwijk, Harm and Sitnikova, Kate (2020) A brief cognitive behavioral intervention is cost-effective for primary care patients with medically unexplained physical symptoms compared to usual care. Journal of Psychosomatic Research. ISSN 0022-3999

This version is available from Sussex Research Online: http://sro.sussex.ac.uk/id/eprint/93354/

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher’s version. Please see the URL above for details on accessing the published version.

Copyright and reuse:
Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.
Title: A brief cognitive behavioral intervention is cost-effective for primary care patients with medically unexplained physical symptoms compared to usual care

Authors: Kate Sitnikova*, Aureliano P. Finch, Stephanie S. Leone, Judith E. Bosmans, Harm W.J. van Marwijk, Henriëtte E. van der Horst, Johannes C. van der Wouden

Address of corresponding author: Amsterdam UMC, Vrije Universiteit Amsterdam, Department of General Practice and Elderly Care Medicine, Amsterdam Public Health Research Institute, De Boelelaan 1117, Amsterdam, Netherlands

E-mail: e.sitnikova@amsterdamumc.nl

Telephone number: +31 (0)20 444 8167

* Corresponding author

Short running head: Cost-effective CBT intervention for MUPS

Competing interests: The authors have no competing interests to report.

Funding: This project was funded by ZonMw (number 80-83700-98-42070), The Netherlands Organization for Health Research and Development. The funding body did not have any role in the trial design, collection, analysis, interpretation of data, or in writing the manuscript.
Introduction

Patients with medically unexplained physical symptoms (MUPS) are frequently encountered in all healthcare settings and particularly in primary care (1-3). If MUPS persist, the symptoms may be considered severe enough to be classified as a DSM-IV somatoform disorder (4), or as a somatic symptom disorder according to the DSM-5 (5). MUPS substantially affect health-related quality of life (HRQoL), cause high levels of functional impairment and are associated with mental disorders, such as anxiety or depression (1, 3, 6). Moreover, MUPS are associated with substantial costs (7). Total societal costs among patients with MUPS amounted to €21.2 billion in a 2010 European study (8).

According to various systematic reviews, cognitive behavioral therapy (CBT) is the most effective form of treatment for MUPS (9, 10). After receiving CBT, a substantial number of patients report less physical symptoms, disability and psychological distress. However, patients do not always turn to healthcare providers who deliver CBT, as these are commonly situated in a mental healthcare setting outside of general practice. Both patients and general practitioners (GPs) may not feel comfortable turning to mental healthcare for physical symptoms and only patients with severe symptoms and high functional impairment are referred (11, 12).

Patients with mild to moderate MUPS may benefit from referral to a mental health nurse practitioner (MHNP) which is advocated in in the current Dutch GP guideline (13). The MHNP is typically a mental health nurse or psychologist within the general practice, who provides counselling to patients with mild psychosocial problems. The MHNP was introduced in 2014 by the Dutch government to decrease the growing mental healthcare costs, to decrease GPs' workload, and to offer more accessible mental health services within the familiar surroundings of a general practice (14).

To establish the effectiveness of CBT for patients with mild to moderate MUPS in primary care, we recently conducted a randomized controlled trial, the Cognitive behavioral Intervention in PRimary care for Undifferentiated Somatoform disorder (CIPRUS) study comparing a CBT-based intervention provided by MHNPs in addition to usual care, to usual care alone (15). The intervention was effective in improving physical functioning and in decreasing pain and limitations due to physical symptoms. It was particularly effective in patients with symptoms that had been present for a limited number of years and who had few or no comorbid physical diseases.

Since healthcare resources are scarce and MUPS are associated with substantial costs (7, 8), it is important to also evaluate the cost-effectiveness of interventions to treat MUPS, besides evaluating their clinical effectiveness. Two systematic reviews (7, 16) show that CBT is cost-effective compared to pharmacological and non-pharmacological treatment and waiting-list controls. However, only a minority of the included studies included both clinical effects and quality adjusted life years (QALYs) as outcome measures. QALYs are generally considered as the most important outcome in health economic evaluations, since this outcome reflects the societal desirability of a specific health state. Additionally, QALYs can be compared across diseases. Traditionally, this was done using life-years gained, but considering that MUPS is not a life-threatening condition this is not an appropriate outcome measure in this context. Therefore, the aim of this study is to conduct an economic
evaluation of a cognitive behavioral intervention delivered by MHNPs for MUPS patients on top of usual care, from a societal perspective. This evaluation includes both QALYs and physical functioning as outcome measures.

Methods

Trial design

We conducted a cluster-randomized controlled trial with 12 months follow-up in the Netherlands between August 2015 and May 2018. The VU University Medical Center Ethics Committee approved the study (number 2014.305, 9 July 2014, amendment 5 August 2016). The design of the trial is described in more detail elsewhere (17). The trial is registered in the Dutch Trial Registry, www.trialregister.nl under NTR4686.

Treatment allocation, participants and procedures

Cluster randomization was used to avoid contamination between treatment groups. Since a MHNP could be affiliated with more than one general practice, a cluster was defined by the MHNP (n=31) rather than the participating general practice (n=85). An independent epidemiologist carried out concealed random allocation of clusters to the intervention or usual care condition using a computer-generated randomization list.

Participants were recruited from 85 general practices throughout the Netherlands. Participants were eligible for the trial if they were 18 years old and above, and had MUPS. MUPS was operationalised as fitting the DSM-IV classification criteria for undifferentiated somatoform disorder (USD). We chose this operationalization to ensure we selected patients who had complaints for at least 6 months and were significantly impaired by these complaints.

Exclusion criteria were: having a medical or psychological disorder that explained the reported symptoms that would allow patients to participate in our study; having a severe psychiatric disorder (e.g. psychotic disorder); currently receiving psychological help for MUPS; having poor language skills or physical handicaps that would prevent patients from understanding the intervention or questionnaires.

GPs selected patients from their electronic databases who had consulted them with one or more symptoms from the ‘Robbins’ list (18) at least twice in the previous 3 months. The Robbins list consists of 23 physical symptoms that are associated with functional somatic syndromes. Potentially eligible patients who met the inclusion criteria received concise information about the study and the Patient Health Questionnaire 15-item somatic symptom severity scale (PHQ-15) (19) from their GP. Interested patients with a PHQ-15 score of at least 5 (low symptom severity) were provided with information on the study and invited to participate in a clinical interview (Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)) (20). Patients meeting the DSM-IV criteria for USD and giving informed consent were included in the study.
Interventions

The intervention consisted of six individual 30-minute sessions with a MHNP in the general practice in addition to usual care. Before delivering the intervention, MHNPs followed two group training sessions lasting 3 to 3.5 hours each. The sessions were led by a clinical psychologist specialised in treating somatoform disorders. MHNPs also received an intervention manual describing each session in detail. Supervision by the clinical psychologist who had trained them was provided if needed.

The intervention consisted of a combination of two CBT methods: the modified version of the consequences model for somatoform disorders (21) and Problem-Solving Treatment (PST) (22). The consequences model focuses on the consequences or problems that arise due to physical symptoms, rather than on their possible (unknown) cause(s). PST is a cognitive behavioural problem-solving approach consisting of seven steps. During the sessions, patients first identified the consequences or problems they experienced in daily life due to MUPS in collaboration with their MHNP. The identified consequences or problems were then tackled using the seven PST steps. The goal was to enhance patients’ problem solving skills in order to deal with the consequences of their physical symptoms and other problems that may arise in daily life. The intervention is described in more detail elsewhere (17).

The usual care group did not receive any additional intervention other than the care they would usually receive from their GP or any other healthcare providers they were referred to for their USD symptoms. Usual care is generally based on the applicable GP guideline and multidisciplinary guideline for management of MUPS and somatoform disorders (13, 23).

Resource use and unit costs

Information on resource use was retrospectively collected at baseline and 4, 8 and 12 months of follow-up using an adapted version of the Trimbos and iMTA questionnaire on Costs associated with Psychiatric Illness (Tic-P) (24). Intervention costs were calculated using a micro-costing bottom-up approach and included costs of training sessions for the MHNPs and the six intervention sessions of 30 minutes. Healthcare costs included primary care costs such as visits to the GP, MHNP, physiotherapist, complementary medicine and psychologists; secondary care costs such as medical specialists, psychotherapists and diagnostics; and medication costs (both prescribed and over-the-counter medication). Other costs included productivity losses resulting from absenteeism and presenteeism, and paid or unpaid help, for instance with domestic work.

Healthcare costs were estimated by multiplying healthcare utilization with the standard prices reported in the Dutch costing guidelines (25). Costs of medication were calculated using prices of the Royal Dutch Society for Pharmacy (26).

Absenteeism from paid work was assessed by asking participants how many of their working days they had called in sick during the previous period of 4 months. Costs of presenteeism were assessed by asking participants how many of their working hours would have to be replaced due to reduced productivity while being present at work. Costs of absenteeism and presenteeism were calculated
using sex-specific mean wages of the Dutch population (27). Absenteeism costs from paid work were estimated according to the friction cost approach. The friction cost approach assumes that a sick employee is replaced by another employee after a certain period of time i.e. the friction period. Productivity losses are assumed to occur during this friction period only. A friction period of 85 days (12 weeks) was used in our analysis.

All costs were indexed for the year 2016. Discounting was not necessary because the time horizon of the economic evaluation was limited to 12 months.

Outcome measures

Primary outcome

The primary outcome of this study was quality adjusted life years (QALYs). QALYs are an index, i.e. a utility, summarizing the length of life and HRQoL (28). HRQoL was measured with the EQ-5D-5L (29) at baseline and at 2, 4, 8 and 12 months after baseline. The EQ-5D-5L is the most frequently used preference-based HRQoL instrument in health technology assessment (30) and has been shown to be valid and responsive across multiple conditions (31). It describes health in terms of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has 5 levels (from 'no problems with...' to 'unable to...'). The health state indicated by patients on the EQ-5D-5L was converted to a utility score using the Dutch EQ-5D-5L tariff (32). The EQ-5D-5L utility scores at different time points were used to calculate QALYs using the area under the curve method. Changes between health states at different time points were considered linear.

Secondary outcomes

All secondary outcomes were assessed at baseline and at 2, 4 and 12 months after baseline. The improvement in patients’ physical functioning during the total 12-months follow-up period was measured by the physical component summary score (PCS) of the RAND-36 questionnaire (33). Higher scores indicate better physical functioning. The PHQ-15 somatic symptom severity scale (19) was used to measure the severity of the somatic symptoms. Anxiety and depressive symptoms were measured using the Hospital Anxiety and Depression Scale (HADS) (34). Higher scores on the PHQ-15 and HADS indicate more severe symptoms.

Sample size

In the clinical trial, we aimed to detect a clinically relevant effect size of 0.4 standard deviations (SD) on the primary outcome (the PCS of the RAND-36), using a two-sided significance level of 5%, a power of 80%, and an allocation ratio of 1:1. We assumed a correlation coefficient of 0.5 for repeated measurements. Using linear mixed models with these assumptions required a sample size of 74 patients per condition. After correcting for the cluster design (assuming an average cluster size of 4 and an intracluster correlation coefficient (ICC) of 0.05) (35) and accounting for a potential dropout rate of 20%, we aimed to include 106 patients in each condition.
Statistical analysis

The analyses were conducted according to the intention-to-treat principle. Missing data on costs and outcomes were imputed using multiple imputations with chained equations (MICE) and stratified by treatment group, using predictive mean matching. An imputation model was created that contained all variables in the analysis models, characteristics differing between groups at baseline, variables related to missing data and variables related to outcome variables. Twenty imputed datasets were created, resulting in a loss of efficiency of less than 5% (36). The imputed datasets were each analysed separately and the results of the analyses were pooled using Rubin’s rules (37).

Bivariate regression analyses were used to estimate differences in costs and effects. Incremental Cost-Effectiveness Ratios (ICERs) were calculated by dividing the difference in costs between the groups by the difference in effects. Non-parametric bias-corrected and accelerated bootstrapping with 5000 replications was used to estimate statistical uncertainty. The bootstrapped cost-effect pairs were plotted on a cost-effectiveness plane. Cost-effectiveness acceptability curves (CEACs) were estimated, showing the probability that the intervention was cost-effective compared to usual care at different ceiling ratios (38). A ceiling ratio represents the maximum amount of money society is willing to pay to gain one unit of effect on the outcome measure. Effect differences for the PHQ-15 and the HADS were multiplied by -1 to enhance interpretability of results. All analyses were performed with Stata SE/14.

Sensitivity analyses

In order to assess the robustness of our results, we conducted multiple sensitivity analyses. First, we performed the economic evaluation from a healthcare perspective, which is the recommended perspective in countries such as the United Kingdom (39). Within the healthcare perspective, only healthcare costs are taken into account. Because the effectiveness of the intervention was particularly pronounced in patients with symptoms below the median duration of symptoms and in patients with fewer comorbid physical diseases (15), we also performed subgroup analyses for patients with a duration of symptoms below and above the median duration of MUPS complaints, and with either 0-2 or 3 or more comorbid physical diseases.

Results

Participants

An overview of patient enrolment, allocation and follow-up is provided in Appendix A. Recruitment took place between August 2015 and March 2017. Invitations were sent by mail to 1806 potential participants. Of these, 234 (13%) expressed an interest to participate in the study and fulfilled the criteria for USD. In total, 117 people were enrolled in the intervention group and 96 in the usual care group.
Patients' baseline characteristics are presented in Table 1. The mean age in both arms was 51.5 years (SD 16.3) and 74.5% of the whole sample were female. Clinically relevant differences were found for gender, education and neurological symptoms.

Costs and effects

Table 2 provides the mean costs and effects over 12 months. Total societal costs in the intervention group were lower (mean difference -€2300, 95% CI -3257 to -134) than in the usual care group and this difference was statistically significant. The main contributors to the cost differences between the two groups were paid and unpaid help, primary care costs and productivity losses in the form of absenteeism.

The mean number of QALYs (primary outcome) was 0.66 (SE 0.01) in the intervention group and 0.65 (SE 0.02) in the usual care group. This difference (0.01) was not statistically significant (95% CI -0.01 to 0.04). The mean PCS was 2.46 (95% CI 1.44 to 3.47) points higher in the intervention group than in the usual care group after 12 months. The mean PHQ-15 score was 0.26 (95% CI -0.28 to 0.81) points higher, and the mean HADS score was 0.07 (95% CI -0.67 to 0.81) points higher in the intervention group than in the usual care group after 12 months. Both differences were not statistically significant.

Cost-effectiveness analysis

Primary outcome

The results of the cost utility analysis (CUA) and cost effectiveness analysis (CEA) are presented in Table 3. The ICER for QALYs was -149,775, which indicates that a gain in 1 QALY is associated with cost savings of €149,775 in the intervention group as compared to usual care. The CE-plane for QALYs (Figure 1a) shows that the majority of the bootstrapped cost-effect pairs (66%) is located in the southeast quadrant (intervention dominant over usual care, i.e. less expensive and more effective). About a quarter (26%) of the cost-effect pairs is located in the southwest quadrant (less effective, less costly). At a willingness to pay of 0 €/QALY gained, the probability that the intervention is cost-effective compared to usual care was 0.93 (Figure 1b). The CEAC is a decreasing function of willingness to pay, because costs in the intervention group were lower than in the usual care group.

Secondary outcomes

The ICER for the PCS was -404, which indicates that one point of improvement on the PCS is associated with cost savings of €404 in the intervention group compared to usual care. The CE-plane for PCS (Figure 2a) shows that the vast majority of the bootstrapped cost-effect pairs (91%) is located in the southeast quadrant (intervention dominant over usual care). At a willingness to pay of €0, the probability of the intervention being cost-effective is 0.92 (Figure 2b).

The ICERs for the PHQ-15 and HADS (PHQ-15: 8,708 and HADS: 32,427) indicate that the intervention did not significantly improve these outcomes, but saved money compared to usual care. The CE-planes and CEACs for these variables can be found in Appendices B and C. The majority of
the bootstrapped cost-effect pairs (PHQ-15: 62% and HADS: 49%) were located in the southwest quadrant (less effective, less costly), but a substantial percentage (PHQ-15: 31% and HADS: 44%) were also located in the southeast quadrant (more effective, less costly). At a willingness to pay of €0/unit of effect, the probability of the intervention being cost-effective compared to usual care was 0.92 for both the PHQ-15 and the HADS (Appendices B and C).

Sensitivity analyses

Healthcare perspective

The results of the analyses from the healthcare perspective are similar to the results from the societal perspective analysis (Tables 2 and 3, and Appendices D). For all outcome measures, the probability of the intervention being cost-effective compared to usual care is 0.78 at a willingness-to-pay of 0 €/incremental unit of effect. The probability is lower than from the societal perspective (0.92), because the cost difference is smaller than from the societal perspective.

Subgroup analyses

The results of the subgroup analyses are presented in Table 4 and Appendix E. For the PCS, the intervention was significantly more effective than usual care in the subgroups with shorter symptom duration and less comorbid diseases. All of the differences in the other outcomes (for QALYs, PHQ-15 and HADS) were not statistically significant. Total societal costs in the intervention group were significantly lower than in the usual care group in the subgroups with longer symptom duration and less comorbid diseases. In the opposite subgroups (shorter symptom duration and more comorbid diseases), the difference in total societal costs was much smaller and not statistically significant. As a consequence, due to the significantly lower societal costs, the intervention was considered dominant over usual care in the subgroups with shorter symptom duration and more comorbid diseases, but less so in the other subgroups.

Discussion

Main findings

We investigated whether a cognitive behavioural intervention for patients with MUPS was cost-effective compared to current usual care in the Netherlands. Total mean healthcare and societal costs were significantly lower in the intervention group compared to the usual care group. Although the difference in QALYs was in favour of the intervention group, this difference was not statistically significant. At a willingness to pay of 0 € per QALY gained, the probability of the intervention being cost-effective was 0.93 from the societal perspective. Therefore, we can consider our intervention to be dominant over usual care.

Even though the difference in the primary outcome, the QALYs, was not statistically significant, the PCS score in the intervention group was significantly higher than in the usual care group. Furthermore, costs were significantly lower in the subgroups with a shorter symptom duration and fewer comorbid
diseases as compared to the subgroups with a longer symptom duration and many comorbid diseases. Finally, the intervention was cost-effective from both the societal and health care perspective.

In both groups, the main contributor to the difference in societal costs were costs of paid and unpaid help. This can probably be explained by the fact that patients with MUPS often experience severe physical limitations due to their symptoms, and are therefore not able to carry out daily tasks on their own (40). The improvement in PCS is thus reflected by an improvement in the ability to carry out these daily tasks. This is also indicated by the much lower absenteeism costs in the intervention group, which are nearly half the absenteeism costs in the usual care group. This suggests that the intervention also enables patients to become more productive at work. In this study, primary care costs were higher than secondary care costs in both groups, although secondary care services are typically more expensive than primary care. Overall, we observed substantial reductions in healthcare costs, which indicates that the intervention is also beneficial from the healthcare perspective.

Comparison to previous studies

Our findings confirm the results from several previous studies evaluating the cost-effectiveness of psychological interventions for patients with MUPS. A group CBT intervention for somatoform disorders also was dominant (less expensive and more effective) compared to a waiting-list control group (41). The findings from our study may be somewhat more robust as we compared our intervention against usual care, which may be considered an active treatment, as opposed to a waiting-list control group. A group intervention, based on CBT and psychodynamic therapy, provided by a GP in collaboration with a ‘psychosomatic specialist’ (physician or psychologist), on top of enhanced medical care, was more effective than enhanced medical care alone, for patients with functional somatic syndromes (42). However, it did not lead to a statistically significant decrease in costs. Finally, two studies investigating the cost-utility of interventions consisting of psycho-educational and CBT techniques for patients with fibromyalgia, who tend to have comparable complaints to MUPS patients, showed that these interventions were cost-effective (lower costs and more effective) compared to usual care (43, 44).

Strengths and limitations

A first strength of this study is that it was designed as a pragmatic trial, thereby mirroring daily practice as much as possible. In addition, we used a societal perspective that included a broad range of costs making it possible to identify potential cost shifts between sectors. Another strength is that we evaluated the impact of the intervention on multiple outcomes measures, such as QALYs, physical functioning (RAND-36 PCS), somatic symptom severity (PHQ-15) and anxiety and depression (HADS). Finally, we carried out several sensitivity and subgroup analyses.

A limitation of the current analysis is that the original power calculation was not based on the EQ-5D-5L or costs, but on the PCS of the RAND-36, which was the primary outcome in the effectiveness trial. However, it may be considered unethical to include more patients than necessary to demonstrate clinical effectiveness (45). Despite this limitation we were able to demonstrate a significant effect on
the costs of the intervention. The observed difference in QALYs based on the EQ-5D-5L was only 0.01 which is rather small, while cost differences were rather large (€2300). The EQ-5D-5L may not have been sensitive enough to pick up the changes in our sample due to the absence of important dimensions of health, relevant for this population, such as relationships, energy and sleep (46).

Another limitation is that the recall period of the questionnaire used to measure costs, the Tic-P, was 4 months. Patients reported that they found this rather long and had difficulty estimating the precise use of healthcare and medication in the previous period. This may have led to a less precise calculation of costs. However, we expect that this potential bias is present in both groups. Thus, this probably did not affect our estimations of the differences between the treatment groups. Moreover, there is evidence that recall up to 6 months is reliable (47).

A final point of consideration is that our intervention was designed and tested for and within the Dutch healthcare setting, where an MHNP is routinely available in general practice. Our findings may be less generalizable to countries with other, very different, healthcare systems or where resources are allocated in another way. Our findings may also be less generalizable to those MUPS populations that do not fulfil the DSM-IV criteria for undifferentiated somatoform disorder.

Implications for practice

Although the Dutch GP guideline for MUPS recommends GPs to refer patients with mild to moderate MUPS to a MHNP, this is still not common practice (48). Considering that the workload of the MHNP is already high, delivering our intervention to all eligible MUPS patients, on top of the MHNPs’ current activities, means that deployment of MNHPs in general practice should be increased. The results of our economic evaluation show that in the long run, it would result in a decrease of costs in primary care, so that such an investment may be considered efficient. Moreover, our intervention provides GPs with an efficient and practical strategy for dealing with patients with MUPS.

Conclusion

Based on the current study, the cognitive behavioural intervention delivered by MHNPs, is considered dominant over usual care. Based on our findings, the intervention could be a valuable addition to usual care in general practice, and in particular for patients with a shorter duration of symptoms and few comorbid physical diseases. However, to implement the intervention on a wider scale, may mean that the deployment of MHNPs needs to be increased.

Acknowledgments

We would like to thank all participants, MHNPs, GPs and other staff working in the general practices. We would also like to thank Sandra Dijkstra-Kersten and Daniëlle Huisman for their help during data collection.
References


